[Contribution from the Department of Chemistry of the University of Kansas]

Synthesis of Some Thioquinazolones of Interest as Potential Ataractic Agents

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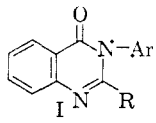
The syntheses and properties are reported for a series of 2-alkylthio-3-phenyl-4-(3H)quinazolones and 2-alkylthio-3-allyl-4-(3H)quinazolones of interest as possible ataractic agents.

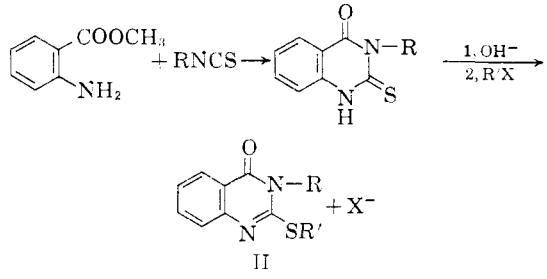
In 1955, Gujral, Saxena and Tiwari[1] observed that some 2-alkyl-3-aryl-4-(3H)quinazolones (I) are potent hypnotic agents in rats. Recently



I

McLamore, P'an and Laubach[2] have reported the preparation and testing of additional members in this series. These workers found that certain of these compounds possess central depressant activities, in higher animals, comparable to those of the most potent barbiturates. Higher dosage levels, however, produced symptoms of central stimulation.

As part of a program on the synthesis and study of compounds of interest as potential ataractic agents, a series of 2-alkylthio-3-phenyl-(or allyl)-4-(3H)quinazolones (II) was prepared. The simplest synthetic route to these products proved to be the alkylation with the appropriate alkyl halides of the sodium salt of the corresponding 2-thio-3-substituted quinazoline-2,4-(1H,3H)diones, pre-

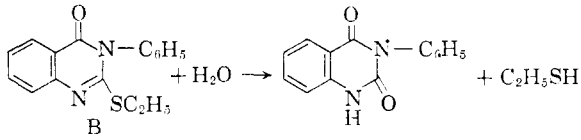


II

R = C_6H_5- or CH_2=$CHCH_2$-

pared by the method of Ghosh.[3] The pertinent data for these compounds, A-K, are summarized in Table I.

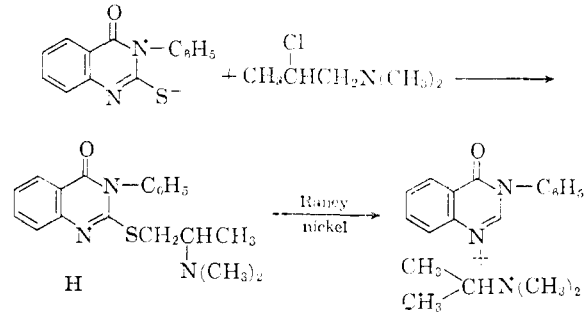
That the alkylation occurred at the sulfur rather than the nitrogen atom was proved for a representative member (B) of the series by hydrolysis to the corresponding mercaptan



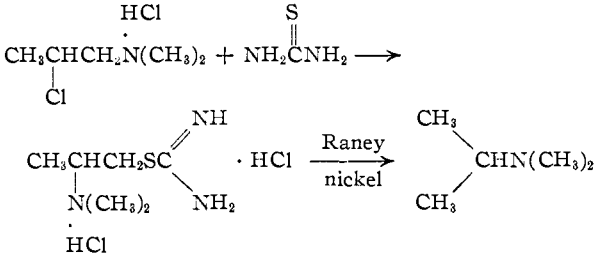
B

The isomeric N-alkylated derivatives corresponding to one (A) of the compounds was prepared by the action of phenyl isothiocyanate on N-methyl-anthranilic acid.[4] The physical properties of the two isomers are markedly different (see Experimental).

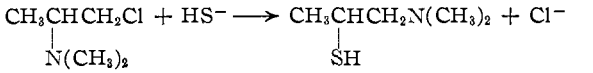
That the alkylation of the sodium salt of 2-thio-3-phenylquinazoline-2,4-(1H,3H)dione with 2-chloro-1-(N,N-dimethylamino)-propane proceeded with rearrangement was demonstrated by Raney nickel desulfurization[5] of the product (H) as outlined.



In a control experiment for this desulfurization, the thiuronium salt prepared from 2-chloro-1-(N,N-dimethylamino)-propane[6] was subjected to the same desulfurization procedure. 2-N,N-



Dimethylaminopropane was isolated (as the picric acid salt), indicating that even under mildly acid conditions such an alkylation occurs with rearrangement.[7] Similar results have been observed under basic conditions by Andrews, Bergel and Morrison.[8]



It has been shown[9] that, under reversible condi-

(1) M. L. Gujral, P. N. Saxena and R. S. Tiwari, *Indian J. Med. Res.*, **43**, 637 (1955); *C. A.*, **50**, 6662 (1956).

(2) W. M. McLamore, S. Y. P'an and G. D. Laubach, Abstracts of Papers, American Chemical Society 133rd Meeting, San Francisco, Calif., April, 1958, p. 12M.

(3) T. N. Ghosh, *J. Indian Chem. Soc.*, **7**, 981 (1930).

(4) See G. Fortmann, *J. prakt. Chem.*, [2] **55**, 123 (1897).

(5) (a) R. Mozingo, D. E. Wolf, W. A. Harris and K. Folkers, This Journal, **65**, 1013 (1943); (b) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughn, Jr., *ibid.*, **67**, 290 (1945); (c) J. A. Zderic, W. A. Bonner and T. W. Greenlee, *ibid.*, **79**, 1696 (1957).

(6) See R. R. Renshaw, P. F. Dreisbach, M. Ziff and D. Green, This Journal, **60**, 1765 (1938).

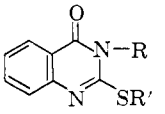
(7) Control experiments have demonstrated that 1-N,N-dimethylaminopropane is not isomerized to 2-N,N-dimethylaminopropane under the conditions employed in these experiments (see Experimental).

(8) K. J. M. Andrews, F. Bergel and A. L. Morrison, *J. Chem. Soc.*, 3483 (1954).

(9) (a) J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, This Journal, **69**, 2961 (1947); (b) W. R. Brode and M. W. Hill, *ibid.*, **69**, 724 (1947); (c) E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948); (d) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948);

TABLE I

2-ALKYLTHIO-4-(3H)QUINAZOLONES



Compound	R	R'	Method	M.p., °C.[a]	Yield, %	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
A	C_6H_5	CH_3	A	130–130.5	99	$C_{15}H_{12}N_2OS$	67.2	67.2	4.5	4.7	10.4	10.4
B	C_6H_5	C_2H_5	A	117–118	80	$C_{16}H_{14}N_2OS$	68.1	68.1	5.0	5.0	9.9	9.8
C	C_6H_5	C_3H_7	A	133–135.5	54	$C_{17}H_{16}N_2OS$	68.9	69.0	5.4	5.5	9.5	9.5
D	C_6H_5	$(CH_3)_2CH$	A	129–129.5	55	$C_{17}H_{16}N_2OS$	68.9	68.7	5.4	5.7	9.5	9.7
E	C_6H_5	C_4H_9	A	131–133	95	$C_{14}H_{18}N_2OS$	69.7	69.6	5.9	6.0	12.0	12.2
F	C_6H_5	$C_6H_5CH_2$	A	176.5–177	95	$C_{21}H_{16}N_2OS$	73.2	72.9	4.7	4.5	8.1	8.1
G	C_6H_5	$(C_2H_5)_2N(CH_2)_2$[c]	B	84.5–85	56	$C_{20}H_{23}N_3OS$	68.0	68.0	6.6	6.7	11.9	11.8
H	C_6H_5	$(CH_3)_2NCH(CH_3)CH_2$[c]	B	159.5–160.5	50	$C_{19}H_{21}N_3OS$	67.2	67.2	6.2	6.3	12.4	12.6
I	C_6H_5	$(CH_3)_2N(CH_2)_2$[c]	B	109–109.5	43	$C_{18}H_{19}N_3OS$	66.4	66.4	5.9	6.1	12.9	12.8
J	CH_2=$CHCH_2$	p-$CH_3OC_6H_4CH_2$[d]	A	85–86	76	$C_{19}H_{18}N_2O_2S$	67.4	67.6	5.4	5.4	8.3	8.2
K	CH_2=$CHCH_2$	o-$ClC_6H_4CH_2$	A	75.5–76	89	$C_{18}H_{15}ClN_2OS$	63.1	63.1	4.4	4.4	8.2	8.5

[a] Melting points were taken on a Kofler hot-stage and are uncorrected. [b] Microanalyses are by Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y. [c] Samples of N,N-diethylaminoethyl chloride hydrochloride, N,N-dimethylaminoethyl chloride hydrochloride and 2-(N,N-dimethylamino)-propyl chloride hydrochloride were kindly supplied by Michigan Chemical Corp., St. Louis, Mich. [d] A sample of anisyl chloride was kindly supplied by Trubek Laboratories, East Rutherford, N. J.

tions, 1-chloro-2-(N,N-diethylamino)-propane is isomerized to the 2-substituted-1-(N,N-diethylamino)-propane. Under apparently irreversible conditions, however, 2-chloro-1-(N,N-diethylamino)-propane is converted to 2-(N,N-diethylamino)-1-propanol.[10] Hine[11] has suggested that in an irreversible attack on an unsymmetrical immonium or sulfonium ion the product resulting from attack at the primary position may perhaps be favored, whereas in a reversible reaction the predominant product is simply the more stable of the two isomers.

Pharmacological testing of these compounds is in progress and will be reported at a future date.

Experimental

2-Thio-3-phenylquinazoline-2,4-(1H,3H)dione was prepared by the method of Ghosh[8] in 72% yield, m.p. 310–311°, reported[12] 304–306°.

2-Thio-3-allylquinazoline-2,4-(1H,3H)dione was prepared by the method of Ghosh[8] in 75% yield, m.p. 210–210.5°, reported[8] 206–207°.

2-Benzylthio-3-phenyl-4-(3H)quinazolone (Method A).—To a solution of 5.00 g. (0.125 mole) of sodium hydroxide in 100 ml. of 50% aqueous ethanol, 10.0 g. (0.0390 mole) of 2-thio-3-phenylquinazoline-2,4-(1H,3H)dione was added and the resulting mixture was stirred until solution was complete (about 10 minutes). Benzyl chloride (6.0 g., 0.048 mole) was then added and the solution was stirred for one hour at 23–25°. After cooling of the resulting mixture to 0°, the product was removed by filtration, washed with water and air-dried to yield 12.8 g. (95%) of white needles, m.p. 176–177°. Recrystallization of the product from aqueous ethanol gave pure 2-benzylthio-3-phenyl-4-(3H)-quinazolone (F), m.p. 176.5–177°.

2-(2'-N,N-Diethylaminoethylthio)-3-phenyl-4-(3H)-quinazolone (Method B).—To a solution of 10.0 g. (0.250 mole) of sodium hydroxide in 170 ml. of 50% aqueous ethanol, 15.0 g. (0.0590 mole) of 2-thio-3-phenyl-2,4-(1H,3H)-quinazolindione was added and the resulting mixture was stirred until solution was complete. N,N-Diethylaminoethyl chloride hydrochloride (10.3 g., 0.0590 mole) was added and the resulting solution stirred for 10 hours at 23–25°. Water (350 ml.) was added, and the mixture was cooled to 0°. The product was removed by filtration, washed with water and dried. One crystallization from aqueous ethanol gave 11.6 g. (56%) of pure 2-(2'-N,N-diethylaminoethylthio)-3-phenyl-4-(3H)quinazolone (I), white needles, m.p. 84–85°. A second crystallization from aqueous ethanol gave white needles, of pure product, m.p. 84.5–85°.

Hydrolysis of 2-Ethylthio-3-phenyl-4-(3H)quinazolone.—To a solution of 2.24 g. of 2-ethylthio-3-phenyl-4-(3H)-quinazolone (B) (m.p. 117–118°) in 30 ml. of 95% ethanol, 60 ml. of 6 *N* hydrochloric acid was added and the resulting solution was heated under reflux for 4 hours. A trap containing 0.7 g. of sodium hydroxide was connected to the top of the reflux condenser during this period.

On cooling of the reaction mixture to 0°, 1.75 g. of white needles, m.p. 186.5–187° (one crystallization from ethanol), separated and were removed by filtration. The mixed m.p. with authentic 3-phenyl-2,4-(1H,3H)quinazolindione (m.p. 187–187.5°) was 186.5–187.5°.

The contents of the sodium hydroxide trap were added to a solution of 2.1 g. of 2,4-dinitrochlorobenzene, and 0.60 g. of ethyl 2,4-dinitrophenyl sulfide, m.p. 115–116.5°, reported[13] 115°, was isolated. This material (0.50 g.) was converted[13] to ethyl 2,4-dinitrophenylsulfone, m.p. 159.5–160°, reported[13] 160°, in 70% yield.

2-Thio-1-methyl-3-phenylquinazoline-2,4-(1H,3H)dione.—To a solution of 15.0 g. of N-methylanthranilic acid and 8.0 g. of pyridine in 40 ml. of absolute ethanol, 13.5 g. of phenyl isothiocyanate was added, and the resulting solution was heated under reflux for 6 hours. The product was removed by filtration and recrystallized from benzene–ethanol to give 20.1 g. of 2-thio-1-methyl-3-phenylquinazoline-2,4-(1H,3H)dione, white needles, m.p. 302.5–303°, reported[4] 288–289°.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.2; H, 4.5; N, 10.5. Found: C, 67.2; H, 4.4; N, 10.3.

Desulfurization of 2-(2'-N,N-Dimethylaminopropylthio)-3-phenyl-4-(3H)quinazolone.—To a solution of 1.5 g. of 2-(2'-N,N-dimethylaminopropylthio)-3-phenyl-4-(3H)quinazolone in 100 ml. of absolute ethanol, 2.0 g. of W-6 Raney nickel catalyst[14] was added and the resulting mixture was heated under reflux for 90 minutes. The catalyst powder was removed by filtration and the filtrate was distilled through a short-path still. A saturated solution of picric acid in 95% ethanol was added to the first 50-ml. fraction of the distillate until the resulting solution was neutral to moist litmus. Concentration of this solution gave 320 mg. of dimethylisopropylammonium picrate, m.p. 242–243° dec., reported[15] 240–241° dec.

(e) E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949); (f) P. Ofner, *ibid.*, 1800 (1951).

(10) (a) S. D. Ross, THIS JOURNAL, **69**, 2982 (1947); (b) R. H. Reitsema, *ibid.*, **71**, 2041 (1949); (c) E. M. Schultz, C. M. Robb and J. M. Sprague, *ibid.*, **69**, 188, 2454 (1947).

(11) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 121.

(12) B. Pawlewski, *Ber.*, **38**, 131 (1905).

(13) See R. W. Bost, J. O. Turner and R. D. Norton, THIS JOURNAL, **54**, 1985 (1932).

(14) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

(15) T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 2607 (1932).

The residue from the distillation was recrystallized four times from aqueous ethanol to give 430 mg. of the starting quinazolone (m.p. 159–160.5°) and 350 mg. of 3-phenyl-4-(3H)quinazolone, m.p. 142–142.5°, reported[16] 139°.

Control Experiment.—To a solution of 0.90 g. of 1-N,N-dimethylaminopropane[17] in 100 ml. of absolute ethanol, 2.0 g. of W-6 Raney nickel catalyst[14] was added and the resulting mixture was heated under reflux for 90 minutes. Dimethyl-*n*-propylammonium picrate, 480 mg., m.p. 111–112°, reported[18] 108–109°, was isolated by the procedure described above.

Desulfurization of 2-N,N-Dimethylamino-1-propylthiuronium Chloride Hydrochloride.—To a solution of 1.0 g. of 2-N,N-dimethylamino-1-propylthiuronium chloride hydrochloride (m.p. 202–204°) prepared by the method of Renshaw, Dreisbach, Ziff and Green[19] in 100 ml. of absolute ethanol, 2.0 g. of W-6 Raney nickel catalyst[14] was added and the resulting mixture was heated under reflux for 90 minutes. The catalyst powder was removed by filtration and the filtrate was distilled through a short-path still. A saturated solution of picric acid in 95% ethanol was added to the first 50-ml. fraction of the distillate until the solution was neutral to moist litmus. Concentration of this solution gave 270 mg. of dimethylisopropylammonium picrate, m.p. 242–243° dec., reported[15] 240–241° dec.

Acknowledgment.—The authors gratefully acknowledge the generous financial support of the Smith, Kline and French Laboratories, Philadelphia, Penna.

(16) C. Paal and M. Busch, *Ber.*, **22**, 2683 (1889).

(17) See L. Spialter and J. A. Pappalardo, *J. Org. Chem.*, **22**, 840 (1957).

(18) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927).

(19) This compound was assigned the 1-N,N-dimethylamino-2-propylthiuronium chloride hydrochloride structure by these workers.

LAWRENCE, KAN.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

The Constituents of *Ecballium elaterium* L. X.[1,2] Proposed Structures for Elatericin A and B

BY DAVID LAVIE AND YOUVAL SHVO

RECEIVED JUNE 22, 1959

Elatericin A has been oxidized with bismuth oxide to elatericin B. These naturally occurring compounds have been identified as tetracyclic triterpenes. Full structures are proposed on the basis of various degradation products.

The oxygen functions and the side chain of elatericin A (Ia) (cucurbitacin D) have been previously described,[3–6] and one oxygen atom out of seven was left undetermined. It is the object of the present paper to identify all the functions, and discuss their respective positions in a proposed full structure. In view of the strong tumor necrotizing properties of this group of compounds,[7a,8] the results of this investigation which culminate with the presentation of a full structure are of interest in the chemotherapy of cancer.

Elatericin A belongs to a group of compounds, isolated from different species of the Cucurbitaceae, for which the general name of cucurbitacins has been proposed.[9] Inasmuch as the respective interrelationship among four of these compounds has been proved by interconversion and a common degradation product, the elucidation of the structure of elatericin A provides information regarding most of the structural features of the whole group.[10] Since 1,2,8-trimethylphenanthrene was isolated from the selenium dehydrogenation of elatericin A, the latter substance as well as cucurbitacin A, C and E (α-elaterin) have most probably tetracyclic triterpenoid structures.[11] Furthermore, the identification of the side chain as shown in Ia supports such a structure, and accounts for three oxygenated groups in that chain.[6]

During periodic acid oxidation of elatericin A (Ia) two moles of the reagent are consumed, one mole being used up for the cleavage of the side chain. The hydroxyl group vicinal to the α,β-unsaturated ketone in this chain, has been previously assumed to be secondary.[3] This assumption was made when it was observed that elatericin A diacetate (Ib) seemed to withstand periodate oxidation. However, it was found subsequently that an uptake of the oxidizing agent does occur at a very slow rate.[12] The water-insoluble moiety of the periodic fission, the bulk of the molecule, possessed a methyl ketone, and was a diacetate which analyzed for $C_{28}H_{38}O_7$; it gave a positive iodoform test, and the infrared spectrum of the carbonyl region displayed bands at 1729 (broad) and 1700 cm.$^{-1}$ (overlapping of hindered and methyl ketone); no hydroxyl or aldehyde bands were recorded; the ultraviolet spectrum showed a weak maximum at 288 mμ (ϵ 200). This oxidation product, hexanorelatericin A diacetate, has therefore structure IIb, and the origin of the methyl ketone is the tertiary hydroxyl neighboring a methyl group in the side chain as shown in I.

(1) This investigation was supported by a research grant C-2810(C2) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Part IX, D. Lavie and D. Willner, *Proc. Chem. Soc.*, 191 (1959).

(3) D. Lavie and Y. Shvo, *Proc. Chem. Soc.*, 220 (1958).

(4) D. Lavie, Y. Shvo and D. Willner, *Chemistry & Industry*, 1361 (1958).

(5) D. Lavie and Y. Shvo, THIS JOURNAL, **81**, 3058 (1959).

(6) D. Lavie, Y. Shvo and D. Willner, *ibid.*, **81**, 3062 (1959).

(7) (a) D. Lavie and D. Willner, *ibid.*, **80**, 710 (1958). (b) In this publication a wrong interpretation of the acetylation product of elatericin B has been given. A careful examination of the infrared spectrum of the diacetate taken in KBr pellet disclosed a shoulder at 1757 and a band at 1200 cm.$^{-1}$ for an enol acetate. Further, the ultraviolet absorption maximum at 231 mμ (ϵ 20,500) indicated unequivocally such a system. Of the two acetoxy groups occurring in elatericin B diacetate, one is therefore an enol acetate.

(8) D. Lavie, D. Willner, M. Belkin and W. G. Hardy, presented at the Symposium on the Chemotherapy of Cancer, Tokyo, October, 1957, abstracts, p. 53; *ACTA, Unio Int. Contra Cancrum*, **15 bis**, 177 (1959).

(9) P. R. Enslin, S. Rehm and D. E. A. Rivett, *J. Sci. Food Agric.*, **8**, 673 (1957), and other papers in this series.

(10) D. Lavie, Y. Shvo and D. Willner; P. R. Enslin, J. M. Hugo and K. B. Norton, *Chemistry & Industry*, 951 (1959).

(11) D. E. A. Rivett and P. R. Enslin, *Proc. Chem. Soc.*, 301 (1958).

(12) D. Lavie and Y. Shvo, *Chemistry & Industry*, 429 (1959); this reference is part VIII in this series.