Anthelmintic Quaternary Salts. II. Thiazolium Salts

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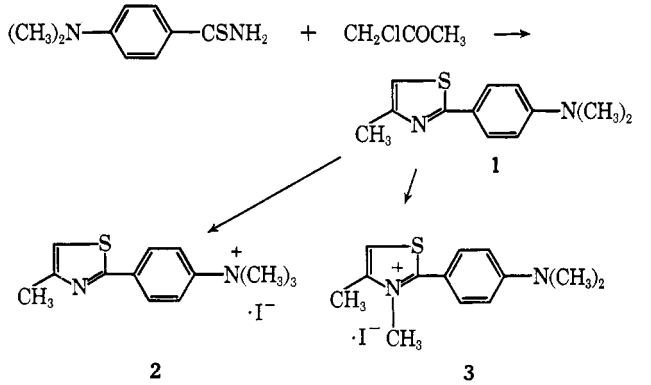
The synthesis of a series of 2-(*p*-dimethylaminophenyl)-3-methylthiazolium salts is described. Several of the compounds with alkyl substituents in the 4 position, or in both 4 and 5 positions, were effective prophylactic agents in protecting pigs from *Ascaris suum* infections.

As part of a continuing program of structure–activity relations among anthelmintics in which two nitrogen atoms bearing a single positive charge are linked by an odd number of methine groups,[1] a series of 2-(*p*-dimethylaminophenyl)-3-methylthiazolium salts were synthesized and evaluated for anthelmintic activity.

Chemistry.—The simplest route to the desired compounds appeared to be the quaternization of 2-*p*-dimethylaminophenylthiazoles. Thus, 2-*p*-dimethylaminophenyl-4-methylthiazole (**1**) (prepared by condensation of *p*-dimethylaminothiobenzamide and chloroacetone) was treated with methyl iodide at 100° (Scheme I). However, both of the possible quaternary salts (**2** and **3**) were formed,[2] and recrystallization of the mixture from methanol gave pure **2**, mp 180–181°. The thiazolium isomer **3** (mp 213°) could not be isolated in good yield from this mixture.

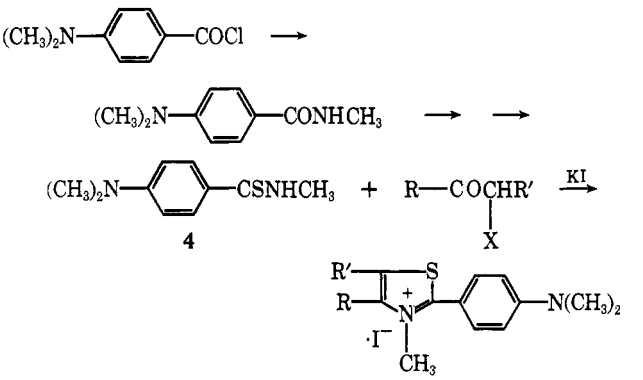
SCHEME I



The isomeric products were readily distinguished by their uv absorption spectra. The thiazole **1** had λ_{max} 342 mμ (400 mμ in acid medium); quaternization to the anilinium isomer **2** caused a hypsochromic shift to λ_{max} 320 mμ, while quaternization to **3** produced a bathochromic shift to λ_{max} 383 mμ. The shift of 17 mμ observed in passing from the protonated thiazolium salt (400 mμ) to the N-methylthiazolium salt (383 mμ) has also been noted in the analogous benzothiazolium compounds[3] and is due to the distortion from coplanarity caused by the methyl group in the quaternized compound.

The formation of the undesired anilinium isomer as a major contaminant (also observed in the quaternization of *p*-2-(dimethylaminophenyl)-4,5,6,7-tetrahydrobenzothiazole) could be avoided by the introduction of the 3-methyl group before closure of the thiazole ring. The condensation of *p*-dimethylamino-N-methylthiobenzamide (**4**) with α-halo ketones and α-haloaldehydes, usually in refluxing 1-propanol, gave the required N-methylthiazolium salts (Scheme II).

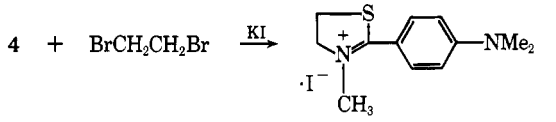
SCHEME II



Compounds **3** and **6–18**, listed in Table I, were prepared in this way from **4** and α-halocarbonyl compounds which were either commercially available or prepared by standard methods. The reaction proceeds *via* an intermediate which could be isolated in some cases. A detailed discussion of the mechanism of this reaction will be the subject of a separate communication.

The parent member of the series, **5**, could not be obtained directly from chloroacetaldehyde, but was prepared in low yield from α,β-dibromoethyl acetate. All of the thiazolium salts had uv maxima in the range 383–389 mμ, except for **11**, in which the 4-phenyl substituent caused a shift to 397 mμ.

In addition to the thiazolium salts, two 2-thiazolinium salts and one dihydro-2-thiazinium salt were prepared for evaluation by condensation with dibromoalkanes. Reaction of **4** with ethylene dibromide in the presence of sodium acetate gave **19**. The 4-ethyl analog **20** (isolated as the perchlorate) and the dihydro-2-thiazinium salt were prepared by analogous reactions with 1,2-dibromobutane and 1,3-dibromopropane.



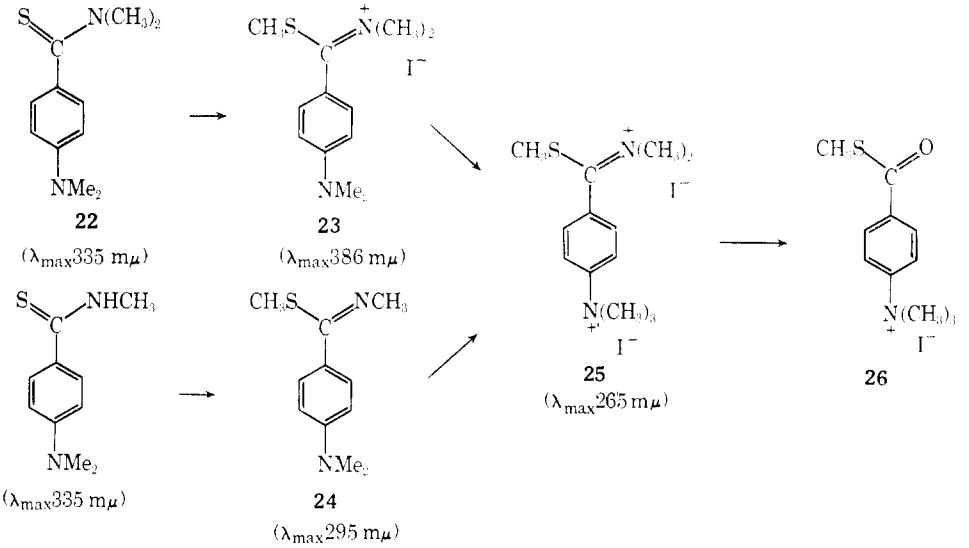
The quaternized thiolimidate **23** was prepared as an open-chain analog of the thiazolium salts to deter-

(1) D. L. Garmaise, C. H. Chambers, J. Komlossy, and R. C. McCrae, *J. Med. Chem.*, **10**, 897 (1967).

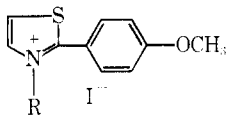
(2) D. L. Garmaise and G. Y. Paris, *Chem. Ind.* (London), 1645 (1967).

(3) A. I. Kiprianov and V. A. Shrubovich, *J. Gen. Chem. USSR*, **26**, 3215 (1956).

mine the importance of the thiazole ring in determining anthelmintic activity. It was prepared by cautious treatment of **22**[4] with methyl iodide. The site of quaternization of **23** was apparent from its uv spectrum, which, with λ_{max} 386 mμ, corresponded exactly to the thiazolium isomers listed in Table I. Unlike the thiazolium salts, however, **23** could be methylated further to the diquaternary salt **25**. The diquaternary salt, which was also prepared from **4** *via* the intermediary thiolbenzimidate **24**, was readily hydrolyzed to yield the thiolbenzoic ester **26**.



Finally, two thiazolium salts with 2-(*p*-anisyl) substituents (**27a** and **27b**) were prepared by standard methods to determine whether or not the *p*-dimethylamino group was essential for anthelmintic activity.



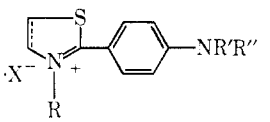
27a, R = CH_3
b, R = C_2H_5

Biological Results.—The compounds were screened initially for activity against *Nematospiroides dubius* and *Ascaris suum* in mice and against a number of gastrointestinal nematodes in lambs. There was no activity against *N. dubius*. Two compounds, **3** (R_1 = CH_3, R_2 = H) and **16** (R_1 = CH_3, R_2 = n-C_4H_9), showed activity against the sheep parasites. However, most of the compounds were very active against *A. suum* in mice, and this led to a study of their prophylactic effectiveness in protecting swine from this parasite. The results are listed in Table II.

A number of thiazolium salts were found to be highly effective in protecting pigs from *A. suum* infections, as evidenced by the virtual absence of larvae in the lungs, and the reduction of liver lesions and lung damage as compared with the unmedicated controls. The unsubstituted thiazolium salt **5** was moderately active, and alkyl substitution in the 4 and 5 positions tended to increase the activity considerably. The most active compounds were **9** and **13**.

The two thiazolinium compounds **19** and **20** were both very active in mice, but **19** was ony moderately active and **20** was inactive in pigs. The dihydrothiazinium derivative **21** was inactive, as was the quaternized thiolimidate **23**. Replacement of the *p*-dimethylamino group by methoxyl caused the elimination of activity. No activity was shown by unquaternized 2-(*p*-dimethylaminophenyl)thiazoles.

The minimum structural requirements for activity in the series may therefore be represented by **28**; the experimental observations were limited to cases in which R = R′ = R″ = CH_3.



28

Experimental Section[5]

***p*-(4-Methyl-2-thiazolyl)phenyltrimethylammonium Iodide (2).**—A solution of *p*-dimethylaminothiobenzamide (prepared by the general method of Taylor and Zoltewicz[6]) (1.8 g, 0.01 mole) and chloroacetone (1 g, 0.01 mole) in EtOH (20 ml) was refluxed for 2 hr. The solution was evaporated and the residue was extracted (H_2O, 150 ml). The aqueous extract was basified and extracted (Et_2O); the ether extract was evaporated and the residue was crystallized from petroleum ether (bp 30–60°) giving 2-(*p*-dimethylaminophenyl)-4-methylthiazole,[7] yield 1.0 g (46%), λ_{max} 342 mμ; sulfate salt in MeOH, λ_{max} 400 mμ.

The thiazole (0.8 g) was heated with MeI (5 ml) at 100° for 30 min. The residue, mp 175–180°, gave two spots on tlc and had uv absorption maxima at 302 and 383 mμ. Crystallization from MeOH gave the pure isomer **2**, mp 180–181°, λ_{max} 302 mμ, yield 1.0 g. *Anal.* ($C_{13}H_{17}IN_2S$) C, H, S; N: calcd, 7.78; found, 7.18.

2-*p*-Dimethylaminophenyl-4,5,6,7-tetrahydrobenzothiazole.—*p*-Dimethylaminothiobenzamide was condensed with 2-chlorocyclohexanone as described above to give the thiazole, mp 142–143° (from MeOH), in 88% yield, λ_{max} 344 mμ; sulfate, λ_{max} 406 mμ. *Anal.* ($C_{15}H_{18}N_2S$) C, H, N, S.

Methylation of the product yielded a mixture of isomers, the uv spectrum of which indicated a preponderance of the anilinium

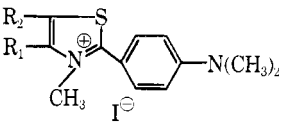
(4) H. Staudinger and N. Kon, *Justus Liebigs Ann. Chem.*, **384**, 38 (1911).

(5) Melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Uv spectra were determined in MeOH using a Beckman DB spectrophotometer.

(6) E. C. Taylor and J. A. Zoltewicz, *J. Amer. Chem. Soc.*, **82**, 2656 (1960).

(7) F. Asinger, M. Thiel, and K. Gewald, *Justus Liebigs Ann. Chem.* **639**, 133 (1961).

TABLE I: 2-(*p*-DIMETHYLAMINOPHENYL)-3-METHYLTHIAZOLIUM IODIDE



No.	Starting ketone	R_1	R_2	Mp, °C	Yield, %	λ_{max}, mμ	Formula[b]
3	CH_3COCH_2Cl	CH_3	H	213 dec	58	383	$C_{13}H_{17}IN_2S$
5	*a*	H	H	220 dec	10	387	$C_{12}H_{15}IN_2S$
6	$CH_3COCHBrCH_3$	CH_3	CH_3	229 dec	51	383	$C_{15}H_{19}IN_2S$
7	$CH_2ClCO(CH_2)_2CH_3$	*n*-C_3H_7	H	198	39	384	$C_{15}H_{21}IN_2S$
8	$CH_3COCHBrC_2H_5$	CH_3	C_2H_5	154–156 dec	22	383	$C_{15}H_{21}IN_2S$
9	$CH_3CHBrCOC_2H_5$	C_2H_5	CH_3	203 dec	30	386	$C_{15}H_{21}IN_2S$
10	$C_2H_5COCHBr(CH_2)_2CH_3$	C_2H_5	*n*-C_3H_7	149 dec	48		$C_{17}H_{25}IN_2S$
11	$C_6H_5COCHBrCH_3$	C_6H_5	CH_3	159–160	64	397	$C_{19}H_{21}IN_2S$
12	$CH_3COCHBrCH(CH_3)_2$	CH_3	*i*-C_3H_7	135 dec	31	389	$C_{16}H_{23}IN_2S$
13	$(CH_2)_4COCHCl$	$(CH_2)_4$		223–224 dec	58	385	$C_{16}H_{21}IN_2S$
14	$(CH_2)_5COCHBr$	$(CH_2)_5$		190 dec	21		$C_{17}H_{23}IN_2S$
15	$CH_2BrCO(CH_2)_4CH_3$	*n*-C_5H_{11}	H	134	33	385	$C_{17}H_{25}IN_2S$
16	$CH_3COCHBr(CH_2)_3CH_3$	CH_3	*n*-C_4H_9	120	70		$C_{17}H_{25}IN_2S$
17	$C_2H_5CHBrCO(CH_2)_2CH_3$	*n*-C_3H_7	C_2H_5	125	28		$C_{17}H_{25}IN_2S$
18	$CH_3COCHBr(CH_2)_7CH_3$	CH_3	*n*-C_8H_{17}	102	26	388	$C_{21}H_{33}IN_2S$

[a] See Experimental Section. [b] All compounds analyzed satisfactorily for C, H, I, N, S, except compound **3** which was analyzed only for C, H, N.

TABLE II

THIAZOLIUM SALTS AND RELATED COMPOUNDS. ACTIVITY AGAINST *Ascaris suum* IN MICE AND IN SWINE

			Ascaris suum		
	Acute toxicity in mice, LD_{50}, mg/kg		In mice[a] lung lesions,	In swine[b] Liver lesions,	Larvae in lungs,
No.	Ip	Oral	% redn	% redn	% redn
3			30		
5	15	50	90	0	80
6	7.5	50	80	90	99
7	7.5	50	70	95	99
8	5	75			
9	10	100	80	99	100
10	3	50	100	99	99
11	75	750	70	20	70
12	150	1500	30	0	10
13	5	75	100	99	100
14	30	150	60		
15	5	75	80	99	100
16			20		
17	100	1000	40	0	0
18	10	150	70		
19	10	50	80	0	50
20	7.5	75	90	30	95
21	15	75	40		
23	20	100	20		
27-a	75	750	20		
27-b	50	500	20		

[a] A dose of 10 mg/kg was administered orally to each of three mice, followed by the administration of an infection of 10^4 embryonated *Ascaris suum* eggs. A second dose of 10 mg/kg was administered 4 hr later. After 8 days the mice were sacrificed and the extent of lung lesions was determined by gross examination of the lungs for the number and size of hemorrhagic areas due to the migration of the *Ascaris* larvae. The table lists the percentage reduction in lung lesions of the treated animals as compared with the unmedicated controls. [b] The test compounds were administered at a level of 0.01% in feed for a period of 10 days to two pigs in concrete-floored pens. An infection of 10^5 embryonated *Ascaris suum* eggs was administered 3 days after the start of the inclusion of the test compound in the feed. The animals were sacrificed after 10 days. The percentage reduction in liver lesions due to migrating *Ascaris* larvae in treated animals as compared with controls was determined by counting the small white scars ("milk spots") found on the surface of the liver. The procedure used to determine the number of larvae in the lungs of the pigs was based on the method described for mice by D. K. Haas (Ph.D. Thesis, University of Wisconsin, Madison, Wis., 1962).

isomer (λ_{max} 320 mμ) over the thiazolium isomer (**13**) (λ_{max} 385 mμ).

***p*-Dimethylamino-N-methylthiobenzamide (4).**—A solution of $MeNH_2$ (14 g, 0.45 mole) in $CHCl_3$ (100 ml) was added to *p*-dimethylaminobenzoyl chloride[3] (13.4 g, 0.073 mole) in $CHCl_3$ (100 ml) at 20°, and the solution was allowed to stand at room temperature. The solution was filtered and the filtrate was washed (H_2O), dried, and evaporated. The residue was crystallized (C_6H_6), giving *p*-dimethylamino-N-methylbenzamide, mp 134–136°, yield 9.5 g (73%). *Anal.* ($C_{10}H_{14}N_2O$) C, H, N.

p-Dimethylamino-N-methylbenzamide (70.0 g, 0.43 mole) was added to P_2S_5 (24.2 g, 0.11 mole) in pyridine (150 ml) and the solution was refluxed for 1 hr. Dilution with ice and H_2O gave the crude product, mp 183–185°, yield 75.0 g (90%). Recrystallization from EtOH raised the melting point to 188–190°, λ_{max} 335 mμ. *Anal.* ($C_{10}H_{14}N_2S$) C, H, N, S.

2-(*p*-Dimethylaminophenyl)-3,4,5-trimethylthiazolium Iodide (6).—A solution of **4** (19.4 g, 0.10 mole) and 3-bromo-2-butanone (15.1 g, 0.10 mole) in *n*-PrOH (100 ml) was heated on the steam bath for 5 hr. The solution was evaporated under reduced pressure, and the residue was extracted (hot H_2O). Addition of KI (20 g) to the aqueous extract gave the product (19.4 g, 51% yield), mp 220° dec. Recrystallization (MeOH–Et_2O) raised the melting point to 229° dec.

The other compounds listed in Table I were prepared in the same way.

2-(*p*-Dimethylaminophenyl)-3-methylthiazolium Iodide (5).—Br_2 (120 g, 0.75 mole) in $CHCl_3$ (100 ml) was added to vinyl acetate (64.5 g, 0.75 mole) in $CHCl_3$ (50 ml) at −40° during a 2-hr period. The solution was allowed to stand at room temperature for 1 hr and was then evaporated to dryness under reduced pressure. The residue of α,β-dibromoethyl acetate was dissolved in EtOH (60 ml) and *p*-dimethylamino-N-methylthiobenzamide (19.4 g, 0.1 mole) was then added. The solution was refluxed for 45 min, and the solvent was evaporated. The residue was extracted (Et_2O), and the ether extract was discarded. The residue was then extracted with H_2O, and the product was precipitated out of the aqueous extract by addition of KI. Repeated recrystallization (MeOH–EtOAc) gave pure **5**, mp 220° dec, yield 3.5 g (10%).

2-(*p*-Dimethylaminophenyl)-3-methyl-2-thiazolinium Iodide (19).—A solution of **4** (9.7 g, 0.05 mole) and ethylene dibromide (10 g, 0.053 mole) in methyl Cellosolve (15 ml) was refluxed for 15 min. NaOAc (4.1 g, 0.05 mole) was added, and the refluxing was continued for 30 min. The mixture was evaporated to dryness under reduced pressure, and the residue was partitioned between H_2O (100 ml) and Et_2O (100 ml). KI (17 g) was added to the aqueous layer, giving the product, mp 185–187.5° (from EtOH), yield 7.5 g (43%), λ_{max} 382 mμ. *Anal.* ($C_{12}H_{17}IN_2S$) C, H, I, N, S.

2-*p*-Dimethylaminophenyl-3-methyl-4-ethyl-2-thiazolinium Perchlorate (20).—A solution of *p*-dimethylamino-N-methylthio-

benzamide (19.4 g, 0.1 mole) and 1,2-dibromobutane (21.6 g, 0.01 mole) in ethoxyethanol was refluxed for 1 hr. NaOAc (8.2 g, 0.01 mole) was added and the refluxing was continued for 1 hr. Ether (50 ml) and H_2O (200 ml) were added and the unreacted thioamide was filtered. The aqueous extract was treated with $NaClO_4$ (5.0 g) to give the product as the perchlorate salt, mp 149–151°, yield 7.0 g (28% based on unrecovered thioamide), λ_{max} 386 mμ. *Anal.* ($C_{14}H_{21}ClN_2O_4S$) C, H, Cl, N, S.

2-(*p*-Dimethylaminophenyl)-3-methyl-4H-5,6-dihydro-1,3-thiazinium Iodide (21).—The thioamide was treated with 1,3-dibromopropane and NaOAc in ethoxyethanol as described above. KI was added to the aqueous solution of the bromide salt to give the iodide, mp 213–214.5° (from EtOH) in 26% yield, λ_{max} 373 mμ. *Anal.* ($C_{13}H_{19}IN_2S$) C, H, I, N, S.

S-Methyl-N-methyl-*p*-dimethylaminothiolbenzimidate (24).—A solution of **4** (1.9 g, 0.01 mole) and MeI (1.42 g, 0.01 mole) in MeOH (10 ml) was refluxed for 1 hr. The solution was evaporated, and the residue was extracted (H_2O). Addition of $NaHCO_3$ to the aqueous extract gave **24**, mp 76–77°, yield 0.7 g (34%), λ_{max} 295 mμ. *Anal.* ($C_{11}H_{16}N_2S$) C, H, N, S.

***p*-Dimethylamino-N,N-dimethylthiobenzamide (22).**—A solution of *p*-dimethylamino-N,N-dimethylbenzamide[4] (17.5 g, 0.09 mole) and P_2S_5 (5.6 g, 0.025 mole) in 100 ml pyridine was refluxed for 40 min. The product was isolated by diluting the reaction mixture with ice–water and recrystallizing the precipitate from MeOH, mp 103–104°, yield 11.5 g (61%), λ_{max} 335, 236 mμ. *Anal.* ($C_{11}H_{16}N_2S$) C, H, N, S.

S-Methyl-N,N-dimethyl-*p*-dimethylaminothiolbenzimidate Iodide (23).—A suspension of *p*-dimethylamino-N,N-dimethylthiobenzamide (2.1 g, 0.01 mole) in Et_2O (20 ml) was treated with excess MeI (3 ml). The solution became clear, and the product then separated out rapidly as an oil which crystallized on standing, yield 3.4 g (97%), mp 120° dec, λ_{max} 386, 265 mμ. *Anal.* ($C_{12}H_{19}IN_2S$) C, H, I, N, S.

Diquaternary salt (25). (a) The thiolbenzimidate (**24**) (0.45 g, 2.2 mmoles) was dissolved in excess MeI (3 ml) and the solution was allowed to stand overnight. Evaporation of the solution gave a quantitative yield of **25**, mp 210° (vigorous decomposition), λ_{max} 265 mμ.

(b) The monoquaternary salt (**23**) (0.35 g) was refluxed with MeI (5 ml) in MeOH (5 ml) for 15 min. Evaporation of the solution gave the same product (0.45 g), mp 210° dec. *Anal.* ($C_{13}H_{22}I_2N_2S$) C, H, I; N: calcd, 5.69; found, 6.27.

A sample of the diquaternary salt was dissolved in H_2O at room temperature. The solution was filtered after 1 hr, and the filtrate was concentrated under reduced pressure, giving S-methyl *p*-dimethylaminothiolbenzoate methiodide (**26**), mp 174–176° (from MeOH–Et_2O). *Anal.* ($C_{11}H_{16}INOS$) C, H, I, N, S.

2-(*p*-Anisyl)-3,4-dimethylthiazolium Iodide (27a).—2-(*p*-Anisyl)-4-methylthiazole,[5] mp 55–57°, was heated with excess MeI in a pressure bottle at 100° for 1 hr. The solid residue was crystallized from MeOH–Et_2O to a melting point of 190–192°, yield 51%, λ_{max} 306 mμ. *Anal.* ($C_{12}H_{14}INOS$) C, H, I, N, O, S.

2-(*p*-Anisyl)-3-ethyl-4-methylthiazolium Iodide (27b).—The thiazole described above was heated with EtI in a pressure bottle at 100° for 6 hr, giving the product, mp 194–196° (from EtOH), in 49% yield, λ_{max} 306 mμ. *Anal.* ($C_{13}H_{16}INOS$) C, H, I, N, O, S.

Acknowledgment.—The authors are indebted to Dr. A. O. Geiszler for invaluable help in the coordination of the research program.

(8) C. M. Suter and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 1585 (1930).

3,4-Dihydro-2(1H)-quinazolinones

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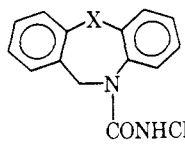
A series of 1- and 3-aminoalkyl-3,4-dihydro-2(1H)-quinazolinones was synthesized and the antiinflammatory activity investigated. Several of the compounds were equal to or better than phenylbutazone in one of the animal models of inflammation.

We have observed consistent but rather weak antiinflammatory activity among many simple dialkylaminoalkylureas. Attempts to increase this activity have involved the preparation of various cyclic derivatives of these compounds. Our first approach involved the synthesis of ureas derived from tricyclic amines of the type I.[1] These derivatives were also



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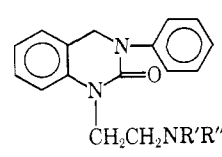
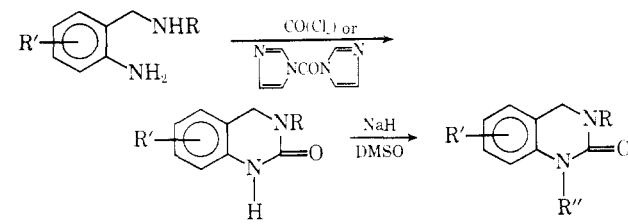


II

active as antiinflammatory agents but the potencies did not approach an acceptable level. Another type of cyclic derivative II, the 3-phenyl-1-dialkylaminoalkyl-3,4-dihydro-2(1H)-quinazolinones, was investigated and the lead compounds exhibited more potent antiinflammatory activity. A large number of compounds were then synthesized including the isomeric 3-dialkylaminoalkyl-3,4-dihydro-2(1H)-quinazolinones, and their antiinflammatory activity was investigated. A stimulus to this work was the fact that 3-phenyl-3,4-dihydro-2(1H)-quinazolinone was the only compound of this type previously reported in the literature.[2]

The 3-substituted 3,4-dihydro-2(1H)-quinazolinones were synthesized *via* ring closure of the appropriate diamine either with phosgene (method E) or with 1,1′-carbonyldiimidazole (method F) as shown in Chart I.

CHART I



The ring closure with phosgene was carried out by the addition of a solution of phosgene in toluene to a solution of the diamine followed by reflux. The yields in this reaction were usually low and the products difficult to purify. In contrast, refluxing an equimolar quantity of the diamine with 1,1′-carbonyldiimidazole in THF gave an excellent yield of the quinazolinone, in many cases analytically pure. Alkylations of the

(1) W. E. Coyne and J. W. Cusic, *J. Med. Chem.*, **10**, 541 (1967).

(2) M. Busch, *Ber.*, **25**, 2853 (1892).