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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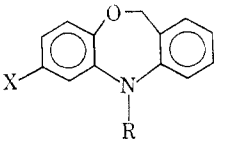
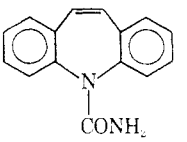
We have observed that the 5,11-dihydrodibenz[*b*,*e*]-[1,4]oxazepine heterocycle (**1**) is unusually sensitive to phosgene;[1] a colorless solution of **1** in toluene containing pyridine darkens immediately, even at −10°, upon the addition of only a few drops of that reactant as a dilute solution in 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.

C_6H_6 gave 1.60 g (16% yield) of **3a**: mp 191–193°; ν (mineral oil) 1675 cm^{-1} (CO); τ (DMSO-*d*) 4.69 (CH_2), 3.82 (NH_2). *Anal.* ($C_{14}H_{11}ClN_2O_2$) Cl, N.

5,11-Dihydrodibenz[*b*,*e*][1,4]oxazepine-5-carboxamide (3b).—The experimental conditions described above were employed with 8.20 g (0.042 mole) of the heterocycle; the intermediate crude carbamoyl chloride could not be induced to crystallize and as a black tar was treated with absolute ethanolic ammonia for 18 hr at 100°. Chromatography on 100 g of activated alumina gave 2.50 g (30% recovery) of unreacted heterocycle and 4.10 g (37% yield) of crude **3b**, mp 195–196°. Recrystallization from C_6H_6 gave 2.75 g (25% yield) of **3b**: mp 201–203°; ν (mineral oil) 1655 cm^{-1} (CO); τ (DMSO-*d*) 4.70 (CH_2), 3.95 (NH_2). *Anal.* ($C_{14}H_{12}N_2O_2$) C, H, N.

Inhibition of Monoamine Oxidase by N-(Phenoxyethyl)cyclopropylamines. Correlation of Inhibition with Hammett Constants and Partition Coefficients

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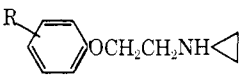
We have investigated the relation of physicochemical properties of a series of N-(phenoxyethyl)cyclopropylamines to their inhibition of the enzyme, monoamine oxidase [E.C. 1.4.3.4 Monoamine:O_2 oxidoreductase (deminating)]. This approach was based upon the success of Hansch and his co-workers[1] in applying substituent constants to correlate structure and activity of a variety of biologically active compounds. They used the Hammett σ, an electronic parameter, and π, a constant derived from the partition coefficient, to correlate with biological activity.

Experimental Section

Compounds of structure



were synthesized as hydrochloride or hydrobromide salts, and their identities were verified by physical methods.[2] Table I shows the R substituent for all compounds included in this study.

Enzyme Inhibition.—Monoamine oxidase inhibition was determined by a method previously described,[3] measuring enzyme activity spectrophotometrically with kynuramine as substrate.[4] Inhibition by four to ten different concentrations of each inhibitor was determined. The inhibitor was, in each case, allowed to react with the enzyme for 30 min prior to the initiation of enzyme action by substrate addition. The results were plotted as percent inhibition *vs.* the negative logarithm of the inhibitor concentration. From the plot, the pI_{50} value (negative logarithm of the inhibitor concentration producing 50% inhibition) was determined. The source of enzyme was mitochondria prepared from rat or human liver by the method of Hogeboom.[5]

(1) (a) C. Hansch, P. P. Maloney, T. Fujita, and R. M. Muir, *Nature*, **194**, 178 (1962); (b) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963); (c) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964); (d) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965); (e) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

(2) J. Mills, R. W. Kattau, I. H. Slater, and R. W. Fuller, *J. Med. Chem.*, **11**, 95 (1968).

(3) R. W. Fuller and C. P. Walters, *Biochem. Pharmacol.*, **14**, 159 (1965).

(4) H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop, and S. Udenfriend, *J. Biol. Chem.*, **235**, 1160 (1960).

(5) G. H. Hogeboom, *Methods Enzymol.*, **1**, 16 (1955).

TABLE I

SUBSTITUENT CONSTANTS

R	$\Sigma\gamma$	$\Sigma\sigma$	$\Sigma\pi$
4-Br	0	0.232	1.02
3,4-Cl_2	−1.0	0.600	1.46
3-NO_2	−1.3	0.710	0.11
4-Me	0	−0.170	0.52
3,5-Cl_2	−2.0	0.746	1.52
3-CF_3	−1.3	0.415	1.07
3-Cl-4-Me	−1.0	0.203	1.28
3-Br	−1.3	0.391	0.94
3-Me-4-Cl	−1.0	0.158	1.21
3-Cl	−1.3	0.373	0.76
4-MeO	0	−0.268	−0.04
3,4-Me_2	−1.0	−0.239	1.03
3,5-Me_2	−2.0	−0.138	1.02
3-Me	−1.3	−0.069	0.51
3,5-Me_2-4-Cl	−2.0	−0.138	1.02
3,4,5-Me_3	−2.0	−0.308	1.54
4-N=NC_6H_5	0	0.640	1.71
4-NH_2	0	−0.660	−1.63

Calculations.—When a correlation of inhibition with σ and π was attempted, it was noted that the *meta* positioning of a substituent had a deleterious effect on the inhibitory activity of the compound. For this reason, an arbitrary parameter, γ, was introduced to account for this assumed steric influence of *meta* substituents. In general, the decrease in inhibitor efficiency produced by a single *meta* substituent on the parent molecule [N-(phenoxyethyl)cyclopropylamine] was about twentyfold, aside from its electronic and partition contributions. With other substituents present, however, this effect was less pronounced; the decrease per substituent in this case was about tenfold. These sterically attributed alterations represent changes in effective concentration of the inhibitor and can be presumed to be logarithmically related to the 50% inhibition level as indicated in the correlation equation. On this basis, γ-substituent constants were assigned as follows: 0 for a *para* substituent, −1.3 for a lone *meta* substituent, and −1.0 for a *meta* substituent in the presence of other substituents. Table I lists substituent constants for all of the compounds reported in this study.

Results and Discussion

Table II shows the inhibition of the rat liver enzyme by 16 *meta*- and *para*-substituted compounds in the

TABLE II

INHIBITION OF RAT LIVER MITOCHONDRIAL MAO

R	pI_{50} Calcd	pI_{50} Obsd
4-Br	6.50	6.64
3,4-Cl_2	6.30	6.30
3-NO_2	5.93	5.76
4-Me	5.77	5.69
3,5-Cl_2	5.67	5.68
3-CF_3	5.67	4.98
3-Cl-4-Me	5.65	5.75
3-Br	5.61	5.64
3-Me-4-Cl	5.56	6.06
3-Cl	5.54	5.82
4-MeO	5.51	5.46
3,4-Me_2	4.91	4.71
3,5-Me_2	4.81	4.85
3-Me	4.81	4.78
3,5-Me_2-4-Cl	4.70	4.70
3,4,5-Me_3	4.04	3.54
Predictions		
4-N=NC_6H_5	7.28	7.56
4-NH_2	4.57	4.40