Acknowledgment.—Thanks are due to Dr. M. L. Dhar for his interest in the work and to our colleagues in the Microanalysis Section and Pharmacology Division for the microanalyses and pharmacological evaluations, respectively.

3a,4,5,6-Tetrahydrosuccinimido[3,4-*b*]-acenaphthen-10-one. A Potent Anticonvulsant[1a]

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Since 2-carboxamide-2a-cyano-2a,3,4,5-tetrahydroacenaphthen-1-one (**2**)[2] is a rigid molecule containing a quaternary carbon atom at a bridgehead, a study of its reactions in acid media was undertaken, in the hope of preparing compounds of high biological activity. The preparation and properties of two of these hydrolysis products and compounds derived from them have been discussed in a previous paper.[3] This work describes the synthesis of 3a,4,5,6-tetrahydrosuccinimido[3,4-*b*]acenaphthen-10-one (**4**), a potent anticonvulsant of low toxicity.

The synthesis of **4** from α-tetralone was achieved in an over-all yield of 50–60%. α-Tetrylidenemalononitrile is readily available by the condensation of α-tetralone with malononitrile,[4] and can be cyclized to 2-carboxamido-3,4-trimethyleno-1-indenone (**1**) by warming in concentrated sulfuric acid on a steam bath for a few minutes.[5] Compound **1** readily adds cyanide ion quantitatively in aqueous *t*-butyl alcohol to form **2**.[2] Treatment of **2** in concentrated sulfuric acid gave nearly pure 2,2a-dicarboxamido-2a,3,4,5-tetrahydroacenaphthen-1-one (**3**) in almost quantitative yield. Efforts to hydrate the hindered nitrile group of **2** under less vigorous conditions, using dilute sulfuric acid, or concentrated HCl or HBr were less successful.

Conversion of **3** into the desired product **4** was accomplished in high yield by heating an acidified diethylene glycol solution of **3** to 120–130° for 0.5 hr. It was apparently necessary to have acid present in order to convert **3** to **4**, since heating **3** in the dry state, or in ethylene glycol or dimethylformamide, failed to form more than traces of **4**. Addition of acid to either of these solvents catalyzed the formation of **4**, but the optimum yield was obtained in diethylene glycol. Since the conversions of **2** to **3** and **3** to **4** are both acid catalyzed, an effort was made to convert **2** directly into **4** under a variety of acidic conditions (see Table I). Although **4** could be obtained directly from **2** in yields of 60–70%, it is apparently advantageous to carry out the reaction in two steps, the first in concentrated aqueous acid, and the second at relatively high temperature in a nonaqueous system.

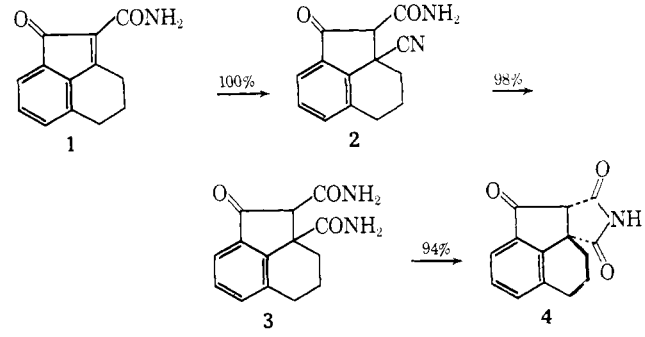
TABLE I

CONVERSION OF **2** TO **4** IN ACID SOLUTIONS

Method[a]	Temp	Time, hr	% yield	Mp, °C[b]
A	Reflux	0.5	82	212–220
B	Stir, rt	3		
	Reflux	0.5	94	170–178
C	Stir, rt	1		
	Reflux	0.5	73	187–204
D	Reflux	1	54	219–224
E	Steam bath	0.16	70	234–238
F	Stir, rt	3		
	Reflux	3	70	212–214

[a] A, 40 ml of H_2O, 40 ml of concentrated H_2SO_4, 40 ml of AcOH; B, 100 ml of 50% H_2SO_4; C, 40 ml of concentrated H_2SO_4 for 1 hr, then diluted with 40 ml of H_2O and reflux; D, 50 ml of concentrated HCl; E, 10 ml of concentrated H_2SO_4 for 10 min on steam bath, poured into 80 ml of 50% AcOH, stirred, and cooled; F, 140 ml of 48% HBr. [b] Melting point of crude product.

It seems probable that addition of cyanide to **1** proceeds in a *trans* manner, producing **2** predominantly as a *cis* racemate. This is borne out by the high yield of



the imide **4**, which would be expected if the two amide functions of **3** are *cis*, but could not occur in a diamide of structure **3** having a *trans* diamide configuration. Tautomerism might also explain the high yield of imide, with the equilibrium shifted by cyclization. However, no evidence for the existence of diastereoisomers has been found in **2** or **3**. It should be noted that both **3** and **4**, as well as **2**, must occur as *dl* pairs, but these have not been resolved. Attempts to resolve **4** are now in progress.

Pharmacological Activity.[6]—The title compound (**4**) has been found to be a potent anticonvulsant of low toxicity. It has an ED_{50} of 35 mg/kg *po* against maximal electroshock (prevention of tonic hind-leg extension in the mouse[7]), and a maximal effective dose of 100 mg/kg *po* against pentamethylenetetrazole-induced convulsions (timed intravenous infusion of pentamethylenetetrazole in the mouse[8]). The LD_{50} was greater than 3000 mg/kg (mouse). This compound is, therefore, not quite as active as diphenylhydantoin in animals and possesses a duration of activity approximately one-third that of diphenylhydantoin, but may

(1) (a) Contribution No. 1515. 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. R., June 1964, and by R. F. W., June 1965. (b) Bristol Laboratories Predoctoral Fellow, 1962. (c) Bristol Laboratories Predoctoral Fellow, 1962–1965.

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

(3) E. Campaigne, W. L. Roelofs, and R. F. Weddleton, *J. Med. Chem.*, **9**, 779 (1966).

(4) D. T. Mowry, *J. Am. Chem. Soc.*, **67**, 1050 (1945).

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

(6) The pharmacological data are supplied through the courtesy of Dr. M. L. Pindell, of the Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y.

(7) A. E. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

(8) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exp. Biol. Med.*, **70**, 254 (1949).

have a favorable therapeutic ratio because of its relatively low toxicity.

Experimental Section[9]

2,2a-Dicarboxamido-2a,3,4,5-tetrahydroacenaphthen-1-one (3).—A quantity of 50.0 g (0.208 mole) of **2**, prepared as previously described,[2] was added in portions to 200 ml of concentrated H_2SO_4 with stirring while the temperature was maintained below 40° by intermittent cooling in an ice bath. After the addition was complete (about 15 min), the solution was stirred at room temperature until a homogeneous orange solution was obtained (about 1.5 hr), poured into 2 l. of ice water with stirring, and left to settle overnight, yielding 52.6 g (98%) of a white precipitate, mp 233–234° dec. A sample recrystallized (EtOH) melted at 239–240°; $\lambda_{max}^{C_2H_5OH}$ 255 mμ (ε 6560), 302 (3710). *Anal.* ($C_{14}H_{14}N_2O_3$) C, H, N.

3a,4,5,6-Tetrahydrosuccinimido[3,4-*b*]acenaphthen-10-one (4).—A slurry of 52.6 g (0.203 mole) of crude **3** in 450 ml of diethylene glycol was stirred with 10 ml of concentrated H_2SO_4. The stirred mixture was heated on a hot plate until a homogeneous orange solution was obtained (at 110°) and then at 120–130° for 30 min, poured into 5 l. of ice–water with stirring and left overnight to settle, yielding 46.0 g (94%) of a white powder, mp 245–257°. One recrystallization from 95% EtOH (about 1.5 l.) gave 32.5 g of colorless plates: mp 253–255°; $\lambda_{max}^{C_2H_5OH}$ 263 mμ (ε 9570), 298 (2220). *Anal.* ($C_{14}H_{11}O_3N$) C, H, N.

Several experiments were carried out in an attempt to convert the cyanide adduct **2** directly to **4**. In each of these experiments, 10 g of **2** was treated as shown in Table I, and the crude product was isolated by pouring the reaction mixture into 1.5 l. of ice water. Yields of crude product are reported in the table, but identification of **4** was by ir spectra and recrystallization from EtOH to mp 252–254°. As can be seen from Table I, method E gave the purest product in 70% yield, but this is still not as high as that obtained by carrying out the preparation of **4** from **2** in two steps.

(9) The uv spectra were determined in 95% EtOH, using a Cary Model 14 quartz spectrometer with hydrogen discharge tube and 1-cm cells, and ir spectra on a Perkin-Elmer Model 137 Infracord. Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated by symbols of the elements, analytical results for those elements were within 0.3% of the theoretical values. The ir spectra were as expected.

5,11-Dihydrodibenz[*b*,*e*][1,4]oxazepine-5-carboxamides. Compounds Potentially Useful in the Treatment of Epilepsy and Trigeminal Neuralgia

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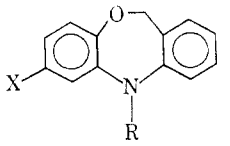
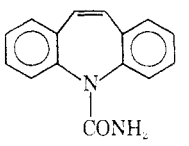
We have observed that the 5,11-dihydrodibenz[*b*,*e*]-[1,4]oxazepine heterocycle (**1**) is unusually sensitive to phosgene;[1] a colorless solution of **1** in toluene containing pyridine darkens immediately, even at −10°, upon the addition of only a few drops of that reactant as a dilute solution in toluene, and turns black long before 1 molar equiv has been added. Work-up of the reaction mixture gives a black tar containing the 5-carbamoyl chloride (**2**) since reaction with ethanolic ammonia at 100° followed by column chromatography gives the 5-carboxamides **3a** and **3b**.



1, X = H, Cl; R = H
2, X = H, Cl; R = COCl
3a, X = Cl; R = $CONH_2$
3b, X = H; R = $CONH_2$



4

Pharmacology.—Compounds **3a**, **3b**, and carbamazepine (**4**) were administered orally as agar suspensions for a comparison of their activities in protecting mice against electroshock- and pentylenetetrazole-induced convulsions;[2] the respective values obtained were (PE_{50}) 14, 29, 19 and (PM_{50}) 105, 75, 88 mg/kg. The three compounds were also compared, *via* the intravenous route, for their ability to reduce the amplitude of either trigeminal or thalamic evoked potentials in the cat.[3] In these studies, **3b** was equipotent while **3a** was somewhat less potent than **4**; however, both **3a** and **3b** appeared to possess a longer duration of action, were less toxic, and demonstrated a more selective depressant effect on the trigeminal sensory system than did **4**.[4]

Experimental Section[5]

7-Chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine-5-carboxamide (3a).—To 8.20 g (0.036 mole) of 7-chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine, 80 ml of anhydrous toluene, and 2.8 g of anhydrous pyridine at −10° was added dropwise with stirring 47 ml of a 15% (w/v) solution of $COCl_2$ in anhydrous toluene. The colorless reaction mixture darkened and quickly became black; it was kept for 2 hr at −10° and overnight at room temperature, the black solution was decanted from a semisolid black sludge, the latter was washed with fresh anhydrous toluene, and the combined toluene solutions were washed (H_2O, saturated NaCl), dried, and concentrated to dryness on the rotary evaporator. The residue showed a strong band at 1735 cm^{-1} but could not be induced to crystallize. It was dissolved in 30 ml of absolute EtOH, 100 ml of 3.3 *N* absolute EtOH–NH_3 was added, and the mixture was heated in a sealed vessel for 18 hr at 100°. The cooled reaction solution was concentrated to dryness on the rotary evaporator to give a dark brown gum; this was extracted with 100 ml of warm C_6H_6, the filtered C_6H_6 solution was poured on a column of 100 g of activated alumina (Harshaw, 80–200 mesh, chromatographic grade) prepared in benzene, and the column was eluted with benzene. The first 200 ml of eluent yielded 1.30 g; the second 200 ml of eluent yielded 0.06 g (total recovery 17%) of starting heterocycle. Subsequent elution with 500 ml of *i*-PrOH followed by concentration gave 2.27 g (23% yield) of crude **3a**, mp 170–175°. Repeated recrystallization from

(1) H. L. Yale and F. A. Sowinski, *J. Med. Chem.*, **10**, 1022 (1967), have shown that sodium hydride in nonprotic solvents may induce dimerization and/or polymerization of **1**. Some of our unpublished studies have also demonstrated a surprising sensitivity of **1** toward sodamide in nonprotic solvents.

(2) For the pharmacology of **4**, see Investigational Brochure (G32883), Geigy Pharmaceuticals, 1965. Clinical trials with **4** as an antiepileptic have been reported; *cf.* F. Martin, M. Movarrekhi, and M. G. Gisiger, *Schweiz. Med. Wochschr.*, **95**, 982 (1965); J. Braunhofer, *Med. Klin.* (Munich), **60**, 343 (1965); and J. Sigwald, M. Bonduelle, C. R. Sallow, P. H. Raverdy, and A. Van Steenbrugge, *Presse. Méd.*, **72**, 2323 (1964).

(3) The test procedure is that of R. Hernandez-Peon, *Neuropsychopharmacology*, **3**, 303 (1962). The clinical use of **4** in trigeminal neuralgia has also been reported; *cf.* S. Passeri and M. Saginario, *Minerva Med.*, **56**, 4079 (1965); R. Becker and T. Balshusemann, *Deut. Med. Wochschr.*, **90**, 2014 (1965); and W. J. G. Burke, J. M. F. Grant, and G. Selby, *Med. J. Australia*, **1**, 494 (1965).

(4) The pharmacological comparison of **3a**, **3b**, and **4** were carried out by Drs. R. G. Babington, J. High, and Z. P. Horovitz of the Department of Pharmacology of The Squibb Institute for Medical Research. The results of their studies will be published elsewhere.

(5) Melting points were taken in capillary tubes in an electrically heated oil bath and are uncorrected. The microanalyses were performed by Mr. J. F. Alicino and his associates and the spectra were determined by Miss B. Keeler and Dr. A. Cohen, all of The Squibb Institute for Medical Research.