Drugs Acting on the Central Nervous System. Syntheses of Substituted Quinazolones and Quinazolines and Triazepino- and Triazocinoquinazolones¹

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In earlier communications,^{2,3} it has been reported that a variety of 3-substituted 4-quinazolones and quinazolo-4-thiones with or without substituents in the 2 position exhibit CNS-depressant activity. In continuation of our program for obtaining a better CNS depressant, we considered it of interest to investigate a series of 2,3-disubstituted 4-quinazolones (I), 2,4disubstituted quinazolines (II), triazepinoquinazolones (III), and triazocinoquinazolones (IV). This communication deals with the syntheses and pharmacological results of such compounds.



2-Mercapto-4-quinazolone⁴ on treatment with EtI in the presence of NaOEt, yielded 2-ethylthio-4quinazolone (4). Its ir spectrum did not show the characteristic $\nu_{\rm SH}$ vibration at 2610 cm⁻¹ but peaks at 3200 (NH) and 1680 cm⁻¹ (>C==O). The selective ethylation of the mercapto group was established by desulfurization of 2-ethvlthio-4-quinazolone with Raney nickel to give 4-quinazolone. Reaction of heterocyclic or aliphatic secondary amines with 2-ethylthio-4quinazolone gave the corresponding 2-substituted 4quinazolones (13-16). Treatment of 2-ethylthio-4quinazolone with dibenzylamine and N-phenylpiperazine (39, 40), under similar conditions, gave the corresponding 2,4-disubstituted products instead of the expected 2-substituted compounds and the identity of the disubstituted compounds was established by mixture melting points with authentic samples, obtained by treating 2,4-dichloroquinazoline with the appropriate amines. No satisfactory explanation can, however, be given for such abnormal behavior.

2-Hydrazino-3-amino-4-quinazolone (11) was prepared by refluxing 2-ethylthio-3-phenyl-4-quinazolone or 2-ethylthio-4-quinazolone with 100% hydrazine hydrate. The ir spectrum of 2-hydrazino-3-amino-4quinazolone showed peaks at 3300, 3450 (NH₂), 1680 cm⁻¹ (>C==O), and a slightly broad peak at 1630 cm⁻¹ (NH₂ and >C==N). Substituted hydrazines, *e.g.*, phenylhydrazine, N-aminohomopiperidine, reacted with 2-ethylthio-4-quinazolone to give 2-phenylhydrazino-3-anilino- (12) and 2-(N-homopiperidylamino)-3-homopiperidyl-4-quinazolones (23), respectively. However, the reaction with N-aminopiperidine yielded 2-(N-piperidylamino)-4-quinazolone (22) instead of the expected 2-(N-piperidylamino)-3-piperidyl-4-quinazolone.

 α , β -Diketones reacted with 2-hydrazino-3-amino-4quinazolone (11) to yield seven- and eight-membered heterocyclic compounds (45–49), respectively. The formation of a seven-membered cyclic system was established by the acid hydrolysis to give back the starting amine and the α -diketone. If spectra of these cyclic compounds did not reveal the presence of $-NH_2$ groups (absence of peaks at 3300, 3450 cm⁻¹) but showed peaks at 3275 (NH vibration), 1690 (>C==O vibration), 1630 cm⁻¹ (conjugated >C==N).

2-Methyl-3-(p-acetylphenyl)-4-quinazolone thiosemicarbazone was cyclized to a 5-carboxymethylthiazolidine derivative by treating with maleic anhydride.⁵ 2-Methyl-3-(p-acetylphenyl)-4-quinazolone² with piperidine and formaldehyde gave the corresponding Mannich base (18).

The reaction of 2,4-dichloroquinazoline⁶ with *p*-aminoacetophenone in the presence of K_2CO_3 gave 2chloro-4-(*p*-acetylanilino)quinazoline (41). Reduction with NaBH₄ yielded the corresponding hydroxy compound (42), which was not resolved. 4-Chloroquinazoline⁷ on fusion with *p*-aminoacetophenone gave 4-(*p*acetylanilino)quinazoline (43) which on reduction with NaBH₄ yielded the corresponding hydroxy compound (44).

Reaction of 3-amino-4-quinazolone with phenylglyoxal and of 2-hydrazino-3-amino-4-quinazolone with 5-nitrofurfural furnished the corresponding Schiff bases (21, 19).

2-Methyl-4-quinazolone and 2-methyl-3-phenyl-4quinazolone on treatment with NBS yielded 2-bromomethyl-4-quinazolone (24) and 2-bromomethyl-3phenyl-4-quinazolone (31), respectively. These, on reduction with Raney nickel, gave 2-methyl-4-quinazolone and 2-methyl-3-phenyl-4-quinazolone while the reaction with alkyl-, arylalkyl-, and heterocyclic amines furnished the corresponding 2-aminomethyl derivatives (25-29, 32-36).

Pharmacology. – Pharmacological screening of these compounds included gross observations, acute toxicity, and anticonvulsant activity (MES)^{*} in mice. The test compounds were administered intraperitoneally. Compounds **4** (LD₅₀ = 1000 mg/kg) showed 60% protection against maximal electroshock (MES) at 250 mg/kg while **39** (LD₅₀ = 400 mg/kg) showed 50% protection (MES) at 100 mg/kg. Compound **15** (LD₅₀ = 100 mg/kg) caused convulsions at 50 mg/kg; **12** and **14** exhibited CNS depressant and stimulant action at their LD₅₀ dose (400, 100 mg/kg), respectively. The remaining compounds were inactive.

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Notes

TABLE I

2,3-DISUBSTITUTED 4-QUINAZOLONES (I)

| No. Fig. H1 To Topmus Analyse 1 SH p -BrC ₄ H, 25% S0 C ₄ H,N ₀ As C, H, N 2 SH p -C ₄ H ₀ O ₆ H, 231% S0 C ₄ H,N ₀ As C, H, N 3 SH 24-Fr ₅ C ₄ H, 232% S5 C ₄ H,N ₀ As C, H, N 4 SC ₄ H, p -B ₂ C ₄ H, 142-163% 72 C ₄ H _N N ₀ S C, H, N 5 SC ₄ H, p -C ₄ H ₀ O ₄ H, 1427-228 S5 C ₄ H _N N ₀ S C, H, N 7 SC ₄ H, p -C ₄ H ₀ O ₄ H, 137-228 S6 C ₄ H ₄ N ₀ O, C, H, N 8 NHNH, p -B ₁ C ₄ H, 138-99 G C ₄ H ₄ N ₀ O, C, H, N 10 NHNH, p -C ₄ H ₁ O ₄ C ₄ H, 137* G C ₄ H ₄ N ₀ O, C, H, N 11 NHHG ₄ H, NH ₄ 109-2204 98 C ₄ H ₄ N ₀ O, C, H, N 12 NHHG ₄ H, NH ₄ 210-2214 96 C ₄ H ₄ N | | P | P | Mp, | Yield, | | |
|--|-----------------|---|--|--------------------------------------|------------------|--|-----------|
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | NO. | Ri CII | | °U | % | Formula | Analyses |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 1 | SH | p-BrC ₆ H ₄ | 285^{a} | 80 | $C_{14}H_9N_2BrOS$ | C, H, N |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 2 | SH | p - $C_2H_5OC_6H_4$ | >310# | 80 | $C_{16}H_{14}N_2O_2S$ | С, Н, М |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 3 | SH | $2,4-F_2C_6H_3$ | 252^{a} | 80 | $C_{14}H_8N_2F_2OS$ | С, Н |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 4 | SC_2H_5 | Н | 162-163° | 72 | $C_{10}H_{10}N_2OS$ | C, H, N |
| 0 SC(Hs) $p \in C(H)C(H)$ 142^{o} 95 $C_{n}(H_{0})F_{N}(O)S)$ C, H, N, N 8 NIINH ₁ $p = C(H)OC(H)$ $131 - 132^{o}$ 85 $C_{n}(H_{0})F_{N}(O)S)$ C, H, N, N 9 NIINH ₁ $p = C(H)OC(H)$ 197^{o} 95 $C_{n}(H_{0})F_{N}(O)$ C, H, N 10 NINH ₁ $24 + F(C_{H_1}$ 188^{o} 90 $C_{n}(H_{0})F_{N}(O)$ C, H, N 11 NINH ₁ $24 + F(C_{H_1}$ 188^{o} 90 $C_{n}(H_{0})F_{N}(O)$ C, H, N 12 NHNHC ₁ L NIIC(II ₁ $222 - 223^{3+i}$ dec 50 $C_{n}(H_{0})F_{N}(O)$ C, H, N 13 N(CH_2(H=CH_1)); H $150 - 151^{o}$ 7 $C_{n}(H_{0})F_{N}(O)$ C, H, N 14 N-Methylpiperazino H $220 - 221^{o}$ 48 $C_{n}(H_{0})F_{N}(O)$ C, H, N 15 1-Homopiperidino H $220 - 221^{o}$ 48 $C_{n}(H_{0})F_{N}(O)$ C, H, N 16 6-Methylpiperazino H $200 - 268 - 269^{o}$ 68 $C_{n}H_{0}N_{0}(O)$ C, H, N 17 CH_s< | 5 | SC_2H_5 | p-BrC ₆ H ₄ | 145-146° | 90 | $C_{16}H_{13}BrN_2OS$ | C, H, N |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 6 | SC ₂ H ₅ | p-C ₂ H ₅ OC ₆ H ₄ | 1420 | 9a 9 a | $C_{18}H_{18}N_2O_2S$ | С, Н, А |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 7 | SC_2H_5 | $2.4 - F_2 C_6 H_3$ | 131-1322 | 85 | $C_{16}H_{12}F_2N_2OS$ | С, Н |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 8 | | p-BrC ₆ H ₄ | 227-228° | 93 | $C_{14}H_{11}BrN_4O$ | C, H, N |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 9 | | p-C ₂ H ₅ OC ₆ H ₄ | 197* | 95 | $C_{16}H_{16}N_4O_2$ | С, Н, М |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 10 | | $2,4-F_2C_6H_3$ | 1880 | 90 | $C_{14}H_{10}F_2N_4O$ | С, Н |
| 12 NHNHCalls 232-233** dec 50 C_allisNO2 C, H, N 13 NC(H_CH=CH_2) _k II 150-151* 7 C_HUNOC C, H, N 14 N-Methylpiperazino H 220-221' 59 C_BH ₀ N,O C, H, N 15 1-Homopiperidino H 209-210' 48 C ₁₄ H ₁ N ₀ O C, H, N 16 6-Methylpyridyl-2-amino H 209-210' 48 C ₁₄ H ₁ N ₀ O C, H, N 17 CH _s CH ₂ =NN=e ⁶ GECHCH,OH 244* 27 C ₂₈ H ₁₈ N ₀ O ₈ C, H, N 18 CH _s CH ₂ =O(CH ₀) _N + 188-189 ^{A,m} 36 C ₂₈ H ₂₈ CN ₃ O C, H, N 20 SC ₁ H ₃ HgCl 244* 19 C ₁₆ H ₂ CN ₂₀ O C, H, N 21 H N=CHCOC ₆ H ₈ 187-188 ^{A/1} 37 C ₁₄ H ₂ N ₂₀ O C, H, N 22 SC ₁ H ₃ HgCl 244* 19 C ₁₆ H ₆ CN ₁₀ OH N, H 23 N-Homopiperidinoamino H 247-248* 41 C ₁₆ H ₁₆ N ₁₀ O C, H, N 24 | 11 | | NH_2 | 219-220ª | 98 | $C_8H_9N_5O$ | С, Н, N |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | 12 | NHNHC ₆ H ₅ | $N \Pi C_6 \Pi_5$ | $232-233^{\circ,i}$ dec | 50 | $C_{20}H_{19}N_5O_2$ | С, Н, N |
| 14 N-Methylpiperazino H 220-221 59 $C_{a}H_{18}N_{0}O$ C, H, N 15 1-Homopiperidino H 209-210* 48 $C_{a}H_{18}N_{0}O$ C, H, N 16 6-Methylpyridyl-2-amino H 268-269* 68 $C_{14}H_{18}N_{0}O$ C, H, N 17 CH_{a} $C_{H,c}=NN=c_{H,c}^{2}$ 244* 27 $C_{22}H_{18}N_{5}O_{8}S$ C, H, N 18 CH_{a} $O_{-}OO(CH_{0}N_{1}^{2})$ 188-189 ^{h,m} 36 $C_{22}H_{45}CIN_{5}O$ C, H, N 19 $NHN=CH_{-}O_{-}^{0}$ NH_{a} 212-213* 98 $C_{10}H_{0}N_{0}O_{4}$ C, H, N 20 $SC_{4}H_{5}$ $HgCl$ 244* 19 $C_{0}H_{6}CIN_{7}OSHg$ N 21 H N=CH_{CO}C_{6}H_{4} 187-188 ^{1,1} 37 $C_{0}H_{0}N_{0}O_{5}$ C, H, N 22 N-Piperidinoamino H 247-248* 41 $C_{14}H_{18}N_{0}O_{5}$ C, H, N 23 N-Homopiperidinoamino 1-Homopiperidino 213-214* 40 $C_{28}H_{3}N_{0}O_{5}$ C, H, N 24 CH_{18}T | 13 | $N(CH_2CH=CH_2)_2$ | 11 | 150-151 | 7 | $C_{14}H_{15}N_{3}O$ | C, H, N |
| 15 1-Homopiperidino H 209-210* 48 $C_{4H_1R_3R_0}$ C, H, N 16 6-Methylpyridyl-2-amino H 268-269* 68 $C_{44H_1R_3R_0}$ C, H, N 17 CH ₄ $C_{4H_2} = NN = C_{4H_1}^{-1} C_{4H_4}^{-1} C_{4H_4}^{-1}$ 27 $C_{22H_{18}N_5Q_6S}^{-1}$ C, H, N 18 CH ₄ $D_{-CO(CH_4)_1} = A_{-CO}^{-1}$ 188-189^{h,m} 36 $C_{22H_{19}CIN_5O}^{-1}$ C, H, N 19 NHN=CH_O_ NH ₄ 212-213* 98 $C_{11}H_{19}N_6O_4$ C, H, N 20 SC ₄ H ₅ HgCl 244* 19 $C_{04}H_{01}N_5O_{7}$ C, H, N 21 H N=CHCOC_6H_4 187-188^{i,1} 37 $C_{04}H_{11}N_5O_{7}$ C, H, N 22 N-Piperiptidinoamino H 247-248* 41 $C_{04}H_{10}N_5O_{7}$ C, H, N 23 N-Piperiptidinoamino H 247-248* 41 $C_{04}H_{10}N_0O_{7}$ C, H, N 24 CH_3Br H 247-248* 41 $C_{04}H_{10}N_0O_{7}$ C, H, N 25 N-Piperipticazinomethyl H 247-248* <td>14</td> <td>N-Methylpiperazino</td> <td>H</td> <td>$220-221^{f}$</td> <td>59</td> <td>$C_{13}H_{16}N_4O$</td> <td>С, Н, N</td> | 14 | N-Methylpiperazino | H | $220-221^{f}$ | 59 | $C_{13}H_{16}N_4O$ | С, Н, N |
| 16 6-Methylpyridyl-2-amino H 268-269* 68 $C_{44}H_{2}N,O$ C, H, N 17 CH ₈ CH ₂ C=NN=C ⁺ CHCH ₄ CO,H 244* 27 $C_{22}H_{18}N_5O_4S$ C, H, N 18 CH ₃ CH ₂ C=NN=C ⁺ CHCH ₄ CO,H 244* 27 $C_{22}H_{18}N_5O_4S$ C, H, N 19 NHN=CH_O ⁻ O ⁻ N ⁰ t NH ₁ 212-213 ⁶ 98 $C_{10}H_{10}N_6O_4$ C, H, N 20 SC ₂ H ₅ HgCl 244* 19 $C_{10}H_6CIN_5OSHg$ N 21 H N=CHCOC ₆ H ₈ 187-188 ^{1,1} 37 $C_{4}H_{10}N_6O_4$ C, H, N 22 N-Piperidinoamino H 247-248 ⁸ 41 $C_{4}H_{10}N_{10}O_6$ C, H, N 24 CH ₃ br H 213-214 ^b 40 $C_{20}H_{20}N_5O_6$ C, H, N 25 N-Methylipperazinomethyl H 149-150 ⁵ 52 $C_{4}H_{10}N_{10}O_6$ C, H, N 26 N-Phenylipperazinomethyl H 126-128 ^a 67 $C_{10}H_{10}N_{10}O_6$ C, H, N 27 1-Pyrrolidinomethyl H 126-128 ^b 67 <td>15</td> <td>1-Homopiperidino</td> <td>Н</td> <td>$209-210^{e}$</td> <td>48</td> <td>$C_{14}H_{17}N_{3}O$</td> <td>С, Н, N</td> | 15 | 1-Homopiperidino | Н | $209-210^{e}$ | 48 | $C_{14}H_{17}N_{3}O$ | С, Н, N |
| 17 CH _a C _B L ₀ = NN = C ^A = CHCH,CO,H 244 ^a 27 C ₂₂ H ₁₅ N ₅ O ₅ S C, H, N 18 CH _a $\bigcirc - cO(CH_{bb})$ N $\leftarrow f$ 188-189 ^{k,m} 36 C ₂₂ H ₁₅ ClN ₅ O C, H, N 19 NHN=CH $_ O^{-} _ ^{NO_{4}}$ NH _a 212-213 ^b 98 C ₁₀ H ₁₀ N ₅ O ₄ C, H, N 20 SC ₂ H ₅ HgCl 244 ⁱ 19 C ₁₀ H ₂ ClN ₅ O ₅ H ₆ C, H, N 21 H N=CHCOC ₆ H ₅ 187-188 ^{j,l} 37 C ₁₆ H ₂ N ₅ O ₂ C, H, N 22 N-Piperidinoamino H 247-248 ^b 41 C ₁₀ H ₂ ClN ₅ O ₂ C, H, N 23 N-Homopiperidinoamino 1-Homopiperidino 213-214 ^b 40 C ₂₀ H ₂₇ N ₅ O C, H, N 24 CH ₃ Br H 192-193 ^b 71 C ₁₆ H ₂₇ N ₅ O C, H, N 25 N-Methylpiperazinomethyl H 192-193 ^b 71 C ₁₆ H ₂₇ N ₅ O C, H, N 26 N-Phenylpiperazinomethyl H 192-128 ^c 67 C ₁₄ H ₁₀ N ₅ O C, H, N 27 1-Pyrrolidinomethyl H 192-128 ^c | 16 | 6-Methylpyridyl-2-amino | H | 268-269° | 68 | $\mathrm{C}_{14}\mathrm{H}_{12}\mathrm{N}_4\mathrm{O}$ | С, Н, N |
| 18 CH ₃ C ₁₀ C(H ₃), C 188-189 ^{4,m} 36 C ₂₃ H ₂₆ ClN ₃ O C, H, N 19 NHN=CH_O_N ^{NQ4} NII ₄ 212-213 ⁵ 98 C ₁₃ H ₁₀ N ₆ O ₄ C, H, N 20 SC ₄ H ₅ HgCl 244 ⁴ 19 C ₁₀ H ₆ ClN ₂ OSHg N 21 H N=CHCOC ₆ H ₅ 187-188 ^{1,1} 37 C ₁₆ H ₁₀ N ₀ O ₃ C, H, N 21 H N=CHCOC ₆ H ₅ 187-188 ^{1,1} 37 C ₁₆ H ₁₀ N ₀ O ₃ C, H, N 23 N-Piperidinoamino H 247-248 ⁵ 41 C ₁₀ H ₁₀ N ₀ O C, H, N 24 CH ₂ Br H >300 ⁶ 55 C ₁₀ H ₂₀ N ₀ O C, H, N 25 N-Methylpiperazinomethyl H 149-150 ⁶ 52 C ₁₄ H ₃ N ₀ O C, H, N 26 N-Phenylpiperazinomethyl H 126-128 ⁴ 67 C ₁₀ H ₃ N ₃ O C, H, N 27 1-Pyrrolidinomethyl H 126-128 ⁴ 67 C ₁₀ H ₃ N ₃ O C, H, N 28 CH ₂ N(CH ₂ C ₆ H ₃) H 223-224 ^{3,n} 10 C ₁₅ H ₃₀ Br ₅ ClN ₂ O C, | 17 | CH_{3} | C ₈ H ₄ C=NN=C CH ₃ HN-CO | 2449 | 27 | $C_{22}H_{1\vartheta}N_5O_4S$ | С, Н, N |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | 18 | CH3 | | 188–189 ^{h, m} | 36 | $\mathrm{C}_{23}\mathrm{H}_{26}\mathrm{ClN}_{3}\mathrm{O}$ | С, Н, N |
| 20 SC_2H_5 $HgCl$ 244^i 19 $C_{10}H_9CIN_2OSHg$ N21HN=CHCOC_6H_5 $187-188^{j,l}$ 37 $C_{16}H_{18}N_6O_3$ C, H, N22N-PiperidinoaminoH $247-248^b$ 41 $C_{13}H_{16}N_6O$ C, H, N23N-Homopiperidinoamino1-Homopiperidino $213-214^b$ 40 $C_{29}H_{29}B_{15}O$ C, H, N24 CH_2Br H $>300^b$ 55 $C_{9}H_7Br_5O$ C, H, N25N-MethylpiperazinomethylH $149-150^c$ 52 $C_{14}H_{18}N_4O$ C, H, N26N-PhenylpiperazinomethylH $126-128^s$ 67 $C_{14}H_{16}N_4O$ C, H, N271-PyrrolidinomethylH $126-128^s$ 67 $C_{14}H_{16}N_4O$ C, H, N28CH_2N(CH_2C_6H_5)2H $185-186^j$ 99 $C_{23}H_{21}N_4O$ C, H, N29CH_2NHNHC_6H_5H $284-285^i$ 77 $C_{15}H_{16}N_4O$ C, H, N30CHBr2 p -BrC6H_4 $223-224^{b,n}$ 10 $C_{16}H_{16}Br_5ClN_2O$ C, H, N31CH_4BrC_6H_5 $146-147^i$ 60 $C_{19}H_{18}N_6O$ C, H, N33N-MethylpiperazinomethylC_6H_5 $137-138^e$ 51 $C_{23}H_{23}N_6O$ C, H, N34N-PhenylpiperazinomethylC_6H_5 $90-98^s$ 40 $C_{24}H_{21}N_6O$ C, H, N356-Methylpipridyl-2-aminomethylC_6H_5 $90-98^s$ 40 $C_{24}H_{21}N_6O$ C, H, N36CH_2NH_6CH_2,C_4h | 19 | NHN=CH | NH_2 | 212-213b | 98 | $C_{13}H_{10}N_6O_4$ | С, Н, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 20 | $\rm SC_2H_5$ | HgCl | 244^{i} | 19 | C ₁₀ H ₉ ClN ₂ OSHg | Ν |
| 22N-PiperidinoaminoH247-248 ^b 41 $C_{13}H_{16}N_{4}O$ C, H, N23N-Homopiperidinoamino1-Homopiperidino213-214 ^b 40 $C_{20}H_{20}N_5O$ C, H, N24 $CH_{4}Br$ H>300 ^b 55 $C_{9}H_{16}Br_{2}O$ C, H, N25N-MethylpiperazinomethylH149-150 ^s 52 $C_{14}H_{18}N_4O$ C, H, N26N-PhenylpiperazinomethylH192-193 ^b 71 $C_{19}H_{20}N_4O$ C, H, N271-PyrrolidinomethylH126-128 ^s 67 $C_{13}H_{16}N_3O$ C, H, N28 $CH_2N(CH_2C_8H_5)_2$ H185-186 ^j 99 $C_{23}H_{21}N_3O$ C, H, N29 $CH_2NHNHC_6H_5$ H284-285 ^j 77 $C_{13}H_{16}R_3ClN_2O$ C, H, N30CHaBr2 p -BrC6II4223-224 ^{b,n} 10 $C_{15}H_{10}Br_3ClN_2O$ C, H, N31CH_4BrC_6H5176 ^j 40 $C_{13}H_{10}Br_3O$ C, H, N321-MorpholinomethylC_6H5161-162 ^{b,o} 52 $C_{20}H_{20}BrN_4O$ 33N-MethylpiperazinomethylC_6H5137-138 ^s 51 $C_{23}H_{24}N_4O$ C, H, N34N-PhenylpiperazinomethylC_6H5137-138 ^s 51 $C_{24}H_{25}N_5O$ C, H, N356-Methylpyridyl-2-aminomethylC_6H595-98 ^s 40 $C_{23}H_{21}N_5O$ C, H, N36CH_2NH(CH_2)_2C_6H_5C_6H595-98 ^s 40 $C_{23}H_{21}N_5O$ C, H, N37CH ₂ OC ₂ H ₅ | 21 | Н | $N = CHCOC_6H_5$ | 187–188 ^{<i>i</i>,<i>l</i>} | 37 | $C_{16}H_{13}N_{3}O_{3}$ | С, Н, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 22 | N-Piperidinoamino | Н | $247 - 248^{b}$ | 41 | $C_{13}H_{16}N_4O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 23 | N-Homopiperidinoamino | 1-Homopiperidino | $213 - 214^{b}$ | 40 | $C_{20}H_{29}N_5O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 24 | CH_2Br | Н | $>300^{k}$ | 55 | $C_9H_7BrN_2O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 25 | N-Methylpiperazinomethyl | н | 149-150° | 52 | $C_{14}H_{18}N_4O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 26 | N-Phenylpiperazinomethyl | Н | $192 - 193^{b}$ | 71 | $C_{19}H_{20}N_4O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 27 | 1-Pyrrolidinomethyl | Н | 126-128* | 67 | $C_{13}H_{15}N_3O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 28 | $CH_2N(CH_2C_6H_5)_2$ | H | $185 - 186^{j}$ | 99 | $C_{23}H_{21}N_3O$ | C, H, N |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | 29 | CH2NHNHC6H5 | H | $284 - 285^{i}$ | 77 | $C_{15}H_{14}N_4O$ | C, H, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 30 | CHBr_2 | $p	ext{-}\mathrm{BrC}_6\mathrm{H}_4$ | $223-224^{b,n}$ | 10 | $C_{15}H_{10}Br_3ClN_2O \cdot 0.5H_2O$ | С, Н, N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 31 | CH ₂ Br | C_6H_5 | 176^{j} | 40 | C15H11BrN2O | C. H. N |
| 33 N-Methylpiperazinomethyl C_6H_5 $161-162^{b,o}$ 52 $C_{20}H_{23}BrN_4O$ 34 N-Phenylpiperazinomethyl C_6H_5 $137-138^{e}$ 51 $C_{25}H_{24}N_4O$ C, H, N 35 6-Methylpyridyl-2-aminomethyl C_6H_5 $202-203^{j}$ 20 $C_{21}H_{18}N_4O$ C, H, N 36 $CH_2NH(CH_2)_2C_6H_5$ C_6H_5 $95-98^{e}$ 40 $C_{23}H_{21}N_5O$ C, H, N 37 $CH_2OC_2H_5$ H $203-204^{j,n}$ dec 17 $C_{11}H_{15}N_3O$ C, H, N 38 1-Tetrahydroquinolinyl H $221-222^{j}$ 12 $C_{17}H_{15}N_3O$ C, H, N 37 CH_2OC_2 H_5 H $221-222^{j}$ 12 $C_{17}H_{15}N_3O$ C, H, N 38 1-Tetrahydroquinolinyl H $221-222^{j}$ 12 $C_{17}H_{15}N_3O$ C, H, N 4 Crwstellized from MacO b Accuraces puriding d Watter $C C$ H $C C$ | 32 | 1-Morpholinomethyl | C_6H_5 | 146-147 | 60 | $C_{19}H_{19}N_{2}O_{2}$ | C. H. N |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | 33 | N-Methylpiperazinomethyl | C ₆ H ₅ | 161-162% | 52 | C.H.BrN.O. | 0, 11, 11 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 00 | 11 high pipe and hearing t | 00113 | 101 102 | 02 | 0.5H.0 | СНИ |
| 35 6-Methylpyridyl-2-aminomethyl $C_{6}H_5$ 202-203i 20 $C_{21}H_{18}N_4O$ C, H, N 36 CH ₂ NH(CH ₂) ₂ C ₆ H ₅ C ₆ H ₅ 95-98* 40 $C_{23}H_{21}N_3O$ C, H, N 37 CH ₂ OC ₂ H ₅ H 203-204 ^{j,n} dec 17 $C_{11}H_{13}ClN_2O_2$. 38 1-Tetrahydroquinolinyl H 221-222' 12 $C_{17}H_{15}N_3O$ C, H, N | 34 | N-Phenylniperazinomethyl | C.H. | 137-138 | 51 | CaHaN.O | C H N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 35 | 6-Methylpyridyl-2-aminomethy | C.H. | 202_203 <i>i</i> | 20 | $C_{25}H_{24}N_{4}O$ | C H N |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 36 | CH _a NH(CH _a) ₂ C _a H. | C.H. | 05-080 | 40 | $C_{21}H_{18} + 40$ | CHN |
| $\begin{array}{cccccccc} 3.6 & CH_2OO_2H_5 & H & 205-204 & CH_1H_1SCH_3O_2 \\ & & & & & & & & \\ 3.8 & 1-Tetrahydroquinolinyl & H & 221-222' & 12 & C_{17}H_1SN_3O & C, H, N \\ Crustellized from Ma CO & Aqueous EtOH & Aqueous puriding & Weter & C.H. patroleum others (hr. 40, CO2) & C.H.$ | 37 | $CH_{0}O_{0}H_{2}$ | ∪6115 H | 202-2041 n doo | 17 | $C_{23} H_{21} H_{3} O$ | 0, 11, N |
| $\frac{0.5H_2O}{38} = \frac{0.5H_2O}{12} = \frac{0.5H_2O}{C_1 + 15N_3O} = \frac{0.5H_2O}{C$ | 01 | V112UV2115 | 11 | 200-204 [,] dec | 11 | 0.540 | CUN |
| $\frac{1}{221-222} = 12 (17\pi 15N_3O = 0, \pi, N)$ | 38 | 1-Tetrahydroquinolinyl | ΤΪ | 991_999/ | 19 | $C_{1}H_{1}N_{1}O$ | CHN |
| | 00 2 Cruztal | lized from Me-CO b Acusous | FtOH & Langous puriding | d Water CI | 14 Tnoted | loum other (hn 40.4 | |

^a Crystallized from Me₂CO. ^o Aqueous EtOH. ^c Aqueous pyridine. ^a Water. ^eC₆H₆-petroleum ether (bp 40-60°). ^fC₆H₆. ^g THF-petroleum ether. ^hEtOH-Et₂O. ⁱ CHCl₃. ⁱ Aqueous DMF. ^kAqueous dioxane. ^l Monohydrate. ^m Monohydrochloride. ⁿ Monohydrochloride hemihydrate. ^o Monohydrobromide hemihydrate.

Experimental Section⁹

2-Mercapto-3-aryl-4-quinazolones (1-3) were prepared according to Dave, et al.¹⁰

2-Ethylthio-4-quinazolone (4).—2-Mercapto-4-quinazolone was added to a solution of Na (0.23 g, 0.01 g-atom) in EtOH (30 ml). After refluxing for 10 min water (15 ml) was added, the mixture was cooled, EtI (0.9 ml, 0.01 mole) was added, and the mixture refluxed for 0.5 hr. The solution was concentrated to half-

volume and allowed to stand at room temperature for 2 hr, when 4 separated out as colorless needles, yield 1.5 g. Desulfurization of this product (0.3 g) with Raney nickel (3.0 g) in boiling EtOH (15 ml) gave 4-quinazolone, mp 210°, mmp (with an authentic sample) 210°.

Compounds 5-7 were prepared similarly.

2-Substituted Amino- and Hydrazino-4-quinazolones.—2-Ethylthio-4-quinazolone was heated with an excess of amine or hydrazine at $120-125^{\circ}$ for 5-6 hr and cooled. In the case of amines, the residue was triturated with Et₂O, filtered, and washed with Et₂O. In the case of hydrazines, the solid that separated out was filtered, washed (H₂O), and dried. The products were finally crystallized from suitable solvents.

Compounds 8-10, 13-16, 22, 23, and 38 were prepared similarly. 2,4-Bis(N-phenylpiperazine)quinazoline (40).—2-Ethylthio-4quinazolone (7.0 g) and N-phenylpiperazine (10.6 ml) were heated

^{(9) (}a) All melting points are uncorrected and were determined in a bath; (b) the physical and analytical data of compounds are given in Tables I-III; and (c) where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

⁽¹⁰⁾ G. R. Dave, G. S. Mewada, and G. C. Amin, J. Indian Chem. Soc., **37**, 595, (1960).

TABLE 11 2,4-Disubstituted Quinazolines (II)

| No. | \mathbf{R}_1 | $\mathbf{R}_{\mathbf{c}}$ | ${}^{\mathrm{M}\mathrm{p}},$ | Yield, | $Formula^d$ |
|-----|------------------------------|--|------------------------------|-------------|--|
| 39 | $N(CH_2C_6H_5)_2$ | $N(CH_2C_6H_5)_2$ | $199-200^{a}$ | 40 | $\mathrm{C}_{86}\mathrm{H}_{32}\mathrm{N}_4$ |
| 40 | N-Phenylpiperazino | N-Phenylpiperazino | 265^{6} | | $C_{28}H_{30}N_6$ |
| 41 | Cl | $\rm NHC_6H_4COCH_{3-}p$ | $205 - 206 \circ$ | 47 | $C_{16}H_{12}ClN_3O$ |
| 42 | Cl | $\rm NHC_6H_4CHOHCH_3-p$ | 194-195° | 70 | $C_{16}H_{14}ClN_3O$ |
| 43 | H | $\rm NHC_6H_4COCH_{3}$ - p | 243-2444 | 44 | $C_{16}H_{18}N_3O$ |
| 44 | II | NHC ₆ H ₄ CHOHCH ₃ -p | $191 - 192^{\circ}$ | 7.5 | $C_{36}H_{15}N_3O$ |
| C | of from C.U. potroloum other | h Curstellized from a queque THE | Constalliged for | MARCH RECHT | d All amproved |

^a Crystallized from C₆H₆-petroleum ether. ^b Crystallized from aqueous THF. ^c Crystallized from aqueous EtOH. ^a All compounds were analyzed for C, II, N.

TABLE III 5H-2,3-Disubstituted Triazepino[1,4,5][2,1-b]quinazolin-11-one (III)

| No. | R | Мр. °С | Yield, Co | $\operatorname{Formula}^{I}$ |
|---------|--|----------------------|---------------|--|
| 45 | 2-Furyl | $223-224^{a,b}$ | 16 | $C_{18}H_{11}N_5O_3\cdot 0.5H_2O$ |
| -46 | C ₆ H ₅ | $231 - 232^{a_{x}c}$ | 36 | $C_{22}H_{17}N_5O_2$ |
| 47 | p-CH ₃ OC ₆ H ₄ | $205-206^{a+d}$ | 48 | ${ m C}_{23}{ m H}_{23}{ m N}_{5}{ m O}_{5}$ |
| 48 | CH_3 | $295-296^{c,e}$ | 23 | $\mathrm{C}_{12}\mathrm{H}_{13}\mathrm{N}_5\mathrm{O}_2$ |
| 112 1 6 | b I have the second diverse the L have the | rdusto e Manohrdusto | (Dibrebute (| A anone DATSO - / All compounds was |

^a Crystallized from aqueous pyridine. ^b Hemihydrate. ^c Monohydrate. ^d Dihydrate. ^c Aqueous DMSO. ^d All compounds were analyzed for C, H, N.

together at 130° for 7 hr. The solid that separated out on cooling was triturated with Et₂O, filtered, and crystallized; yield 8.5 g. Compound **39** was prepared similarly.

2-Hydrazino-3-amino-4-quinazolone (11). A.—2-Ethylthio-4quinazolone (1.00 g, 0.005 mole) was refluxed with hydrazine hydrate (100%, 10 ml) for 10 hr, cooled, and filtered; the residue was washed (H₂O), and crystallized (hot H₂O) to yield 0.8 g.

B.--2-Ethylthio-3-phenyl-4-quinazolone (2.0 g) was heated with hydrazine hydrate (100%, 14 ml) for 10 hr, cooled, filtered, washed (H₂O), dried, and crystallized (hot H₂O), yield 1.0 g.

2-(5-Nitrofurfurylidene)hydrazino-3-amino-4-quinazolone (19).—5-Nitrofurfural diacetate (2.0 g, 0.01 mole) was added cautiously to a mixture of H_2O (17 ml), EtOH (3 ml), and concentrated H_2SO_4 (1 ml). After warming the reaction mixture on a water bath for 5 min, 2-hydrazino-3-amino-4-quinazolone was added and heating was continued for 1 hr, after which the product was cooled, filtered, washed (H_2O), and crystallized from EtOH, yield 3.0 g.

5H-2,3-Diphenyltriazepino[1,4,5] [2,1-b] quinazolin-11-one (46).—A solution of 2-hydrazino-3-amino-4-quinazolone (1.9 g, 0.01 mole) and benzil (2.1 g, 0.01 mole) in xylene (80 ml) was refluxed for 17 hr, cooled, and filtered. The residue was washed (C_6H_6 , EtOH) and, after boiling with H₂O, crystallized from aqueous pyridine. Chromatography over alumina, using CHCl₃ as eluent, gave an analytically pure sample, yield 1.3 g.

Compounds 45, 47, 48 were prepared by a similar procedure. 6H,3H-2,4-Dimethyltriazocino[1,5,6][2,1-b]quinazolin-12-one

(49) (IV).—Freshly distilled acetylacetone (1 ml, 0.01 mole) was added to a solution of 2-hydrazino-3-amino-4-quinazolone (1.0 g, 0.005 mole) in *i*-PrOH (50 ml). The reaction mixture was refluxed for 12 hr and cooled, and the solvent was removed. Chromatography over alumina, using C_6H_6 as the eluent, gave a glassy substance which solidified on trituration with 10% HCl. It was filtered, washed (H₂O), and crystallized from Et₂O-Me₂CO (2:1) to give pale yellow crystals, yield 0.6 g (50%), mp 133-134°. Anal. (C₁₃H₁₃N₆O) C, H, N.

Acid Hydrolysis of 5H,2,3-Dianisyltriazepino[1,4,5][2,1-b]quinazolin-11-one.—A mixture of compound 46 and HBr (48%, 10 ml) was refluxed for 8 hr, cooled, filtered, and washed (H_2O), and the residue was boiled with EtOH and filtered. The EtOHinsoluble portion was identified as 2-hydrazino-3-amino-4quinazolone hydrobromide (mp 273°, nmp with authentic sample 273°); the EtOH-soluble solid was anisil (mp 132°, mmp 132°).

1-(5-Carboxymethylthiozolidine-2,4-dione)-2-p-(4-oxoquinazoline-2-methyl)-3- α -methylbenzalazine (17) was prepared according to Krbavĉiĉ, et al.,⁵ by cyclizing 2-methyl 3-(p-acetylphenyl)-4-quinazolone thiosemicarbazone with maleic anhydride in boiling THF.

2-Methyl-3-(γ -piperidinopropiophenyl)-4-quinazolone HCl (18),---2-Methyl-3-(p-acetylphenyl)-4-quinazolone (2.0 g) was added to piperidine (0.75 ml), concentrated HCl (0.5 ml), and

aqueous formaldehyde solution (35%, 2 moles, 1 ml) in EtOH (30 ml). The reaction mixture was refluxed for 4 hr, the solvent was removed, and the residual viscous oil was triturated with 10% HCl to give the hydrochloride of the Mannich base, which was crystallized from dry EtOH-Et₂O, yield 1.0 g.

4-(*p*-Acetylanilino)quinazoline (43).—An intimate mixture of 4-chloroquinazoline (1.0 g) and *p*-aminoacetophenone (0.82 g) was heated over a small flame for 5 min, cooled, washed (10% NaHCO₃, H₂O), and crystallized from aqueous EtOH, yield 0.7 g.

2-Chloro-4-(*p*-acetylanilino)quinazoline (41).--2,4-Dichloroquinazoline (2.0 g, 0.01 mole) was treated with *p*-aminoacetophenone (1.3 g, 0.01 mole) in EtOH (25 ml), in the presence of K_2CO_3 (1.38 g, 0.01 mole), refluxed for 2.5 hr, cooled, diluted with H_2O , filtered, washed (H₂O), and crystallized from aqueous EtOH, yield 1.4 g.

Reduction of 41 with NaBH₄.—To a solution of **41** (2.98 g, 0.01 mole) in EtOH (80 ml), NaBH₄ (0.7 g, 0.02 mole) was added. After refluxing for 4 hr the solvent was removed *in vacuo*, the residue was dissolved in AcOH and the solution was made basic with NaHCO₃ to yield **42**, yield 2.1 g.

Compound 44 was prepared similarly.

2-Ethylthio-3-chloromercuri-4-quinazolone (20).--2-Ethylthio-4-quinazolone (1.0 g, 0.005 mole) was added to a solution of Na (0.12 g, 0.005 g-atom) in EtOH (20 ml) followed by HgCl₂ (1.3 g, 0.005 mole) in EtOH (10 ml). A buff-colored solid separated out, which was filtered, washed (H₂O), and crystallized from CHCl₃, yield 0.3 g.

3-Phenylglyoxalidine-4-quinazolone (21).—Phenylglyoxal (2.6 g., 0.02 mole) was added to a solution of 3-amino-4-quinazolone (3.2 g, 0.02 mole) in EtOH (100 ml). After refluxing for 3.5 hr, excess solvent was removed *in vacuo*, Et₂O was added, and the resulting solid was crystallized from DMF-H₂O; yield 3 g.

2-Bromomethyl-4-quinazolone (24).—To a well-stirred solution of 2-methyl-4-quinazolone (4.7 g) in dry DMF (80 ml), NBS (5.2 g) was added, and stirring continued, at room temperature, for 18 hr. The product was filtered, washed well with Et_2O , and dried, yield 4.0 g. Compound **31** was prepared likewise.

2-(N-Methylpiperazino)methyl-4-quinazolone (25).—A mixture of 2-bromomethyl-4-quinazolone (4.0 g, 1.66 moles) and Nmethylpiperazine (5.0 g, 5 moles) was heated over a steam bath for 1 hr and cooled; the residue was extracted with C_6H_6 , boiled with activated charcoal, filtered, concentrated, and diluted with petroleum ether (bp 40–60°). The colorless needles that separated out were further purified by chromatography over alumina using CHCl₃ as an eluent, yield 2.5 g.

Compounds 26-29 and 32-36 were prepared similarly.

2-Ethoxymethyl-4-quinazolone (37).—To a solution of Na (0.12 g) in absolute EtOH was added 2-bromomethyl-4-quinazolone (1.2 g) and the reaction mixture was heated over steam bath for 1 hr, cooled, triturated with 10% HCl, and filtered. The residue was washed (H₂O) and crystallized from DMF-H₂O; yield 0.2 g.

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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 $120-130^{\circ}$ 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

TABLE I

| Ce | ONVERSION OF 2 | to 4 in A | CID SOLUTI | IONS |
|--------------|----------------|-----------|------------|---------------------|
| $Method^{a}$ | Temp | Time, hr | % yield | Mp, $^{\circ}C^{h}$ |
| Α | Reflux | 0.5 | 82 | 212 - 220 |
| В | Stir, rt | 3 | | |
| | Reflux | 0.5 | 94 | 170 - 178 |
| \mathbf{C} | Stir, rt | 1 | | |
| | Reflux | 0.5 | 73 | 187 - 204 |
| D | Reflux | 1 | 54 | 219-224 |
| \mathbf{E} | Steam bath | 0.16 | 70 | 234 - 238 |
| \mathbf{F} | Stir, rt | 3 | | |
| | Reflux | 3 | 70 | 212 - 214 |
| 1 10 1 | | | | |

^a A, 40 ml of H₂O, 40 ml of concentrated H₂SO₄, 40 ml of AcOH; B, 100 ml of 50% H₂SO₄; C, 40 ml of concentrated H₂SO₄ for 1 hr, then diluted with 40 ml of H₂O and reflux; D, 50 ml of concentrated HCl; E, 10 ml of concentrated H₂SO₄ 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.

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.

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 ED₅₀ of 35 mg/kg *po* against maximal electroshock (prevention of tonic hind-leg extension in the mouse⁷), and a maximal effective dose of 100 mg/kg *po* against pentamethylenetetrazole-induced convulsions (timed intravenous infusion of pentamethylenetetrazole in the mouse⁸). The LD₅₀ 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

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