oration of the tocopheryl acetate or its adsorption to the mortar and pestle during the grinding process.

CONCLUSIONS

The solid dispersion principle was tested on five poorly soluble liquid compounds by using PEG 6000 as a carrier. They were prepared by the melting method. Below the 10% concentration, they could be pulverized, encapsulated, and tableted. The preparations were reproducible, and the active ingredients were distributed homogeneously in the solid matrix. The active ingredients were found to be released rapidly from the matrix, with complete dissolution time ranging from 4 to 14 min. This approach represents a new method for the formulation of liquid medicinal compounds, either water soluble or insoluble. It is proposed that one can formulate a prolonged or sustained-release dosage form of drugs by the careful control of the carriers.

REFERENCES

(1) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866(1961).

(2) K. Sekiguchi, N. Obi, and Y. Ueda, *ibid.*, **12**, 139(1964).

(3) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55**, 487(1966).

(4) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *ibid.*, **55**, 581(1966).

(5) T. Tachibana and A. Nakamura, *Kolloid-Z. Polym.*, **203**, 130(1965).

(6) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55**, 1323 (1966).

(7) M. H. Malone, H. I. Hochman, and K. A. Nieforth, *ibid.*, **55**, 972(1966).

(8) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *ibid.*, **58**, 538(1969).

(9) W. L. Chiou and S. Riegelman, *ibid.*, **58**, 1505(1969).

(10) W. L. Chiou and S. Riegelman, to be published.

(11) D. J. Allen and K. C. Kwan, *J. Pharm. Sci.*, **58**, 1190(1969).

(12) W. I. Higuchi, N. A. Mir, and S. J. Desai, *ibid.*, **54**, 1405 (1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 28, 1969, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication July 14, 1970.

Synthesis and Anticonvulsant Activity of Substituted 2-Thioquinazolin-4-ones I: Preliminary Studies

ARTHUR C. GLASSER*, LOUIS DIAMOND, and GEORGE COMBS

Abstract □ A series of 2-thioquinazolin-4-ones with varying substituents on position 2, 3, or 6 was synthesized and studied for their ability to prevent maximal electroshock and chemoshock seizures in mice within the dosage range of 10–600 mg./kg. The 2-ethylthio-3-(2-phenyl)ethylquinazolin-4-one exhibited full protection against electroshock at the 100-mg./kg. level. The compound 2-carboxymethylthio-3-(2-phenyl)ethylquinazolin-4-one showed full protection against electroshock at the 600-mg./kg. level and partial activity at the 100-mg./kg. level. Other than these examples of activity, there was little significant activity in the remaining members of the series, with 2-ethylthio-3-phenylquinazolin-4-one showing only partial protection at both the 600- and 100-mg./kg. levels. With one exception within the dosage range studied, none of the compounds appeared to be active in preventing pentylenetetrazole seizures, thus indicating that the compounds possibly act in an analogous manner to diphenylhydantoin and related molecules.

Keyphrases □ 2-Thioquinazolin-4-ones, substituted—synthesis, anticonvulsant activity evaluated □ Anticonvulsants, synthesized, evaluated—substituted 2-thioquinazolin-4-ones □ Pentylenetetrazole-induced seizures—evaluation of substituted 2-thioquinazolin-4-ones anticonvulsant activity

Despite the many significant advancements that have occurred in recent years, newer, safer, and more effective CNS depressant drugs are needed for therapeutic application as anticonvulsant, sedative, or hypnotic agents. In approaching this problem, it was thought that the broad spectrum of physiological activities of the 4-quinazolones would make them good candidates for study; indeed, CNS depressant drugs have been developed from this class. The history of the development of 2-methyl-3-*o*-tolyl-4-quinazolone, methaqualone, was reviewed recently by Cain (1), and Boissier *et al.* (2) showed the *ortho*-chloro compound to be the most active from a study of the *ortho*-, *meta*-, and *para*-isomers. Hayao *et al.* (3) reported on the synthesis of a series of 3-substituted-2,4-(1*H*,3*H*)-quinazolinediones. In their examination for CNS depressant effects, one of the series was reported to approach chlorpromazine in its activity upon experimental animals (3). Burkhalter and Scarborough (4) previously reported that 2,4-(1*H*,3*H*)-quinazolinedione and the 1,3-dimethyl derivative showed protective action against electroshock and pentylenetetrazole-induced seizures in mice. Gujral *et al.* (5, 6) also noted hypnotic and anticonvulsant properties in a series of 2-alkyl-3-aryl-4-(3*H*)-quinazolones. This work was confirmed by Boissier (7). The substance 2-methyl-3-*p*-bromophenyl-4-quinazolone was reported by Bianchi and David (8) to have strong anticonvulsant properties against pentylenetetrazole-induced seizures. Gupta *et al.* (9) continued their study of substituted-4-quinazolones as CNS depressants in a report on some 2,3-disubstituted derivatives, and Chaurasia (10) reported the synthesis of potential antimalarial and ataractic thioquinazolone derivatives.

The present series of thioquinazolin-4-ones resulted from the observation of a marked decrease in coordination (11), as shown by the rota-rod test (12) and narrow strip (horizontal and inclined) test (13) when a suspension of 3-phenyl-2-thioquinazolin-4-one, which was prepared as a part of another study, was administered intraperitoneally to mice at a dosage level of 100 mg./kg. As an expansion of this observation, it was of interest to determine the effect of substituting the thio group, the aromatic ring, and altering the substituent at the 3-nitrogen to gain information as to potential anticonvulsant activity in the general structure. The results of the syntheses are summarized in Tables I and II.

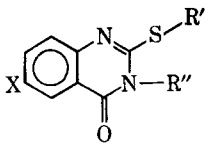

Table I—Substituted 2-Thio-(3*H*)-quinazolin-4-ones

Number	R′	R″	X	M.p.[a]	Yield, %	Recrystallization Solvent[b]	Anal., %[c] Calcd.	Found
1	—Et	—$CH_2CH_2\phi$	—Cl	101–103°	74	EtOH	C, 62.70 H, 5.01 N, 8.10	C, 62.82 H, 4.95 N, 8.08
2	—Et	—ϕ	—H	105–107°	66	EtOH	C, 68.10 H, 5.01 N, 9.90	C, 68.21 H, 5.11 N, 10.12
3	—Et	—$CH_2CH_2\phi$	—H	81–83°	85	EtOH	C, 69.70 H, 5.80 N, 9.01	C, 69.62 H, 5.93 N, 8.94
4	—CH_2CO_2H	—$CH_2CH_2\phi$	—H	151–153°	45	Ac	C, 63.50 H, 4.70 N, 8.20	C, 63.11 H, 4.84 N, 7.91
5	—CH_2CO_2H	—ϕ	—H	273–274°	37	Ac	C, 61.50 H, 3.86 N, 8.99	C, 61.26 H, 3.91 N, 9.01

[a] Mel-Temp apparatus, corrected. [b] Ac = acetone; DMF = dimethylformamide. [c] Microanalyses performed by Dr. Kurt Eder, Geneva, Switzerland, and Galbraith Laboratories, Knoxville, Tenn.

PHARMACOLOGY

The anticonvulsant activity of each compound was evaluated by means of maximal electroshock seizure (MES) and pentylenetetrazole seizure threshold (PST) tests (13). A group of three male albino mice was used for each test, and the results were compared with saline-treated control groups. The animals were stimulated with 60-cycle alternating current for 200 msec. *via* a pair of earclip electrodes. A variable transformer was used to regulate the applied voltage. The desired stimulus duration was obtained by the inclusion of a relay in the circuit, which was operated by a Grass S-4 square-wave stimulator. A cathode ray oscilloscope (CRO) was used to monitor the voltage drop across a 10-ohm resistor coupled in series with the animal; thus the corresponding current could be calculated. The sweep on the CRO screen was triggered by the stimulator, so accurate readings could be obtained with each shock. Preliminary studies showed that 12–16 mamp. was required to produce a convulsive seizure pattern having a tonic flexor phase, a tonic extensor phase, and a clonic phase.

After adequate control data were obtained, each group of animals received, intraperitoneally, 10, 100, or 600 mg./kg. of the drug under study; the MES tests were repeated 1, 2, and 3 hr. after drug administration. All drugs were administered as suspensions in 0.5% methylcellulose (4000 cps.). An animal was considered to be protected if the tonic extensor phase of the seizure pattern was absent.

A similar experimental design was used for conducting the PST tests. Animals received pentylenetetrazole, 85 mg./kg. s.c., 2 hr. after administration of a test compound. Animals that showed no convulsive activity of any kind during a 30-min. observation period were considered protected.

The ability of the selected experimental testing procedures to detect anticonvulsant activity was assessed by including in the study three agents known to provide significant protection against either electrically or chemically induced seizures—*viz.*, diphenylhydantoin, phenobarbital, and trimethadione.

The neurologic status of each animal was evaluated prior to each test for anticonvulsant activity. Toxicity was considered present if the animal failed to exhibit a righting reflex or a hind-limb placing reaction or if the animal's equilibrium, gait, or stance deviated from normal. The results of the MES and PST tests are summarized in Tables III and IV.

CHEMISTRY

The compounds studied were prepared by reaction of the appropriate anthranilic acids with phenethyl isothiocyanate or phenyl isothiocyanate in ethyl alcohol or dimethylformamide (DMF) at reflux. The thiosubstituted compounds were prepared by the action of ethyl iodide or chloroacetic acid upon the quinazolones in alcoholic sodium hydroxide solution (14). Selective thioethylation of quinazolones under these conditions can be confirmed through desulfurization with Raney nickel (14). Phenethyl isothiocyanate was prepared in 63% yield by a modified Kaluza synthesis according to

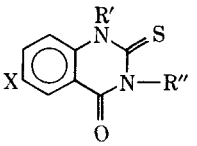

Table II—Substituted 2-Thio-(1*H*,3*H*)-quinazolin-4-ones

Number	R′	R″	X	M.p.[a]	Yield, %	Recrystallization Solvent[b]	Anal., %[c] Calcd.	Found
1	—H	—$CH_2CH_2\phi$	—H	244–245°	33	Ac	C, 68.10 H, 5.00 N, 9.90	C, 68.20 H, 5.15 N, 9.81
2	—H	—$CH_2CH_2\phi$	—Cl	242–244°	53	Ac	C, 60.70 H, 4.10 N, 8.80	C, 60.77 H, 4.02 N, 8.96
3	—H	—ϕ	—H	304–305°[d]	85	DMF	C, 66.10 H, 3.97 N, 11.01	C, 65.91 H, 4.13 N, 11.17

[a–c] The same as in Table I. [d] Literature 304–306°, B. Pawlewski, *Chem. Ber.*, **38**, 131(1905).

Table III—Maximal Electroshock Seizure Tests

Compound Number	Dose, mg./kg.	—Number of Animals Protected— 1 hr.	2 hr.	3 hr.	—Number of Animals Showing Toxicity— 1 hr.	2 hr.	3 hr.
1	600	0/3	0/3	0/3	0/3	0/3	0/3
2	600	2/3	2/3	2/3	3/3	3/3	3/3
	100	1/3	1/3	1/3	0/3	0/3	0/3
3	600	3/3	3/3	3/3	3/3	3/3	3/3
	100	3/3	3/3	3/3	0/3	0/3	0/3
	10	0/3	0/3	0/3	0/3	0/3	0/3
4	600	0/3	1/3	1/3	0/3	0/3	0/3
5	600	3/3	3/3	3/3	0/3	0/3	0/3
	100	1/3	1/3	1/3	0/3	0/3	0/3
6	600	3/3	3/3	3/3	0/3	2/3	2/3
	100	0/3	0/3	0/3	0/3	0/3	0/3
7	Not tested						
8	600	0/3	0/3	0/3	0/3	0/3	0/3
Diphenylhydantoin	25	3/3	3/3	3/3	0/3	0/3	
Phenobarbital	25	3/3	3/3	3/3	0/3	0/3	0/3
Normal saline	1 ml.	0/3	0/3	0/3	0/3	0/3	0/3

Table IV—Pentylenetetrazole Seizure Threshold Tests

Compound Number	Dose, mg./kg.	Number of Animals Protected 2 hr. after Administration
1	600	0/3
2	100	0/3
3	100	0/3
4	600	0/3
5	600	0/3
6	600	3/3
	100	0/3
7	Not tested	
8	600	0/3
Trimethadione	600	3/3
Normal saline	1 ml.	0/3

Hodgkins and Reeves (15). The anthranilic acids and phenyl isothiocyanate were commercial products purified as necessary before use.

EXPERIMENTAL[1]

Phenethyl Isothiocyanate—Into a 1000-ml. three-necked flask equipped with a dropping funnel, mechanical stirrer, and reflux condenser, there were added 68.3 g. (0.9 mole) of carbon disulfide and 80 ml. of 11 *M* sodium hydroxide solution. The flask was cooled to 0° with an ice–salt bath. 2-Phenethylamine, 109 g. (0.9 mole), was added dropwise over a period of 30 min. with stirring. The reaction was allowed to warm to room temperature and then was heated on a water bath for 1.5 hr. The solution was cooled to room temperature, and 87.5 ml. (0.9 mole) ethylchloroformate was added dropwise to the solution with stirring; the stirring was continued for 30 min. The isothiocyanate appeared as a lower layer and was separated and dried over magnesium sulfate overnight. The product was distilled under reduced pressure for a yield of 92.5 g. (63%) of a colorless liquid, b.p. 146–148° at 15 mm., lit. 141–144° at 11 mm. (16).

Anal.—Calcd. for C_9H_9NS: C, 66.20; H, 5.60; N, 8.60. Found: C, 66.17; H, 5.76; N, 8.39.

2-Thio-3-phenethyl-6-chloroquinazolin-4-one—Into a 250-ml. boiling flask equipped with a reflux condenser, there were added 16.3 g. (0.1 mole) phenethyl isothiocyanate, 17.2 g. (0.1 mole) 2-amino-5-chlorobenzoic acid, and 50 ml. of DMF. The solution was refluxed 2.5 hr. and allowed to stand overnight in a refrigerator. Filtration of the cooled reaction mixture yielded a crystalline solid, m.p. 231–235°, which, upon recrystallization from acetone, yielded 16.7 g. (53%) of a crystalline solid, m.p. 242–244°.

Anal.—Calcd. for $C_{16}H_{13}ClN_2OS$: C, 60.70; H, 4.10; N, 8.81. Found: C, 60.77; H, 4.02; N, 8.96.

2-Ethylthio-3-phenethyl-6-chloroquinazolin-4-one—2-Thio-3-phenethyl-6-chloroquinazolin-4-one (5.7 g., 0.02 mole) was added to a solution of 5 g. of sodium hydroxide in 85 ml. of an ethyl alcohol–water (50:50) solution. The solution was mixed, and 6 g. (4 ml.) of ethyl iodide was added; then the solution was stirred for 1.5 hr. The product separated out and was filtered, washed with EtOH–H_2O, and dried. Upon recrystallization from alcohol, 4.6 g. (74%) of colorless crystals, m.p. 101–103°, was obtained.

Anal.—Calcd. for $C_{18}H_{17}ClN_2OS$: C, 62.70; H, 5.01; N, 8.10. Found: C, 62.82; H, 4.95; N. 8.08.

[1] Melting points were taken on a Mel-Temp block and are corrected. Structural correlations by means of IR were made using a Beckman IR-8.

REFERENCES

(1) C. K. Cain, *Annu. Rep. Med. Chem.*, **1965**, 31.

(2) J. R. Boissier, C. Dumont, and R. Ratouis, *Therapie*, **22**, 129(1967).

(3) S. Hayao, H. T. Havera, W. G. Stycher, T. J. Leipzig, R. Kulp, and H. E. Hartzler, *J. Med. Chem.*, **8**, 807(1965).

(4) J. H. Burkhalter and H. D. Scarborough, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 545(1955).

(5) M. L. Gujral, P. M. Saxena, and R. S. Tiwari, *Indian J. Med. Res.*, **43**, 637(1955).

(6) M. L. Gujral, K. N. Sareen, and R. P. Kohle, *ibid.*, **45**, 207 (1957).

(7) J. R. Boissier, *Therapie*, **13**, 30(1958).

(8) C. Bianchi and A. David, *J. Pharm. Pharmacol.*, **12**, 501 (1960).

(9) C. M. Gupta, A. P. Bhaduri, and N. M. Khanna, *J. Med. Chem.*, **11**, 392(1968).

(10) M. R. Chaurasia, *Ag. Biol. Chem.*, **32**, 711(1968).

(11) Unpublished results.

(12) N. W. Dunham and T. S. Miya, *J. Amer. Pharm. Ass., Sci. Ed.*, **46**, 208(1957).

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

(14) P. N. Bhargava and V. M. Choubey, *J. Med. Chem.*, **12**, 553(1969).

(15) J. E. Hodgkins and W. P. Reeves, *J. Org. Chem.*, **29**, 3098 (1964).

(16) J. VonBraun and H. Deutsch, *Chem. Ber.*, **45**, 2188(1912).

ACKNOWLEDGMENTS AND ADDRESSES

Received May 7, 1970, from the *Departments of Pharmaceutical Chemistry and Materia Medica, College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication June 23, 1970.

This investigation was supported by Grant MH-17022, National Institute of Mental Health, U. S. Public Health Service.

* To whom inquiries should be addressed. Present address: College of Pharmacy, University of Cincinnati, Cincinnati, OH 45221