the ring size of the N-cycloaliphatic group is noted. As the size of the ring is increased, potency is decreased.

In summary, the N-cycloaliphatic carbamates in which the 1,1-diaryl substituents are phenyl, fluorophenyl, or methylphenyl and in which terminal position of the acetylene is unsubstituted represent the most desirable compounds with respect to antitumor and toxicological properties.

Experimental Section

All melting points were determined using a Mel-Temp melting point apparatus and are uncorrected. The ir and nmr spectra determined on all compounds were as expected. Analytical results obtained for C, H, and N were within ±0.4% of the theoretical values.

Pharmacological Methods for Intrathecal Studies.—Polyethylene glycol 200 (PEG 200) was used as a vehicle because of the aqueous insolubility of the carbamates. It was known that 0.2 ml/kg of PEG 200 injected into the cerebrospinal fluid caused only transient motor incoordination. Solutions were prepared by dissolving the carbamates (**29**, **31**, **48**, **49**, **50**) in warm (55°) PEG 200 in concentrations varying from 12.5 to 50.0 mg/ml.

In some experiments the dogs were unanesthetized; in others, administration of the carbamates was performed under intravenous methohexital sodium (12.5 mg/kg) anesthesia. The carbamate solutions were routinely administered in 0.1-ml/kg volumes. The dogs were loosely confined in pens and were watched for the development of any neurological deficit. The onset, duration, and intensity of effects were recorded. Dogs considered normal 2 weeks after treatment were returned to stock.

General Synthetic Procedure.—All of the compounds were made by the following general procedure and are listed in Tables I and II.

A solution of 0.1 mole of the 2-propyn-1-ol and 0.12 mole of the cycloalkyl isocyanate in 50 ml of CH_2Cl_2 to which one drop of H_2O, one drop of EtOH, and 0.01 mole of K_2CO_3 had been added was heated at reflux temperature for 2–20 hr (if MeCN was used as solvent, heating was for 0.5–1.0 hr). After cooling, the reaction mixture was diluted with more CH_2Cl_2 and washed (H_2O). After drying ($MgSO_4$), the solvent was removed at reduced pressure, and the residue was crystallized from C_5H_{12}–petroleum ether (bp 35–60°). Recrystallization using the same type of solvent was performed when necessary.

Acknowledgment.—The microanalyses were performed by Messrs. George Maciak, Raymond Cain, Buddy Cantrell, David Cline, and Robert Meister. Appreciation is given to Mrs. Virginia Bothwell and Messrs. James Mattingly, Edward Priller, and Paul Craig for assistance in testing these compounds in the animal tumor screen. Many of the intermediate compounds were prepared by Mr. Lawrence White. We are most grateful to Mr. Donald Pavey for his technical assistance in preparing these compounds.

Anticonvulsant Semicarbazides

WILLIAM E. COYNE AND JOHN W. CUSIC

Division of Chemical Research, G. D. Searle & Co., Chicago, Illinois 60680

Received June 10, 1968

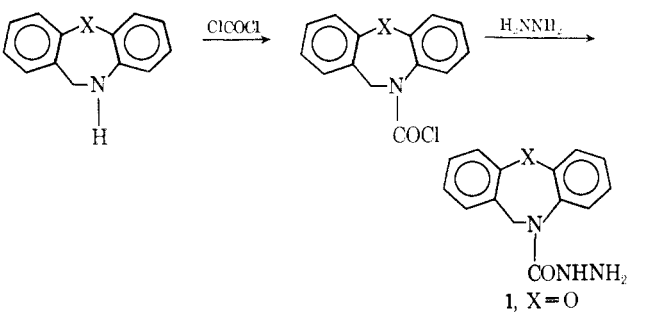
A series of semicarbazides was synthesized from various tricyclic amines and the structure–activity relationships of their anticonvulsant activity was investigated.

During the course of our investigation of carbamoyl derivatives of tricyclic amines, we prepared 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carboxylic acid hydrazide (**1**) and found it to have potent anticonvulsant and analgetic properties. The scope of this activity was examined by preparing a series of similar hydrazides in which substitution on the nitrogen functions and aryl groups was investigated as well as compounds in which the oxygen bridge was replaced by S, NCH_3, CH_2CH_2, CH=CH, and a single bond.

The desired semicarbazides were synthesized from the tricyclic amines *via* the carbamoyl chlorides as seen in Scheme I. Most of the tricyclic amines employed and the carbamoyl chlorides of these amines have been described by us previously.[1] Treatment of the carbamoyl chlorides with hydrazine or substituted hydrazines gave the expected products in good yield. Acylation of the semicarbazides obtained above gave the terminal acyl derivatives as confirmed by spectral comparison with standard compounds. The unsubstituted semicarbazides condensed readily with aldehydes but were inert to ketones such as acetone, acetophenone, and cyclohexanone.

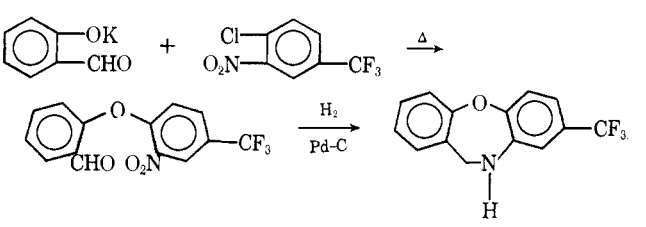
Two new tricyclic amines were prepared for structure–activity studies. 8-Trifluoromethyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine was obtained in a two-step synthesis shown in Scheme II. Condensation of 2-nitro-4-trifluoromethylchlorobenzene with potassium salicylaldehyde gave O-(2-nitro-4-trifluoromethylphenyl)salicylaldehyde which was subsequently hydrogenated with Pd–C to give an excellent yield of the desired amine.

SCHEME I



1, X = O

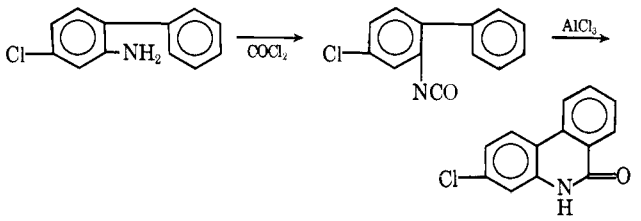
SCHEME II



(1) W. E. Coyne and J. W. Cusic, *J. Med. Chem.*, **10**, 541 (1967).

The synthesis of 2-chloro-5,6-dihydrophenanthridine was accomplished as seen in Scheme III. The isocyanate of 2-amino-4-chlorobiphenyl[2] was treated with $AlCl_3$[3,4] to give 3-chlorophenanthridone. Reduction of this lactam with $LiAlH_4$ gave the desired amine. A similar sequence starting with 2-aminodiphenyl sulfide gave an excellent yield of 10,11-dihydrodibenz[*b*,*f*][1,4]thiazepine.[4]

SCHEME III



Biological Activity.—Anticonvulsant potencies (ED_{50}) were determined for two types of convulsant challenge: one electrical and one chemical. The methods employed were essentially the same as those reported by Swinyard, *et al.*,[5] for the maximal electroshock seizure test (MES test, 50 mA ac, 0.2 sec, corneal electrodes) and the subcutaneous pentylenetetrazole test (sc Met test, 85 mg/kg). The end point employed in the MES test was abolition specifically of the hind leg tonic-extensor component of the maximal seizure, while in the sc Met test, inhibition of all seizure components was required. Acute neurotoxicity (ND_{50}) was measured by the method of Dunham and Miya,[6] and was based on a subject's inability to remain for 1 min on a slowly rotating rod. ED_{50} values for anticonvulsant and ND_{50} values for neurotoxicity measures were calculated according to the method of Litchfield and Wilcoxon.[7]

The results of the anticonvulsant testing for the more interesting compounds is seen in Table I. None of the compounds was active against pentylenetetrazole-induced convulsions. Compounds **18** and **19** which are known anticonvulsants[8] were included for comparison.

In general, the oxygen-bridged compounds were the most interesting with some activity residing in compounds where the oxygen bridge was replaced by a methylene or a single bond. Addition of a chlorine atom *meta* to the amino group in **1** increased the anticonvulsant potency but also the neurotoxicity (**2**). Only minor substitution of the hydrazine moiety retained activity, the most interesting substituents being methyl (**7** and **10**) and acetyl (**5** and **8**). These derivatives retained their anticonvulsant activity but were less neurotoxic. Compounds with peak time less than 1 hr have too short a duration of activity to be promising. The best compound is probably **8** which has peak time at 2.5 hr with a 10:1 neurotoxic:anticonvulsant ratio.

The analgetic potency, as determined by the hydrochloric acid induced writhing in the mouse[9] was measured for these compounds. Compound **1** had an ED_{50} of 26 mg/kg, equal to its anticonvulsant potency. However, the other derivatives were only weakly active in this test.

To compare the activity of this series with the known anticonvulsants (**18**, **19**),[8] two ureas were synthesized (**20**, **21**). There was no observable anticonvulsant activity for these derivatives indicating the hydrazides are the important compounds in this series.

Experimental Section

8-Trifluoromethyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carbonyl Chloride.—To a stirred solution of 13 g of phosgene in 50 ml of toluene at 5° was added 150 ml of anhydrous ether followed by a dropwise addition of a solution of 18.9 g (0.0714 mole) of 8-trifluoromethyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine and 7.2 g (0.0714 mole) of triethylamine in 200 ml of ether. After addition, the suspension was stirred for 2 hr at 5° and filtered, and the filtrate was evaporated. The residue obtained was dissolved in 200 ml of hot petroleum ether (bp 60–90°), filtered, and cooled to yield 19.25 g of light yellow crystals, mp 102–105°. *Anal.* ($C_{15}H_9ClF_3NO_2$) C, H, N.

In a similar manner, 10,11-dihydrodibenz[*b*,*f*][1,4]thiazepine was converted to **10,11-dihydrodibenz[*b*,*f*][1,4]thiazepin-10-carbonyl chloride,** mp 111–114°. *Anal.* ($C_{14}H_{10}ClN_2O$) C, H, N.

Similarly, 3-chloro-5,6-dihydrophenanthridine was converted to **3-chloro-5,6-dihydrophenanthridine-5-carbonyl chloride,** mp 137–139°. *Anal.* ($C_{14}H_9Cl_2NO$) C, H, N.

3-Chloro-5,6-dihydrophenanthridone.—To a stirred solution of 39.0 g of 2-amino-4-chlorobiphenyl in 300 ml of toluene at 0° was added dropwise a solution of 36 g of $COCl_2$ in 75 ml of toluene. After the addition the solution was a cloudy red color. The solution was warmed slowly to reflux while a slow stream of $COCl_2$ was passed through, followed by a reflux period of 15 min. The solvent was distilled leaving an amber oil identified by ir as 4-chlorobiphenyl 2-isocyanate. The isocyanate in 100 ml of *o*-dichlorobenzene was added to a stirred suspension of 25.0 g of $AlCl_3$ in 200 ml of *o*-$Cl_2C_6H_4$ at 90–100°. The resulting mixture was heated at 120° for 1 hr, cooled, and decomposed by the addition of ice. Excess *o*-$Cl_2C_6H_4$ was removed by steam distillation. The aqueous suspension was filtered and the residue was triturated with hot acetone and filtered to give 38.0 g of white crystals, mp 292°. *Anal.* Calcd for $C_{13}H_8ClNO$: C, 67.98; H, 3.51; N, 6.10. Found: C, 67.50; H, 3.86; N, 5.56.

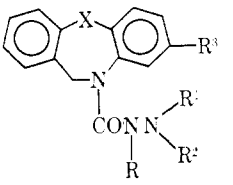
3-Chloro-5,6-dihydrophenanthridine.—To a stirred suspension under N_2 of 20 g of $LiAlH_4$ in 500 ml of dioxane at 95° was added a suspension of 38 g of 3-chlorophenanthridine in 750 ml of dioxane. After refluxing for 18 hr the mixture was decomposed by careful successive addition of 20 ml of H_2O, 20 ml of 15% aqueous NaOH solution, and 60 ml of H_2O. The suspension was filtered and the solvent was removed leaving a yellow solid. After two recrystallizations from EtOH, 13.1 g of yellowish white crystals were obtained, mp 120–122°. *Anal.* ($C_{13}H_{10}ClN$) C, H, N, Cl.

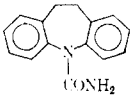
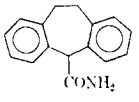
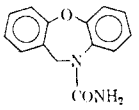
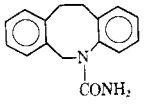
O-(2-Nitro-4-trifluoromethylphenyl)salicylaldehyde.—To 200 g of 4-chloro-3-nitrobenzotrifluoride at 160° was added 160 g of potassium phthalaldehyde, with stirring, over a period of 0.5 hr. After addition an exothermic reaction occurred and the temperature rose to 195° to give an amber liquid. The mixture was heated at 150° for 1 hr, cooled, ice and H_2O were added, and the suspension was extracted (Et_2O). The ether extract (1.5 l.) was dried, charcoaled, and filtered. On evaporation an oil was obtained which crystallized from benzene–petroleum ether (bp 30–60°). Recrystallization from the same solvent mixture gave 122.1 g of yellowish white crystals, mp 79–81°. *Anal.* ($C_{14}H_8F_3NO_4$) C, H, N.

8-Trifluoromethyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine.—A solution of 55.0 g of O-(2-nitro-4-trifluoromethylphenyl)salicylaldehyde was hydrogenated at 0.703 kg/cm² using 15 g of Raney nickel catalyst. Filtration and evaporation of the EtOH gave an oil which crystallized on standing. Recrystallization from petroleum ether (bp 30–60°) gave 40.65 g of yellowish white crystals, mp 86–88°. *Anal.* ($C_{14}H_{10}F_3NO$) C, H, N, F.

(2) K. Hoegerle and D. L'Ecuyer, *Can. J. Chem.*, **37**, 2068 (1959).
(3) J. M. Butler, *J. Am. Chem. Soc.*, **71**, 2578 (1949).
(4) J. Schmutz, F. Kunzle, F. Hunziker, and A. Burki, *Helv. Chim. Acta*, **48**, 336 (1965).
(5) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).
(6) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1957).
(7) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
(8) M. A. Davis, S. O. Winthrop, R. A. Thomas, F. Herr, M. Cllarest, and R. Gaudry, *J. Med. Chem.*, **7**, 88 (1964).
(9) E. T. Eckhardt, F. Cheplovitz, M. Lipo, and W. M. Govier, *Proc. Soc. Exptl. Biol. Med.*, **98**, 186 (1958).

TABLE I



Compd	X	R	R′	R²	R³	Salt	Mp, °C	Solvent	Formula[b]	mg/kg (duration of effect, hr) MES	mg/kg (duration of effect, hr) ND
1	O	H	H	H	H		170–173	EtOH	$C_{17}H_{13}N_3O_2$	24 (1)	74 (1)
2	O	H	H	H	Cl		179–181	EtOH	$C_{14}H_{12}ClN_3O_2$	14.8 (1)	58 (1)
3	O	H			H		167–169	EtOH	$C_{19}H_{22}N_4O_2$	>50	
4	O	H	H	C_6H_5	H		145–146	EtOH	$C_{20}H_{17}N_3O_2$		
5	O	H	H	$COCH_3$	H		164–166	EtOH	$C_{16}H_{15}N_3O_3$	27 (1)	140 (1)
6	O	H			H		174–176	EtOH	$C_{19}H_{21}N_3O_2$		
7	O	H	CH_3	CH_3	Cl	$C_2H_2O_4$	162–166	EtOH	$C_{18}H_{18}ClN_3O_6$	29 (1)	150 (1)
8	O	H	H	$COCH_3$	Cl		193–195	EtOH	$C_{16}H_{14}ClN_3O_3$	42 (2.5)	400 (2.5)
9	O	H	H	H	CF_3		111–113	C_6H_6–SSB	$C_{15}H_{12}F_3N_3O_2$		
10	O	CH_3	H	CH_3	Cl	$C_2H_2O_4$	140–142	EtOH	$C_{18}H_{18}ClN_3O_6$	50	...
11	CH_2	H	H	H	H		171–178	EtOH	$C_{15}H_{15}N_3O$	27 (1)	86 (1)
12	—[a]	H	H	H	H	HCl	183–186	EtOH	$C_{14}H_{14}ClN_3O$	15 (1)	~100 (1)
13	—[a]	H	H	H	Cl		133–136	EtOH	$C_{14}H_{12}ClN_3O$	34 (0.5)	400 (0.5)
14	NCH_3	H	H	H	H		171–175	EtOH	$C_{15}H_{16}N_4O$		
15	CH=CH	H	H	H	H		167–180	EtOH	$C_{16}H_{15}N_3O$		
16	CH_2CH_2	H	H	H	H		183–184	EtOH	$C_{16}H_{17}N_3O$		
17	S	H	H	H	H		142–143	EtOH	$C_{14}H_{13}N_3OS$		
18										20 ± 1.3	176 ± 22
19										33 ± 3.5	400 ± 44
20							165–167	EtOH	$C_{11}H_{12}N_2O_2$	>50	
21							231–232	EtOH	$C_{16}H_{16}N_2O$	>50	
Dilantin										9 (2.5)	86 (2.5)

[a] Denotes single bond between two rings. [b] All compounds were analyzed for C, H, and N.

Preparation of Hydrazides from the Carbamoyl Chlorides.—To a stirred solution of 0.066 mole of 100% hydrazine hydrate in 25 ml of EtOH at 10° was added dropwise a solution of 0.022 mole of the carbamoyl chloride in 150 ml of a 1:1 Et_2O–CH_2Cl_2 mixture. After addition the mixture was allowed to come to room temperature and stirred for 18 hr. The solvents were removed *in vacuo*, the residue was triturated with H_2O, and the solid was filtered. Recrystallization from the appropriate solvent gave the desired semicarbazide (Table I).

1-(10,11-Dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carbonyl)-2-acetylhydrazine (5).—To a stirred solution of 7.5 g of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carboxylic acid hydrazide in 60 ml of pyridine at 5° was added dropwise 15 ml of Ac_2O. After addition the solution was allowed to come to room temperature and stirred for 18 hr. The solvents were removed *in vacuo* and the residue was triturated with H_2O and then Et_2O to give a white solid. Recrystallization from EtOH gave 0.9 g of white crystals, mp 158–160°.

1-(8-Chloro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carbonyl)-2-acetylhydrazine (8).—To a stirred suspension of 5.72 g (0.02 mole) of 8-chloro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carboxylic acid hydrazide in 250 ml of benzene at 25° was added 2.5 g of triethylamine followed by 1.57 g (0.02 mole) of AcCl dropwise. After addition, the reaction was stirred for 1 hr at 25° and then 1 hr at reflux. The mixture was cooled and poured into H_2O to yield white crystals. Recrystallization from EtOH gave 4.3 g of white crystals, mp 193–195°.

10,11-Dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carboxamide (20).—A solution of 3.5 g of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-10-carbonyl chloride in 100 ml of 30% aqueous NH_3 with enough EtOH to solubilize the compound was stirred at 25° for 2 hr. The solid obtained on cooling was filtered and recrystallized from EtOH to give 2.5 g of white crystals, mp 165–167°.

In a similar manner, 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocin-11-carbonyl chloride was converted to **5,6,11,12-tetrahydrodibenz[*b*,*f*]azocin-11-carboxamide (21)**, mp 231–232°.

Acknowledgments.—The authors are indebted to the following persons for their contributions to this work: Dr. C. R. Craig, Mr. J. Westney, and Mr. D. L. Knapp for biological testing of these compounds, Dr. R. T. Dillon and his staff for microanalytical results, and Mr. W. M. Selby and Mr. J. D. Choi for hydrogenations.