Drugs Acting on the Central Nervous System. Syntheses of Substituted Quinazolones and Quinazolines and Triazepino- and Triazocinoquinazolones[1]

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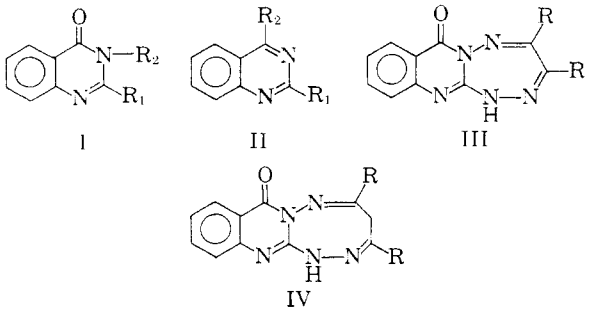
In earlier communications,[2,3] it has been reported that a variety of 3-substituted 4-quinazolones and quinazolo-4-thiones with or without substituents in the 2 position exhibit CNS-depressant activity. In continuation of our program for obtaining a better CNS depressant, we considered it of interest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



I II III

IV

2-Mercapto-4-quinazolone[4] on treatment with EtI in the presence of NaOEt, yielded 2-ethylthio-4-quinazolone (**4**). Its ir spectrum did not show the characteristic ν_{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-ethylthio-4-quinazolone with Raney nickel to give 4-quinazolone. Reaction of heterocyclic or aliphatic secondary amines with 2-ethylthio-4-quinazolone gave the corresponding 2-substituted 4-quinazolones (**13**–**16**). Treatment of 2-ethylthio-4-quinazolone 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-4-quinazolone showed peaks at 3300, 3450 (NH_2), 1680 cm^{-1} (>C=O), and a slightly broad peak at 1630 cm^{-1} (NH_2 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-4-quinazolone (**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. Ir 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-quinazolone[2] with piperidine and formaldehyde gave the corresponding Mannich base (**18**).

The reaction of 2,4-dichloroquinazoline[6] with *p*-aminoacetophenone in the presence of K_2CO_3 gave 2-chloro-4-(*p*-acetylanilino)quinazoline (**41**). Reduction with $NaBH_4$ yielded the corresponding hydroxy compound (**42**), which was not resolved. 4-Chloroquinazoline[7] on fusion with *p*-aminoacetophenone gave 4-(*p*-acetylanilino)quinazoline (**43**) which on reduction with $NaBH_4$ 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-4-quinazolone on treatment with NBS yielded 2-bromomethyl-4-quinazolone (**24**) and 2-bromomethyl-3-phenyl-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)[8] in mice. The test compounds were administered intraperitoneally. Compounds **4** (LD_{50} = 1000 mg/kg) showed 60% protection against maximal electroshock (MES) at 250 mg/kg while **39** (LD_{50} = 400 mg/kg) showed 50% protection (MES) at 100 mg/kg. Compound **15** (LD_{50} = 100 mg/kg) caused convulsions at 50 mg/kg; **12** and **14** exhibited CNS depressant and stimulant action at their LD_{50} dose (400, 100 mg/kg), respectively. The remaining compounds were inactive.

(1) Communication No. 1191 from the Central Drug Research Institute, Lucknow, India.

(2) A. P. Bhaduri and N. M. Khanna, *Indian J. Chem.*, **4**, 447 (1966).

(3) A. P. Bhaduri, N. M. Khanna, and M. L. Dhar, *ibid.*, **2**, 159 (1964).

(4) D. S. Bariana, H. S. Sachdev, and K. S. Narang, *J. Indian Chem. Soc.*, **32**, 648 (1955).

(5) A. Krbavčić, M. Plut, A. Pollock, M. Tisler, M. Liker, and P. Schauer, *J. Med. Chem.*, **9**, 430 (1966).

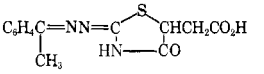
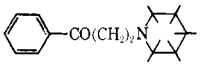
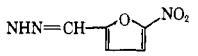
(6) F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 775 (1947).

(7) T. Stephen and H. Stephen, *ibid.*, 4178 (1956).

(8) E. A. Swinyard, W. E. Brown, and L. S. Woodman, *J. Pharmacol. Expl. Therap.*, **106**, 319 (1952).

TABLE I

2,3-DISUBSTITUTED 4-QUINAZOLONES (I)

No.	R_1	R_2	Mp, °C	Yield, %	Formula	Analyses
1	SH	*p*-BrC_6H_4	285[a]	80	$C_{14}H_9N_2BrOS$	C, H, N
2	SH	*p*-$C_2H_5OC_6H_4$	>310[a]	80	$C_{16}H_{14}N_2O_2S$	C, H, N
3	SH	2,4-$F_2C_6H_3$	252[a]	85	$C_{14}H_8N_2F_2OS$	C, H
4	SC_2H_5	H	162–163[b]	72	$C_{10}H_{10}N_2OS$	C, H, N
5	SC_2H_5	*p*-BrC_6H_4	145–146[b]	90	$C_{16}H_{13}BrN_2OS$	C, H, N
6	SC_2H_5	*p*-$C_2H_5OC_6H_4$	142[b]	95	$C_{18}H_{18}N_2O_2S$	C, H, N
7	SC_2H_5	2,4-$F_2C_6H_3$	131–132[b]	85	$C_{16}H_{12}F_2N_2OS$	C, H
8	$NHNH_2$	*p*-BrC_6H_4	227–228[c]	93	$C_{14}H_{11}BrN_4O$	C, H, N
9	$NHNH_2$	*p*-$C_2H_5OC_6H_4$	197[b]	95	$C_{16}H_{16}N_4O_2$	C, H, N
10	$NHNH_2$	2,4-$F_2C_6H_3$	188[b]	90	$C_{14}H_{10}F_2N_4O$	C, H
11	$NHNH_2$	NH_2	219–220[d]	98	$C_8H_9N_5O$	C, H, N
12	$NHNHC_6H_5$	NHC_6H_5	232–233[b,l] dec	50	$C_{20}H_{19}N_5O_2$	C, H, N
13	$N(CH_2CH{=}CH_2)_2$	H	150–151[e]	7	$C_{14}H_{15}N_3O$	C, H, N
14	N-Methylpiperazino	H	220–221[f]	59	$C_{13}H_{16}N_4O$	C, H, N
15	1-Homopiperidino	H	209–210[e]	48	$C_{14}H_{17}N_3O$	C, H, N
16	6-Methylpyridyl-2-amino	H	268–269[c]	68	$C_{14}H_{12}N_4O$	C, H, N
17	CH_3		244[g]	27	$C_{22}H_{19}N_5O_4S$	C, H, N
18	CH_3		188–189[h,m]	36	$C_{23}H_{26}ClN_3O$	C, H, N
19		NH_2	212–213[b]	98	$C_{13}H_{10}N_6O_4$	C, H, N
20	SC_2H_5	HgCl	244[i]	19	$C_{10}H_9ClN_2OSHg$	N
21	H	$N{=}CHCOC_6H_5$	187–188[j,l]	37	$C_{16}H_{13}N_3O_3$	C, H, N
22	N-Piperidinoamino	H	247–248[b]	41	$C_{13}H_{16}N_4O$	C, H, N
23	N-Homopiperidinoamino	1-Homopiperidino	213–214[b]	40	$C_{20}H_{29}N_5O$	C, H, N
24	CH_2Br	H	>300[k]	55	$C_9H_7BrN_2O$	C, H, N
25	N-Methylpiperazinomethyl	H	149–150[e]	52	$C_{14}H_{18}N_4O$	C, H, N
26	N-Phenylpiperazinomethyl	H	192–193[b]	71	$C_{19}H_{20}N_4O$	C, H, N
27	1-Pyrrolidinomethyl	H	126–128[e]	67	$C_{13}H_{15}N_3O$	C, H, N
28	$CH_2N(CH_2C_6H_5)_2$	H	185–186[j]	99	$C_{23}H_{21}N_3O$	C, H, N
29	$CH_2NHNHC_6H_5$	H	284–285[j]	77	$C_{15}H_{14}N_4O$	C, H, N
30	$CHBr_2$	*p*-BrC_6H_4	223–224[b,n]	10	$C_{15}H_{10}Br_3ClN_2O\cdot 0.5H_2O$	C, H, N
31	CH_2Br	C_6H_5	176[j]	40	$C_{15}H_{11}BrN_2O$	C, H, N
32	1-Morpholinomethyl	C_6H_5	146–147[f]	60	$C_{19}H_{19}N_3O_2$	C, H, N
33	N-Methylpiperazinomethyl	C_6H_5	161–162[b,o]	52	$C_{20}H_{23}BrN_4O\cdot 0.5H_2O$	C, H, N
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	$C_{23}H_{21}N_3O$	C, H, N
37	$CH_2OC_2H_5$	H	203–204[j,n] dec	17	$C_{11}H_{13}ClN_2O_2\cdot 0.5H_2O$	C, H, N
38	1-Tetrahydroquinolinyl	H	221–222[f]	12	$C_{17}H_{15}N_3O$	C, H, N

[a] Crystallized from Me_2CO. [b] Aqueous EtOH. [c] Aqueous pyridine. [d] Water. [e] C_6H_6–petroleum ether (bp 40–60°). [f] C_6H_6. [g] THF–petroleum ether. [h] EtOH–Et_2O. [i] $CHCl_3$. [j] Aqueous DMF. [k] Aqueous dioxane. [l] Monohydrate. [m] Monohydrochloride. [n] Monohydrochloride hemihydrate. [o] Monohydrobromide hemihydrate.

Experimental Section[9]

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° for 5–6 hr and cooled. In the case of amines, the residue was triturated with Et_2O, filtered, and washed with Et_2O. In the case of hydrazines, the solid that separated out was filtered, washed (H_2O), 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-4-quinazolone (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 ±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 II

2,4-DISUBSTITUTED QUINAZOLINES (II)

No.	R_1	R_2	Mp, °C	Yield, %	Formula[d]
39	$N(CH_2C_6H_5)_2$	$N(CH_2C_6H_5)_2$	199–200[a]	40	$C_{36}H_{32}N_4$
40	N-Phenylpiperazino	N-Phenylpiperazino	265[b]	54	$C_{28}H_{30}N_6$
41	Cl	$NHC_6H_4COCH_3$-*p*	205–206[c]	47	$C_{16}H_{12}ClN_3O$
42	Cl	$NHC_6H_4CHOHCH_3$-*p*	194–195[c]	70	$C_{16}H_{14}ClN_3O$
43	H	$NHC_6H_4COCH_3$-*p*	243–244[c]	44	$C_{16}H_{13}N_3O$
44	H	$NHC_6H_4CHOHCH_3$-*p*	191–192[c]	75	$C_{16}H_{15}N_3O$

[a] Crystallized from C_6H_6–petroleum ether. [b] Crystallized from aqueous THF. [c] Crystallized from aqueous EtOH. [d] All compounds were analyzed for C, H, N.

TABLE III

5H-2,3-DISUBSTITUTED TRIAZEPINO[1,4,5][2,1-*b*]QUINAZOLIN-11-ONE (III)

No.	R	Mp, °C	Yield, %	Formula[f]
45	2-Furyl	223–224[a,b]	16	$C_{18}H_{11}N_5O_3 \cdot 0.5H_2O$
46	C_6H_5	231–232[a,c]	36	$C_{22}H_{17}N_5O_2$
47	*p*-$CH_3OC_6H_4$	205–206[a,d]	48	$C_{23}H_{23}N_5O_5$
48	CH_3	295–296[c,e]	23	$C_{12}H_{13}N_5O_2$

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

together at 130° for 7 hr. The solid that separated out on cooling was triturated with Et_2O, filtered, and crystallized; yield 8.5 g. Compound **39** was prepared similarly.

2-Hydrazino-3-amino-4-quinazolone (11). A.—2-Ethylthio-4-quinazolone (1.00 g, 0.005 mole) was refluxed with hydrazine hydrate (100%, 10 ml) for 10 hr, cooled, and filtered; the residue was washed (H_2O), and crystallized (hot H_2O) 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 (H_2O), dried, and crystallized (hot H_2O), 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 H_2O, crystallized from aqueous pyridine. Chromatography over alumina, using $CHCl_3$ 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 (H_2O), and crystallized from Et_2O–Me_2CO (2:1) to give pale yellow crystals, yield 0.6 g (50%), mp 133–134°. *Anal.* ($C_{13}H_{13}N_5O$) 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 EtOH-insoluble portion was identified as 2-hydrazino-3-amino-4-quinazolone hydrobromide (mp 273°, mmp 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 Krbavčič, *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–Et_2O, 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% $NaHCO_3$, H_2O), 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 (H_2O), and crystallized from aqueous EtOH, yield 1.4 g.

Reduction of 41 with $NaBH_4$.—To a solution of **41** (2.98 g, 0.01 mole) in EtOH (80 ml), $NaBH_4$ (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 $NaHCO_3$ 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 $HgCl_2$ (1.3 g, 0.005 mole) in EtOH (10 ml). A buff-colored solid separated out, which was filtered, washed (H_2O), and crystallized from $CHCl_3$, 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*, Et_2O was added, and the resulting solid was crystallized from DMF–H_2O; 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 N-methylpiperazine (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 $CHCl_3$ 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 (H_2O) and crystallized from DMF–H_2O; 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° 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.

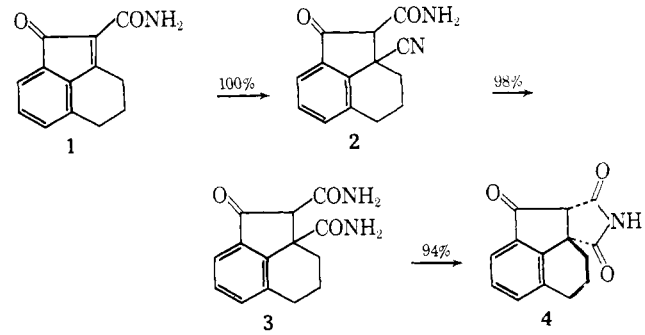
TABLE I

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

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