Firefly larvae tests were carried out by Professor A. D. Carlson and Miss Nancy Littell, Department of Biological Sciences, State University of New York, Stony Brook, N. Y. Light output from emitting cells was monitored by a phototube during exposure to a soln of test compd[24] (Table IX).

Rate Studies.—Soln of *N*-ethyl-2,3-dimethylmaleimide in 0.5 *M* phosphate buffer (stable for >24 hr) were degassed by alternate exposure to vacuum and N_2 (6 cycles). The buffer was then poured into a side arm contg the appropriate amt of GSH. After shaking briefly to ensure soln, the cell contg the reaction soln was placed in the light path of a Cary Model 14 spectrophotometer. Reaction was followed first at 3050 A, then by complete spectroscopic curves. Optical densities at different times at 305.0 nm were measured and the rate constants computed with the aid of a second-order rate equation and a General Electric Computer. A complete description of the kinetic properties of *N*-alkylmaleimides will appear in a future article.

(24) A. D. Carlson, *J. Exp. Biol.*, **48**, 381 (1968); **49**, 195 (1968).

Tetracyclic Quinazolinone Derivatives

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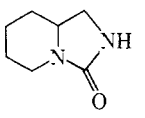
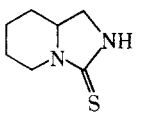
The preparation of 1,6,7,8,9,9a-hexahydro-4-methylthio-2*H*-pyrido[1,2-*c*]pyrimidine and 1,5,6,7,8,8a-hexahydro-3-methylthioimidazo[1,5-*a*]pyridine and their reactions with isatoic anhydride and with anthranilic acid are described. The pharmacology of the reaction products is discussed.

Recently Ziegler and coworkers[1] investigated the reaction of isatoic anhydride with 2-methylmercaptoimidazoline. We now would like to describe the reaction of 2 novel bicyclic mercaptomethylureas with a variety of isatoic anhydrides and anthranilic acids and discuss the pharmacological properties of the reaction products.

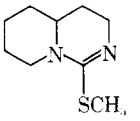
The first saturated imidazo[1,5-*a*]pyridine, namely, the urea **1**, was reported by Winterfeld and Schueler.[2] When we allowed pipecolylamine[3] to react with CS_2[4] the thiourea **2** was obtained, which on reaction with MeI yielded **3**. Analogously the homolog **4** was prepared from 2-(2-aminoethyl)piperidine.[5]



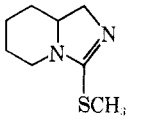
1



2

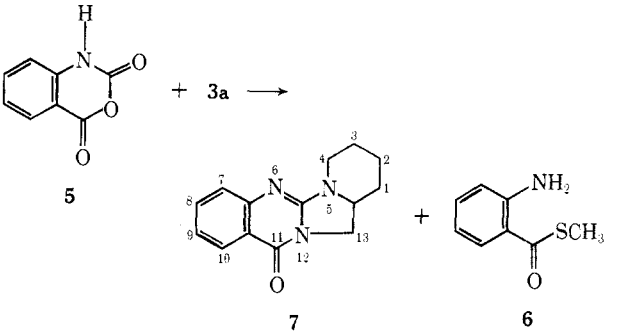


4, ·HI
4a



3, ·HI
3a

When equimolar amounts of the free base **3a** and of isatoic anhydride (**5**) were allowed to react at 100° in dioxane, 2 new products were formed. One was identified as thioanthranilic acid *S*-Me ester (**6**)[6] and the other was the expected tetracyclic material **7**. Compd



5 **7** **6**

4a did not react with **5** under similar conditions, but the desired **8** (see Table I) was obtained when **5** was replaced by anthranilic acid. In the same manner, 4,5-dimethoxyanthranilic acid and several other anthranilic acids (see Experimental Section and Table I) could be treated with **3a** and **4a**.

Pharmacology.—In the course of preliminary investigations on the pharmacological activities of a series of tetracyclic quinazolinone derivatives, it was noted that these substances provided a profile of CNS-depressant activity not unlike that obtained with standard sedative–hypnotics. Each of the present series of compds was submitted to a battery of behavioral and drug-interaction tests in mice, with selected compds being further investigated in behavioral tests in squirrel monkeys. The results with the test compds were compared to those obtained with methaqualone, glutethimide, and/or phenobarbital.

All substances (suspended in 0.5% carboxymethyl cellulose soln) were submitted to a preliminary screen in mice to determine effects on behavior.[7,8] Initial studies on lethality of a few selected compds (following ip administration to mice) indicated that a general

(1) E. Ziegler, W. Steiger, and Th. Kappe, *Monatsh. Chem.*, **99**, 1499 (1968).

(2) K. Winterfeld and H. Schueler, *Arch. Pharm.*, **293**, 203 (1960).

(3) J. R. Norton, A. A. Benson, R. A. Seibert, and F. W. Bergstroem, *J. Amer. Chem. Soc.*, **68**, 1330 (1946).

(4) H. Behringer and H. Meier, *Justus Liebigs Ann. Chem.*, **607**, 67 (1957).

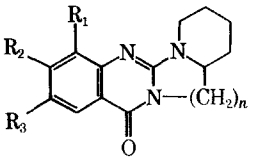
(5) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).

(6) This material is probably formed by reaction of liberated methylmercaptan with unreacted **5**.

(7) S. Irwin, "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Publishers, Chicago, Ill., 1964, pp 36–54.

(8) G. Chen, *Symp. Sedative Hypn. Drugs*, **1953**, 45 (1954).

TABLE I



Compd	n	R_1	R_2	R_3	LD_{50},[a] mg/kg ip	Behavior[b] (ED_{50}, mg/kg ip)	Anticonvulsant act.—*N*-SA[c] (ED_{50}, mg/kg ip)	Anticonvulsant act.—MES[d] (ED_{50}, mg/kg ip)	Barbiturate[e] reinduction (RD_{50}, mg/kg ip)	Rotarod[f] (ND_{50}, mg/kg ip)	Amphetamine[g] interaction (% change @ mg/kg ip)	Fighting mice[h] (ED_{50}, mg/kg ip)	Continuous avoidance,[i] squirrel monkeys (ED_{50}, mg/kg po)
7	1	H	H	H	366.1	$Ataxia_{50}$, 156.2; $docility_{50}$, 300.0; LRR_{50}, 300.0	Na[j] @ 150.0	Na @ 150.0	121.8	39.6%↓ @ 150.0	76.6%↑ @ 150.0	Nt[k]	>40.0
7a	1	H	OCH_3	OCH_3	366.7	$Ataxia_{50}$, 95.0; $docility_{50}$, 100.0; LRR_{50}, 127.7	Nt	Nt	25.0	44.7	47.8%↓ @ 25.0	Nt	40.0
7b	1	H	NO_2	H	81.3	$St\ tail_{50}$, 37.5; $ataxia_{50}$, 64.2; CD_{50}, 75.0	Na @ 37.5	Na @ 37.5	Na @ 37.5	19.2%↓ @ 37.5	Na @ 37.5	Nt	Nt
7c	1	H	CH_3	H	>200.0	$Docility_{50}$, >200.0; $ataxia_{50}$, >200.0; LRR_{50}, >200.0	Na @ 200.0	Na @ 200.0	Na @ 200.0	78.7	33.5%↓ @ 50.0	Nt	Nt
7d	1	H	H	Cl	300.0	$Ataxia_{50}$, 293.3; $docility_{50}$, >300.0 LRR_{50}, >300.0	Na @ 200.0	Na @ 200.0	Na @ 200.0	120.0	59.2%↓ @ 100.0	45.0	Nt
7e	1	CH_3	H	H	>200.0	$Docility_{50}$, >200.0; $ataxia_{50}$, >200.0; LRR_{50}, >200.0	162.5	150.1	Na @ 200.0	121.7	67.0%↓ @ 50.0	Nt	Nt
7f	1	H	OCH_3	H	>200.0	$Docility_{50}$, >200.0; $ataxia_{50}$, >200.0; LRR_{50}, >200.0	Na @ 200.0	Na @ 200.0	Na @ 200.0	168.6	44.5%↑ @ 100.0	Nt	Nt
8	2	H	H	H	650.0	$Ataxia_{50}$, 240.0; $docility_{50}$, 291.8; LRR_{50}, 306.2	Na @ 200.0	125.0	125.0	32.4%↓ @ 200.0	90.0%↑ @ 12.5	Nt	Nt
8a	2	H	OCH_3	OCH_3	466.7	$Ataxia_{50}$, 147.1; $docility_{50}$, 155.0; LRR_{50}, 244.4	183.3	300.0	200.0	100.0	Na @ 200.0	Nt	Nt

[a] Determined by the method of Litchfield and Wilcoxon using 10 animals per dose (J. T. Litchfield and F. Wilcoxon, *J. Pharmacol Exp. Ther.*, **96,** 99 (1949)). [b] Anal. of behavior used modification of method of S. Irwin ("Animal and Clinical Pharmacologic Techniques in Drug Evaluation," Year Book Publishers, 1964, pp 36–54); LRR = loss of righting reflex, St tail = straub tail, CD = convulsive dose; 10 animals per dose. [c] *N*-SA = *N*-sulfamoylazepine, a substance producing pentylenetetrazole-like convulsions and used in place of the standard in these laboratories; 10 animals were used per dose. [d] MES = Maximal electroshock; method of J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9,** 231 (1946), was used with 10 animals per dose. [e] Modified method of C. F. Winter, *J. Pharmacol. Exp. Ther.*, **94,** 7 (1948), was used in which animals were administered compd immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time. [f] Method of N. W. Dunham and T. S. Miya, *J. Pharm. Sci.*, **46,** 208 (1957); 10 animals per dose, ND = neurological deficit. [g] Detd in mice using standard photocell activity cages manufactured by Woodward Research Corp., Herndon, Va.: dose of *dl*-amphetamine: 4.0 mg/kg ip; 5 mice per group. [h] Modification of method of R. E. Tedeschi, *et al.*, *J. Pharmacol. Exp. Ther.*, **125,** 28 (1959). [i] Method of M. Sidman, *Science*, **118,** 157 (1953); monkeys were trained on a shock–shock interval of 5 sec and a response–shock interval of 20 sec (SS-5; RS-20). [j] Na = not active at dose indicated. [k] Nt = not tested.

TABLE II

Compd	No.	LD_{50},[a] mg/kg ip	Behavior[b] (ED_{50}, mg/kg ip)	Anticonvulsant act. *N*-SA[c] (ED_{50}, mg/kg ip)	Anticonvulsant act. MES[d] (ED_{50}, mg/kg ip)	Barbiturate[e] reinduction (ND_{50}, mg/kg ip)	Rotarod[f] (ND_{50}, mg/kg ip)	Amphetamine[g] interaction (% change @ mg/kg ip)	Fighting mice[h] (ED_{50}, mg/kg ip)	Continuous[i] avoidance, squirrel monkeys (ED_{50}, mg/kg, po)
Methaqualone	I	366.7	Ataxia$_{50}$, 21.0; docility$_{50}$, 61.5; LRR$_{50}$, 36.2	Na[j] @ 25.0	Na @ 25.0	22.9	26.1	Na @ 25.0	52.0	20.0
Glutethimide	II	550.0	Ataxia$_{50}$, 100.0; docility$_{50}$, 169.2; LRR$_{50}$, 229.0	Na @ 400.0	24.7	112.5	37.0	Na @ 25.0	Nt[k]	>40.0
Phenobarbital	III	233.3	Ataxia$_{50}$, 62.5; docility$_{50}$, 61.0; LRR$_{50}$, 83.0	8.0	15.4	65.6	49.6	81.6% ↑ @ 37.5	Nt	Nt
Thiothixene	IV	>800.0	Ataxia$_{50}$, 200.0; docility$_{50}$, >200.0; LRR$_{50}$, >200.0	Na @ 100.0	Na @ 100.0	91.7	16.0	50.0% ↓ @ 37.5	4.2	Nt

[a]–[k] See corresponding footnotes in Table I.

dosage range of 12.5–200 mg/kg ip would allow comparison of substances within the series and the selected standards. Anticonvulsant activity was studied in mice, using as indices the antagonism to *N*-sulfomoylazepine[9] and the antagonism to maximal electroshock.[10] General CNS-depressant activity was defined by the ability of substances to produce, in mice, neurologic deficit on the rotarod[11] and by their abilities to reinduce "anesthesia" following recovery of loss of righting reflex obtained with hexobarbital.[12] Interaction with amphetamine-induced stimulation of locomotor activity in mice was used to further define the CNS-depressant profile of compds in the series.[13]

Secondary evaluation consisted of evaluation of selected compds in the shock-induced aggressive mouse test[14] and in squirrel monkeys trained in a continuous avoidance procedure.[15]

As can be seen in Table I, only **7b** provided a relatively high toxicity in mice and, unlike others in the series, this substance demonstrated a profile of CNS-stimulant activity. As regards effects on spontaneous behavior, only **7a**, **8a**, and **8** (the dimethoxy derivatives of pyridoimidazo- and pyridopyrimidoquinazolinones and the unsubstituted pyridopyrimidoquinazolinone, resp) produced significant depression of behavior and CNS reflexes at subtoxic doses. The unsubstituted pyridoimidazo- or pyridopyrimidoquinazolinones **7** and **8** provided only weak activity in drug-interaction studies, except for potentiation of amphetamine-induced stimulation of locomotor activity. This latter effect became more obvious with lower doses of the test compd providing a dose–response curve often observed with sedative–hypnotic substances or antidepressants. Although **7e**, **8**, and **8a** were shown to be anticonvulsants, these activities were considered at best weak and did not appear to contribute to possible structure–activity relationships within the present series. Probably the most significant activity demonstrated by compds within the series was that relating to reinduction of anesthesia following hexobarbital. Although no structure–activity relationships could be described, **7a** provided activity in this test comparable to those obtained with standard substances (see Table II). To further define the relative CNS-depressant activity, **7** and **7a** were administered orally to squirrel monkeys on a continuous avoidance schedule. Figure 1 presents the cumulative recordings obtained with **7**, **7a**, methaqualone, and glutethimide (Doriden), with results indicating that the CNS-depressant activities of **7** and **7a** in this test lie between those of the 2 standards. Additional evidence of CNS-depressant activity is provided

(9) *N*-Sulfamoylazepine (*N*-SA), synthesized at Sandoz, Hanover, N. J., has been found to produce a convulsive syndrome in mice or rats which is similar to that obtained with pentylenetetrazol (PTZ). In addition to its being slightly more active than PTZ, *N*-SA also provides more reproducible results than does the standard. For these reasons, *N*-SA is used in these laboratories to replace PTZ.

(10) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1964).

(11) N. W. Dunham and T. S. Miya, *J. Pharm. Sci.*, **46**, 208 (1957).

(12) C. F. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 (1948).

(13) Locomotor activity in mice was measured using mice (5/group) placed in darkened circular actophotometers (manufactured by Woodward Research Corp., Herndon, Va.). Compds were administered ip 15 min previous to ip injection of 5.0 mg/kg of *dl*-amphetamine SO_4. Activity was then measured (by the animals interrupting photocell beams) for 6 consecutive 10-min periods.

(14) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **125**, 28 (1959).

(15) M. Sidman, *Science*, **118**, 157 (1953).

by the ability of substances to antagonize amphetamine-induced stimulation of locomotor activity in mice. In this respect, compds in the present series separated into two categories: those potentiating amphetamine (**7** and **8**) and those antagonizing amphetamine (**7a**, **7d**, and **7**). Because amphetamine antagonism has been used in the past as a measure of potential tranquilizing activity, **7d** was further tested in the fighting mouse test.[14] As can be seen from Table I, **7d** provided antagonism of shock-induced fighting in mice at doses below those showing antagonism of amphetamine.

The results presented in these studies indicate that certain pyridoimidazoquinazolinones and pyridopyrimidoquinazolinones possess CNS-depressant activities with profiles demonstrated over a broad range of testing procedures, suggesting that the compds are sedatives and/or tranquilizers.

Experimental Section†

All compds were checked by ir and nmr spectroscopy (Perkin-Elmer 237 and Varian A-60, resp) and their spectra were found to be in agreement with the assigned structures. Melting points were determined with a Hoover capillary melting point apparatus and are uncor. No attempt has been made to optimize the yields in the described reactions.

1,5,6,7,8,8a-Hexahydroimidazo[1,5-*a*]pyridine-3(2*H*)-thione (2).—A soln of pipecolylamine (37 g) in pyridine (250 ml) was slowly treated with CS_2 (40 g). After the initial exothermic reaction had subsided the mixt was heated at 100° for 6 hr. The solvent was evapd, and the crude residue was crystd from Et_2O–pentane (48.1 g, 95%), mp 81–85°. *Anal.* ($C_7H_{12}N_2S$) N, S.

1,5,6,7,8,8a-Hexahydro-3-methylthioimidazo[1,5-*a*]pyridine·HI (3).—A stirred soln of the thiourea **2** (108 g) in MeOH (500 ml) was treated with MeI (110 g) and was allowed to remain at room temp for 18 hr. The soln was concd *in vacuo* to 250 ml, treated with charcoal, and filtered. On addn of Et_2O, 117 g (80%) of the reaction product **2** pptd, mp 153–156°. *Anal.* ($C_8H_{15}N_2SI$) N, S.

1,6,7,8,9,9a-Hexahydro-4-methylthio-2*H*-pyrido[1,2-*c*]pyrimidine·HI (4).—A soln of 2-(2-aminoethyl)piperidine[5] (90 g) in pyridine (500 ml) was treated slowly with CS_2 (90 ml). The mixt was heated for 16 hr at 110°, cooled, and evapd to dryness. The crude residue (104 g) was dissolved in 500 ml of EtOH, MeI (100 g) was added, and the mixt was refluxed for 1 hr. The solvent was evapd *in vacuo*. The residue was dissolved in EtOH, the soln was treated with charcoal, and the hydroiodide **4** (138 g, 70%) was pptd by addn of Et_2O, mp 178–180°. *Anal.* ($C_9H_{17}N_2SI$) C, H, S, I.

Free Bases (3a and 4a) from 3 and 4, Resp.—**3** (200 g) was dissolved in 2 *N* NaOH (250 ml), and the mixt was extd with CH_2Cl_2 (2 × 250 ml). The org phase was dried (Na_2SO_4) and evapd *in vacuo*. The crude residue was used for further reactions. Compd **4a** was prepd analogously from **4**.

1,2,3,4,13,13a-Hexahydro-11*H*-pyrido[1′,2′:3,4]imidazo[2,1-*b*]quinazolin-11-one·HCl (7).—A soln of **3a** (10 g) in dioxane (100 ml) was mixed with isatoic anhydride (12 g) and was heated for 4 hr at 100°. The solvent was evapd, and the remaining oil (20.6 g) was chromatogd on silica gel (Merck AG, 0.05–0.2 mm). The head fractions were collected (14.4 g) and dissolved in MeOH (75 ml), and the soln was satd with anhyd HCl. The pptd product was collected and recrystd (MeOH), yield 5.5 g 37% of **7**, mp 307–310°. *Anal.* ($C_{14}H_{15}N_3O\cdot HCl$) N, O, Cl.

8,9-Dimethoxy-1,2,3,4,13,13a-hexahydro-11*H*-pyrido[1′,2′:3,4]imidazo[2,1-*b*]quinazolin-11-one (7a).—A soln of 4,5-dimethoxyanthranilic acid (4g) and **3a** (3 g) in DMAC (75 ml) was heated at 130° for 20 hr. The mixt was evapd to dryness, and the residue was dissolved in CH_2Cl_2. This soln was extd with 2 *N* NaOH and with H_2O. After drying (Na_2SO_4) the soln was satd with anhyd HCl and the pptd hydrochloride (3.4 g, mp 304°) was removed by filtration. It was dissolved in a min amount of H_2O and the soln was made alk by the addn of 2 *N* NaOH. The resulting ppt was washed with H_2O and dried *in vacuo* at 80° (2.5 g, 47%), mp 163–164°. *Anal.* ($C_{16}H_{19}N_3O_3$) C, H, N.

Using the above procedure **10,11-dimethoxy-2,3,4,4a,5,6-hexahydro-1*H*,8*H*-pyrido[1′,2′:3,4]pyrimidino[2,1-*b*]quinazolin-8-one (8a)** (mp 208–209°) was prepd in 31% yield from 4,5-dimethoxyanthranilic acid and **4a**. *Anal.* ($C_{17}H_{21}N_3O_3$) C, N.

1,2,3,4,13,13a-Hexahydro-8-nitro-11*H*-pyrido[1′,2:3,4]imidazo[2,1-*b*]quinazolin-11-one (7b).—A mixt of 4-nitroanthranilic acid (5 g) and **3a** (6.0 g) in DMAC (50 ml) was heated for 1 hr at 160 to 170°. After cooling, the soln was poured onto ice and made alk (2 *N* NaOH). The mixt was extd twice with EtOAc, and the org phase was dried (Na_2SO_4) and evapd *in vacuo*. The remaining oil (11 g) was dissolved in $CHCl_3$ and chromatogd on silica gel (Merck AG, 0.05–0.2 mm); 2.5 g of **7b**, was eluted. The crude oil was crystd from CH_2Cl_2–EtOAc (2.0 g, 26%), mp 188–191°. *Anal.* ($C_{14}H_{14}N_4O_3$) C, H, N, O.

Analogously **1,2,3,4,13,13a-hexahydro-8-methyl-11*H*-pyrido[1′,2′:3,4]imidazo[2,1-*b*]quinazolin-11-one (7c)** was prepd in 30% yield from 4-methylanthranilic acid and **3a**, mp 181–184°. *Anal.* ($C_{15}H_{17}N_3O$) C, H, N.

9-Chloro-1,2,3,4,13,13a-hexahydro-11*H*-pyrido[1′,2′:3,4]imidazo[2,1-*b*]quinazolin-11-one·HCl (7d) was prepd in 35% yield by the above procedure from **3a** and 6-chloroisatoic anhydride, mp 290–294°. *Anal.* ($C_{14}H_{14}ClN_3O\cdot HCl$) C, H, Cl, N, O.

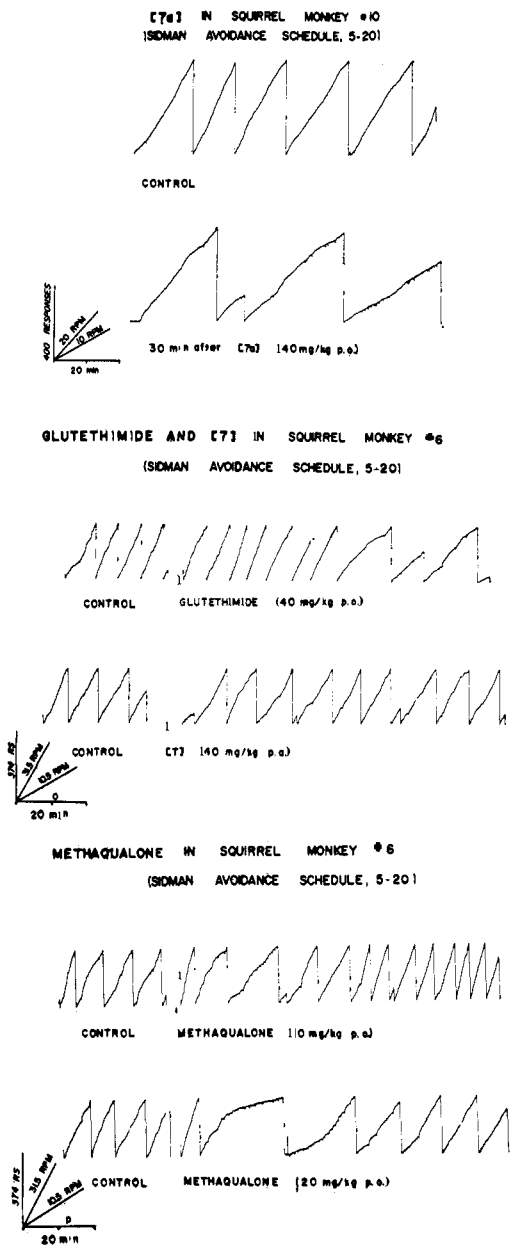


Figure 1.

† Where analyses are indicated only by symbols of the elements, anal. results for these elements were within ±0.4% of the theor values.

2,3,4,4a,5,6-Hexahydro-1*H*,8*H*-pyrido[1′,2′:3,4]pyrimidino-[2,1-*b*]quinazolin-8-one·HCl (8).—To a suspension of anthranilic acid (13.7 g) in dimethylacetamide (100 ml) **4a** (20 g) was added, and the mixt was heated to 150–160° for 3 hr. After cooling the solvent was evapd *in vacuo*, and the residue was dissolved in $CHCl_3$. The soln was extd with 2 *N* NaOH and with H_2O. The org phase was dried (Na_2SO_4) and evapd, and the residue was chromatogd on silica gel (Merck AG, 0.05–0.2 mm). The product was eluted with $CHCl_3$. After evapn the residue was dissolved in EtOH (80 ml), and the soln was satd with anhyd HCl. On addn of Et_2O (300 ml) the hydrochloride crystd, it was removed by filtration (5.9 g, 20%) and dried *in vacuo* (0.1 mm) at 60°, mp 267–270°. *Anal.* ($C_{15}H_{18}N_3OCl$) N, O, Cl.

Analogously **1,2,3,4,13,13a-hexahydro-7-methyl-11*H*-pyrido-[1′,2′:3,4]imidazo[2,1-*b*]quinazolin-11-one (7e)** was prepd in 10% yield by the above procedure from **3a** and 3-methylanthranilic acid, mp 129–130°. *Anal.* ($C_{15}H_{17}N_3O$) C, H, N.

1,2,3,4,13,13a-Hexahydro-8-methoxy-11*H*-pyrido[1′,2′:3,4]-imidazo[2,1-*b*]quinazolin-11-one (7f).—A mixt of 4-methoxyanthranilic acid (6.0 g) and **3a** (6.0 g) in 25 ml of DMAC was heated for 4 hr at 150–160°. The solvent was evapd and the remaining solid dissolved in CH_2Cl_2. The soln was washed with 2 *N* NaOH (50 ml) twice with water (100 ml), dried (Na_2SO_4), and evapd *in vacuo*. The residue crystd from Et_2O, 4.0 g (42%), mp 154–157°. *Anal.* ($C_{16}H_{17}N_3O_2$) C, H, N, O.

Acknowledgment.—We wish to thank Mr. Urs Stoeckli and Mrs. Nancy Engstrom for running the ir and nmr spectra.

Notes

Nucleic Acids. 12. Synthesis of the L Enantiomer of 1-β-Arabinofuranosylcytosine and of $O^2,O^{2'}$-Anhydro-1-β-D-arabinofuranosylcytosine

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1-β-D-Arabinofuranosylcytosine[1a,b] (cytarabine, *ara*-cytidine, *ara*-C, cytosine arabinoside, Cytosar), has proven efficacious in the treatment of acute leukemias and lymphomas[2a–f] and is an inhibitor of DNA synthesis,[3a–e] DNA viruses,[4a,b] and rodent tumors,[5a–j] and inhibits growth of various mammalian cell lines.[3a–e]

A derivative of *ara*-C, 5′-(1-adamantoyl)-*ara*-C, has been shown to possess superior therapeutic properties (compared to *ara*-C) in the treatment of L1210 leukemic mice[6] and to possess greater immunosuppressive activity in this species[7a,b] and in the rat.[7b,8] Recent reports have described the synthesis of a series of 5′ esters of *ara*-C and the superiority of some of these derivatives as antileukemic and immunosuppressant drugs.[9a,b]

Sanchez and Orgel have recently described a convenient synthesis of *ara*-C utilizing 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (I) as the key intermediate.[10] In this synthesis, cyanamide is treated with D(−)-arabinose to yield the sugar–oxazoline derivative (I), which is then condensed with cyanoacetylene to give the $O^2,O^{2'}$-anhydro derivative (II) of *ara*-C. II, without isolation, is hydrolyzed to *ara*-C. Utilizing this synthetic route, but substituting 2-amino-β-L-arabinofurano[1′2′:4,5]-2-oxazoline for the D isomer, we have prepared the L enantiomer of *ara*-C and have tested it for biological activity. We have further devised a method for the isolation of the $O^2,O^{2'}$-anhydro derivative II of D-*ara*-C, a compd that may prove to be an intermediate for the preparation of a number of derivatives of *ara*-C itself.

The preparation of $O^2,O^{2'}$-anhydro-1-β-D-arabinofuranosylcytosine was first reported by Walwick, *et al.*,[1b] who obtained this product in the form of its hydrochloride by the action of prostatic phosphatase on the 3′,5′-diphosphate of the anhydro derivative. This diphosphate had been obtained by phosphorylation of cytidine with polyphosphoric acid. Nagyvary[11] prepared the 3′-phosphate ester of the $O^2,O^{2'}$-anhydronucleoside *via* a polytrimethyl silylated derivative of cytidine 2′,3′-cyclic phosphate. The 3′-phosphate can be dephosphorylated enzymatically. Doerr and Fox[12] had prepared this anhydro nucleoside from 2′-deoxy-2′-chlorocytidine. None of these methods offers a convenient process for the preparation of the anhydro compd. We have now prepared $O^2,O^{2'}$-anhydro-1-β-D-arabinofuranosylcytosine directly from the aminooxazoline. For this purpose, the aminooxazoline I was converted to its hydrochloride and this was condensed with cyanoacetylene to give directly II·HCl.

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