lized with isopropyl ether. Recrystallization of the solid from isopropyl ether gave 6.8 g (92%) of *erythro*-(−)-2-methyl-2-(α-methyl-β-ethoxyphenethyl)-*p*-toluic acid hydrazide: mp 124–125; ν_{max} (mull) 3240 sharp (NH), 1645 (hydrazide carbonyl), and 1085, 1075 (ether) cm^{-1}; nmr, $J_{\alpha-\beta}$ 2.4 cps, C_2H_5O shown as triplet at −1.3 ppm and quartet at −3.5 ppm; $[\alpha]^{27}D$ −50.63° (*c* 2.5, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03. Found: C, 73.59; H, 7.86.

Acknowledgment.—The authors express their appreciation to Dr. J. Heeschen, Chemical Physics Laboratory, for recording and interpreting nmr spectra.

The Chemical, Spectral, and Biological Properties of Monomethine Cyanine Dyes Containing 1,3-Benzoxazine and Quinazoline Nuclei

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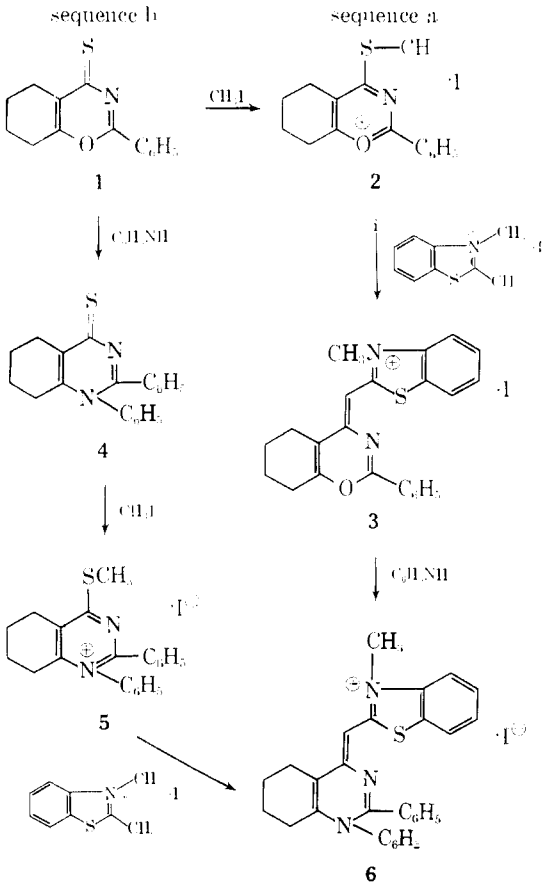
The quaternary salts, 5,6,7,8-tetrahydro-4-methylthio-2-phenylbenzoxazin-1-ium iodide and 5,6,7,8-tetrahydro-1,2-disubstituted 4-methylthioquinazolin-1-ium iodides readily interact with the alkyl iodide salts of 2-methylbenzoxazole, 2-methylbenzothiazole, and 2-methylquinoline to yield monomethine cyanine dyes. The chemical, spectral, and biological properties of these substances are discussed.

The principal use of quaternary nitrogen containing heterocycles has been in the synthesis of cyanine dyes.[1] Although virtually all such heterocyclic compounds have been studied extensively in this regard, the quinazoline group has received relatively little attention.[2-4] This is particularly evident in the case of the quaternary salts of 4-methylthioquinazoline since it has remained undetermined whether the 1- or the 3-nitrogen becomes quaternarized in the reaction of the heterocyclic base with the alkyl halide.[5] It appeared to us that this difficulty could be easily circumvented if the N-1 of the heterocyclic base were already substituted.

In a previous communication from our laboratory, we reported on the synthesis of 5,6,7,8-tetrahydro-1,2-disubstituted quinazoline-4-thiones *via* condensation of morpholinocyclohexene with aroyl isothiocyanates or interaction of 5,6,7,8-tetrahydro-2-substituted 1,3-benzoxazine-4-thione with primary amines.[6] Another aspect of this study has shown that such tetrahydroquinazolines can be readily formed through condensation of morpholinocyclohexene with N-substituted-imidoyl isothiocyanates.[7,8] Consequently, the resulting heterocycles readily lent themselves to quaternarization to form reactive intermediates which could be employed in cyanine dye synthesis. In Scheme I are shown two sequences whereby the desired dyes were prepared.

In sequence a, 5,6,7,8-tetrahydro-2-phenyl-1,3-benzoxazine-4-thione (**1**) was quaternarized according to the method of Hünig and Hübner[9] to 5,6,7,8-tetrahydro-4-methylthio-2-phenyl-1,3-benzoxazin-1-ium iodide (**2**).

SCHEME I

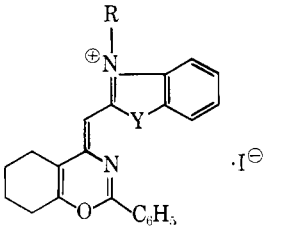


The latter substance was then allowed to react with the appropriate heterocyclic intermediate containing an activated methyl group (*e.g.*, 2-methylbenzothiazole methiodide). In this way, for example, there was formed a 40% yield of 2-[(5,6,7,8-tetrahydro-2-phenyl-4H-1,3-benzoxazin-4-ylidene)methyl]-3-methylbenzothiazolium iodide (**3**). Compound **3** was dissolved in aniline[10] and the resulting solution was heated under

(1) F. Hamer in "Chemistry of Heterocyclic Compounds," The Cyanine Dyes and Related Compounds, Vol. 18, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964.
(2) W. König, German Patent 410,487 (June 4, 1922).
(3) F. M. Hamer, I. M. Heilbron, J. H. Reade, and H. M. Walls, *J. Chem. Soc.*, 251 (1932).
(4) R. M. Anker and A. H. Cook, *ibid.*, 489 (1944).
(5) J. D. Kendall, British Patent 425,609 (Sept 12, 1933).
(6) R. W. J. Carney, J. Wojtkunski, and G. deStevens, *J. Org. Chem.*, **29**, 2887 (1964).
(7) H. M. Blatter and H. Lukaszewski, *ibid.*, **31**, 722 (1966).
(8) G. deStevens, H. M. Blatter, and R. W. J. Carney, *Angew. Chem.*, **78**, 125 (1966).
(9) S. Hünig and K. Hübner, *Chem. Ber.*, **95**, 937 (1962).
(10) In sequence a and b aniline has been used for illustrative and brevity purposes. However, it is emphasized that most primary amines can be used in these reactions.

TABLE I

5,6,7,8-TETRAHYDRO-1,3-BENZOXAZINE DYES

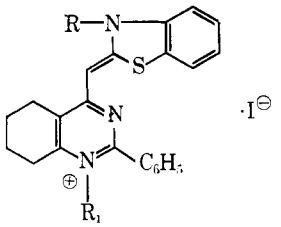


Compd	R	Y	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	λ_{max}^{MeOH}, mμ	ε
3	CH_3	S	310–311[a]	$C_{23}H_{21}IN_2OS$	55.21	54.92	4.23	4.17	5.60	5.70	440	36,940
9	C_2H_5	S	290–291[a]	$C_{24}H_{23}IN_2OS$	56.04	56.09	4.51	4.76	5.45	5.24	440	39,480
10	CH_3	O	269–270[b]	$C_{23}H_{21}IN_2O_2$	57.03	56.60	4.37	4.43	5.79	5.60	405, 417	39,010, 38,820
11	CH_3	CH=CH	274–275[b]	$C_{25}H_{23}IN_2O$	60.73	60.89	4.69	4.81	5.67	5.84	444	42,930
12	C_2H_5	CH=CH	262–264[b]	$C_{26}H_{25}IN_2O$	61.42	61.19	4.96	5.02	5.51	5.49	444	45,100

[a] Recrystallized from methanol. [b] Recrystallized from ethanol.

TABLE II

5,6,7,8-TETRAHYDROQUINAZOLINE DYES



Compd	R	R_1	Method of synthesis	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	λ_{max}^{MeOH}, mμ	ε
6	CH_3	C_6H_5	A, B	312–314[a]	$C_{29}H_{26}IN_3S$	60.52	60.46	4.56	4.86	7.30	6.63	448	87,360
13	CH_3	$(CH_2)_9CH_3$	B	214–215[a]	$C_{33}H_{42}IN_3S$	61.99	61.92	6.62	6.58	6.59	6.40	449	85,290
14	CH_3	*p*-FC_6H_4	A, B	271–272[a]	$C_{29}H_{25}FIN_3S$	58.68	58.31	4.25	4.45	7.09	6.73	450	78,490
15	CH_3		A	266–267[b]	$C_{25}H_{26}IN_4S$	58.33	57.75	4.38	4.60	9.72	9.31	452	80,710
16	CH_3	$CH_2CH_2N(C_2H_5)_2$	A	192–193[a,c]	$C_{29}H_{38}IN_4S$	57.75	57.79	6.41	6.33	8.69	8.77	449	79,841
17	CH_3		A	314–315[b]	$C_{31}H_{31}IN_4S$	60.19	60.17	5.05	5.28	9.07	8.79	449	87,600
18	CH_3	$CH_2CH_2N(CH_3)_2$	A	228–230[b]	$C_{27}H_{31}IN_4S$	56.84	57.00	5.47	5.65	9.83	9.57	447	77,840
19	C_2H_5	$(CH_2)_9CH_3$	A	241–243[a]	$C_{34}H_{44}IN_3S$	62.51	62.28	6.78	6.87	6.44	6.40	446	85,100
20	C_2H_5	*p*-FC_6H_4	A	285–287[a]	$C_{30}H_{27}FIN_3S$	59.31	59.33	4.48	4.56	6.92	6.94	450	81,160

[a] Recrystallized from ethanol. [b] Recrystallized from methanol. [c] Analysis includes 1 mole of ethanol.

reflux to give rise to **6** in 39% yield. It was also possible to prepare **6** *via* sequence b. Thus, **4**, prepared as previously described,[6-8] was converted to **5** which in turn readily condensed with 2-methylbenzothiazole methiodide to give a 52% yield of 2-[(5,6,7,8-tetrahydro-1,2-diphenyl-4(1H)-quinazolinylidene)methyl]-3-methylbenzothiazolium iodide (**6**). Other methine cyanine dyes prepared in this investigation are listed in Tables I–IV.

We have noted that cyanine dyes containing the 5,6,7,8-tetrahydro-1,3-benzoxazine nucleus have not been heretofore reported. The essentially unique features associated with **6** and related substances are (a) cyanine dyes of the quinazoline class have now been synthesized in which the substituent on nitrogen is fixed to position 1, and (b) for the first time quinazoline cyanine dyes have been prepared in which the quaternary nitrogen (N-1 in this case) is directly substituted with an aromatic group.

Spectral Properties.—Several features concerning the ultraviolet absorption spectra of these dyes are of interest. First of all, within the group comprising the 5,6,7,8-tetrahydro-1,3-benzoxazinium cyanines (see Table I), the compound containing the benzoxazole nucleus gave two maxima at 405 and 417 mμ. The absorption maximum for **3** was observed at 440 mμ and the maximum for 2-[(5,6,7,8-tetrahydro-2-phenyl-4H-1,3-benzoxazin-4-ylidene)methyl]-2-methylquinolin-1-ium iodide was seen at 444 mμ. Therefore, a rather small bathochromic shift (only 4 mμ) was noted in going from a cyanine containing benzothiazole to a heterocycle of greater basicity such as 2-quinoline.[11] The pronounced bathochromic shift in going from benzoxazole-containing cyanine to that containing benzothiazole is in keeping with the greater basicity of the latter heterocycle.

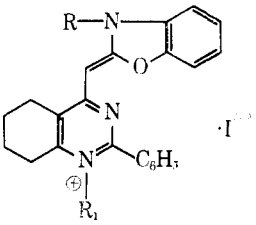
The ultraviolet absorption spectra of the 5,6,7,8-tetrahydroquinazolium dyes appeared to be more consistent with the Brooker rules.[12]

(11) L. G. S. Brooker, "Frontiers in Chemistry," Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1945.

(12) L. G. S. Brooker, Abstracts, I.U.P.A.C., Zürich, 1956; also see ref 1, Chapter 16, p 685.

TABLE III

5,6,7,8-TETRAHYDROQUINAZOLINE DYES

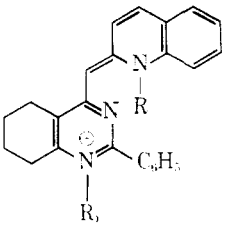


Compd	R	R_1	Method of synthesis	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	λ_{max}^{MeOH}, mμ	ε
21	CH_3	$(CH_2)_8CH_3$	A	190–191[a]	$C_{32}H_{42}IN_3O$	63.55	63.74	6.79	6.98	6.76	6.50	424	76,490
22	C_2H_5	$(CH_2)_8CH_3$	A	190–192[a]	$C_{34}H_{44}IN_3O$	64.04	63.84	6.95	7.19	6.59	6.75	424	80,440
23	C_3H_7	$(CH_2)_8CH_3$	A	174–176[a]	$C_{36}H_{46}IN_3O$	64.50	64.71	7.11	7.24	6.45	6.39	425	80,790
24	n-C_4H_9	$(CH_2)_8CH_3$	A	75–76[c]	$C_{38}H_{48}IN_3O$	64.95	64.82	7.26	7.35	6.32	6.15	425	79,200
25	C_2H_5	$(CH_2)_7CH_3$	A	221–223[a]	$C_{33}H_{40}IN_3O$	63.04	63.23	6.61	6.82	6.89	6.61	424	84,840
26	C_2H_5	$(CH_2)_{10}CH_3$	A	181–183[a]	$C_{35}H_{46}IN_3O$	64.50	64.49	7.11	7.26	6.45	6.47	424	76,450
27	CH_3	p-FC_6H_4	B[b]	272–274[c]	$C_{29}H_{25}F1N_3O$	60.32	60.19	4.37	4.75	7.29	7.05	427	73,420

[a] Recrystallized from 2-propanol. [b] Reaction run in dimethyl sulfoxide at steam-bath temperature. [c] Recrystallized from methanol.

TABLE IV

5,6,7,8-TETRAHYDROQUINAZOLINE DYES



Compd	R	R_1	Method of synthesis	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	λ_{max}^{MeOH}, mμ	ε
28	CH_3	$(CH_2)_8CH_3$	A	147–149[a]	$C_{36}H_{44}IN_3$	66.34	66.53	7.00	7.07	6.63	6.43	328, 467, 493	7300, 58,380, 93,070
29	CH_3	p-FC_6H_4	A	220–223[a]	$C_{31}H_{25}F1N_3$	63.38	63.67	4.64	4.76	7.15	7.06	324, 465, 492	8460, 59,970, 97,480
30	C_2H_5	p-FC_6H_4	B	252–253[a]	$C_{32}H_{28}F1N_3$	63.90	63.32	4.86	4.88	6.99	6.60	322, 465, 493	8560, 58,940, 98,620

[a] Crystallized from ethanol.

Compounds of type **6** (Scheme I) containing the benzoxazole moiety absorb at approximately 424 mμ, whereas the benzothiazole-containing derivatives cause a bathochromic shift of 25 mμ to give a maximum at 449 mμ. This is in accordance with the greater basicity of benzothiazole relative to benzoxazole. The additional bathochromic shift in going from benzothiazole- to 2-quinoline-containing dyes (*i.e.*, principal maxima at 328, 467, and 493 mμ) is again due to the greater basicity of the 2-quinoline moiety.

It is worthy of note that the tetrahydrobenzoxazinium dyes absorbed at shorter wavelengths than the corresponding tetrahydroquinazolinium dyes. Moreover, the extinction coefficients of the latter substances are at least twice as great as the former. These differences can be attributed to the significant contribution to resonance stabilization by the unshared pair of electrons on the N-1 of the tetrahydroquinazoline.

Finally, it was of interest to determine the effect of variation of substituent on N-1 of the quinazoline moiety on the absorption maximum of these cyanines. In this study only the methine cyanine system containing the tetrahydroquinazoline and benzothiazole moieties was investigated extensively. All parameters were fixed with the exception of substituent changes on N-1. Surprisingly, it was observed that these changes had little, if any, influence on the absorption maximum.

Biological Properties.—Browning[13] and co-workers for a number of years evaluated several members of the cyanine dye class for their chemotherapeutic effects. However, none of these substances was found to have useful properties. Dewar[14] in 1944 prepared some symmetrical trimethine cyanines with complex nuclei for testing as antimalarials, but these were also found to be ineffective. A few years later Brooker and Sweet reported that certain cyanine dyes exhibited pronounced antifilarial, anthelmintic, antimalarial, and antibacterial properties.[15] The first therapeutically useful cyanine was bis{6-dimethylamino-2-[2-(2,5-dimethyl-1-phenyl-3-pyrrolyl)vinyl]-1-methylquinolinium} 4,4′-methylenebis(3-hydroxy-2-naphthoate) (**7**) (pyrvinium pamoate). This compound is a potent

(13) C. H. Browning, J. B. Cohen, S. Ellingworth, and R. Gulbransen, *Proc. Roy. Soc.* (London), **B100**, 293 (1926); **103**, 404 (1928); **105**, 99 (1929); **110**, 372 (1932).

(14) M. J. S. Dewar, *J. Chem. Soc.*, 615 (1944).

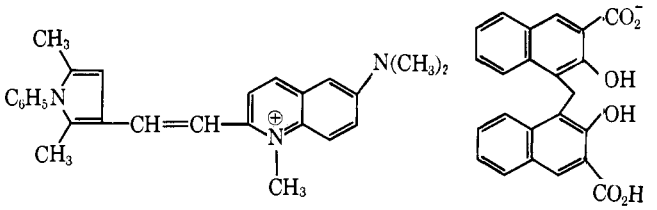
(15) L. G. S. Brooker and L. A. Sweet, *Science*, **105**, 496 (1947).

TABLE V

ANTIMICROBIAL AND ANTHELMINTIC ACTIVITIES OF CERTAIN CYANINE DYES GROUPED ACCORDING TO THEIR STRUCTURES AS SHOWN IN TABLES I–IV

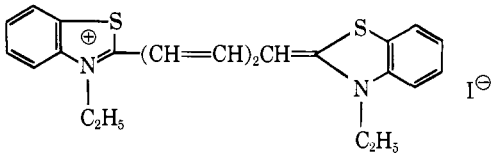
Compd	Minimum inhib concn,[a] μg/ml, *in vitro vs.* Gram-positive bacteria[b]	Gram-negative bacteria[c]	Yeasts[d]	*Trichophyton mentagrophytes*	Dose, mg/kg, and oral activity[e] *vs. Nippostrongylus brasiliensis* in mice
Group I					
3	1–2	20–200	1–4	200	100 Inactive
9	2–4	10–200	<1–4	>200	100 Inactive
10	20–50	50–200	10–50	>200	100 Inactive
11	1–20	50–200	0.5–20	>200	200 Inactive
12	2–10	10–200	<1–2	200	200 Inactive
Group II					
6	1–4	10–50	2–4	200	100 Inactive
13	1–4	10–20	1–4	100	100 Active, 50 inactive
14	1–4	50–200	4–10	200	250 Inactive
15	2–20	50–200	4–50	>200	100 Inactive
16	4–10	20–50	10–20	>200	100 Inactive
17	2–50	50–200	10–20	50	100 Inactive
18	2–20	10–200	10–50	200	100 Inactive
19	<1	4–20	<1–2	200	100 Active, 50 inactive
20	4–20	50–200	4–20	20	200 Sl active
Group III					
21	0.5–1	4–10	1	20	100 Active, 50 sl active
22	<1	10	<1	<1	50 Active, 25 inactive
23	<1–2	4	<1	2	50 Active, 25 sl active
24	<1–2	10–20	<1–2	4	50 Active, 25 sl active
25	<0.5–4	20–50	<0.5	2	50 Active, 25 inactive
26	<1–2	10–20	<1	4	100 Sl active
27	1–50	200	50	100	100 Inactive
Group IV					
28	1–2	2–20	0.5–2	1	200 Sl active
29	4–10	50–200	4–10	<200	50 Active
30	4–20	50–200	2–10	200	250 Inactive

[a] Minimum inhibitory concentration is the lowest drug concentration which caused stasis of growth at the following times after inoculation: for bacteria, 1 day; for yeasts, 2 days; for *Trichophyton*, 4 days; for *Mycobacterium*, 7 days. [b] *Diplococcus pneumoniae, Staphylococcus aureus, Mycobacterium tuberculosis.* [c] *Escherichia coli, Pseudomonas aeruginosa, Salmonella choleraesuis.* [d] *Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum.* [e] Active = 75–100% reduction in worm burdens; sl active = 50–74% reduction in worm burdens.



7

oxyuricide presenting a high cure rate following a single dose of 5 mg/kg in humans.[16] Recently, dithiazanine **8** has been reported to show good activity against *Trichuris trichiura* and *Strongyloides stercoralis*.[17]



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Consequently, the compounds described in this paper were submitted for evaluation in our chemotherapy program.

The antimicrobial and anthelmintic activities of the compounds are shown in Table V. The *in vitro* antimicrobial end points were determined by the tube dilution method.[18] The anthelmintic activity was determined in mice treated orally for 3 consecutive days at the dose levels indicated and examined for worms at necropsy the day following the last treatment.[19]

As a group, the compounds listed in Table III had the greatest activity against both the helminths and the microorganisms. Certain representatives of the groups with benzothiazole (Table II) and quinoline (Table IV) had good activity against four of the five test organisms, but none of these substances had as good a spectrum against bacteria, fungi, and helminths as did the compounds of Table III.

Compounds **22**, **24**, and **26** also produced slight activity against *Trypanosoma cruzi* when administered subcutaneously to mice at 5 mg/kg/day for 15 days.[20] This regimen of treatment caused delays in death of from 1 to 2 weeks beyond those of the untreated controls but effected no cures.

(16) J. W. Beck, G. Saavedra, G. J. Antell, and B. Tejeiro, *Am. J. Trop. Med. Hyg.*, **8**, 349 (1959).

(17) F. J. Aquilar, *ibid.*, **8**, 305 (1959).

(18) E. H. Northey, American Chemical Society Monograph Series, No. 106, Reinhold Publishing Corp., New York, N. Y., 1948, p 390.

(19) O. D. Standen in "Experimental Chemotherapy," R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 20.

(20) R. Hewitt, J. Entwistle, and E. Gill, *J. Parasitol.*, **49**, 72 (1963).

Although several of the compounds were able to effect reductions of more than 90% in the worm burdens in mice with *Nippostrongylus brasiliensis*, this activity was only observed at doses near the toxic levels and it appears unlikely that they will be useful in anthelmintic therapy.

Experimental Section[21]

General Procedure for the Preparation of Methine Cyanine Iodides.—The legend in Tables II–IV described the methods whereby the methine cyanines were prepared. A representative example of each of these methods is herein outlined.

Method A.—5,6,7,8-Tetrahydro-4-methylthio-2-phenyl-1,3-benzoxazin-1-ium iodide[9] (23.0 g, 0.06 mole), 2-methylbenzothiazole methiodide (7.5 g, 0.06 mole), 350 ml of ethanol, and 10 ml of triethylamine were combined and heated near reflux for 1 hr. After cooling the reaction mixture, the solid was collected on a filter to yield 14.7 g (49%) of crude material. Recrystallization of this material from methanol yielded 2-[(5,6,7,8-tetrahydro-2-phenyl-4H-1,3-benzoxazin-4-ylidene)methyl]-3-methylbenzothiazolium iodide (**3**). See Table I for analytical data of this substance and other compounds prepared by this method.

(21) Melting points were obtained on a Thomas–Hoover capillary melting point apparatus and are corrected. Ultraviolet spectra were recorded on a Cary 14 recording spectrophotometer.

Compound **3** (1.0 g, 0.002 mole) and 10 ml of aniline were refluxed for 1 hr. Upon cooling, a solid formed which was collected and crystallized from ethanol to yield 400 mg (35%) of 2-[(5,6,7,8-tetrahydro-1,2-diphenyl-4(1H)-quinazolidene methyl]-3-methylbenzothiazolium iodide (**6**).

Method B. 5,6,7,8-Tetrahydro-1,2-diphenyl-4-methylthioquinazolin-1-ium Iodide (5).—To 5,6,7,8-Tetrahydro-1,2-diphenyl-4-quinazolinethione (4.0 g, 0.012 mole) in 200 ml of acetone there was added dropwise 1.7 g (0.012 mole) of methyl iodide. After refluxing the reaction mixture overnight the solvent was removed *in vacuo* to give a yellow solid. Crystallization of this material from acetone gave 3.2 g of **5**, mp 262–263°.

Anal. Calcd for $C_{21}H_{21}IN_2S$: C, 54.78; H, 4.60; N, 6.09. Found: C, 54.63; H, 4.92; N, 5.88.

5,6,7,8-Tetrahydro-1-*p*-fluorophenyl-2-phenyl-4-methylthioquinazolin-1-ium iodide was prepared as above.

Anal. Calcd for $C_{21}H_{20}FIN_2S$: C, 52.72; H, 4.22; N, 5.86. Found: C, 52.67; H, 4.44; N, 5.67.

5,6,7,8-Tetrahydro-1-decyl-2-phenyl-4-methylthioquinazolin-1-ium iodide was prepared as above.

Anal. Calcd for $C_{25}H_{33}IN_2S$: C, 57.24; H, 7.11; N, 5.34. Found: C, 56.94; H, 7.51; N, 5.07.

5,6,7,8-Tetrahydro-1,2-diphenyl-4-methylthioquinazolin-1-ium iodide (**5**) (2.5 g, 0.0054 mole), 2-methylbenzothiazole methiodide (1.6 g, 0.0054 mole), 50 ml of ethanol, and 2 ml of triethylamine were combined and the solution was heated under reflux for 16 hr. After cooling the solution in an ice bath, the crystals were collected and recrystallized from ethanol to yield 1.6 g (52%) of **6**.

Notes

Tremorine-Antagonistic Cyclic Ketals. The Reactions of Epoxy Ethers with Ethylene Chlorohydrin[1]

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As part of a study of unsymmetrical amino ketals possessing pharmacological activity,[3] we have examined the reactions of epoxy ethers (I)[4,5] with ethylene chlorohydrin. In one instance spontaneous rearrangement of Ia to 1-methoxy-1-phenyl-2-propanone was observed.[6] Treatment of Ia with ethylene chlorohydrin afforded a small amount of α-methoxypropiophenone and a mixture of dioxanes (III and IV) (see Scheme I). The strong methoxyl peak (3.2 ppm) of IV was apparent in the nmr spectrum of a crude product mixture (Figure 1a). Purification resulted in the loss of the methoxyl signal and an nmr spectrum consistent with structure III (Figure 1b). The dioxane ring proton quartet at 4.0 ppm (J = 7 cps) was distinguished from the chloroethoxyl multiplet at 3.7 ppm in a 100-Mc spectrum. The second reaction product (IV) was never isolated in pure form and its structure is inferred solely on the basis of the similarity of its nmr spectral features to those of the major product (III) with the additional methoxyl peak and the absence of any obvious differences in the infrared spectra of pure and impure samples of III. In addition, analytical data on impure samples could be rationalized on the presence of amounts of IV consistent with the indications of thin layer chromatograms and nmr spectra. Similarly, no direct evidence is available for the intermediate formation of the monomeric chloro ketal (IIa). The intervention of IIa is probable, however, as analogous compounds were isolated in connection with other epoxy ethers.[3] Furthermore, the dimerization of IIa with elimination of alkoxyl in the presence of excess ethylene chlorohydrin provides a logical route to III and IV. Analogous dimerization of α-hydroxy ketals and acetals has been reported.[3,7] Chemical evidence substantiated the above conclusions. The ketal dioxane (III) was resistant to basic hydrolytic conditions, but unstable in acid media. Treatment of III with hydrochloric acid in aqueous dioxane resulted in a yellow oil believed to be a mixture of the isomeric hydroxy ketones Va and Vb. The infrared spectrum of the yellow oil was similar to that obtained from a sample of Va prepared by the method of Temni-

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