# The Effects of Aliphatic and Cycloalkyl Substituents on a Ring–Chain Tautomeric Equilibrium[1]

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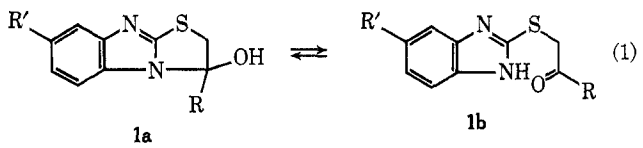
Reaction of 2-mercaptobenzimidazole with a variety of α-halo ketones ($RCOCH_2X$, where R = alkyl or cycloalkyl and X = bromine or chlorine) gave products capable of exhibiting carbinolamine–amino ketone ring–chain tautomerism. The tautomeric equilibrium, determined by infrared and nuclear magnetic resonance spectral measurements, is controlled by the inductive effect of the R group for all but the most bulky nonconjugative substituents. Only the chain tautomer exists in the solid state or solution when the substituent is capable of conjugating with the carbonyl group.

Jones,[4] in a review article published in 1963, noted that there were few examples of ring–chain tautomerism where both ring and chain tautomers were present in solution. The past 7 years, however, have witnessed the appearance of numerous publications describing systems exhibiting dynamic ring–chain tautomerism including: 1,3,4-thiadiazolidine-2-thiones,[5] oxazolidines,[6] 1,3-oxazines,[7,8] 1,2,5-oxadiazines,[9] 1,3,4-oxadiazines,[10,11] pyrimido[4,5-*d*]pyrimidines,[12] thiazolo[3,2-*a*]-benzimidazoles,[13] lactones,[14] and azidopurines.[15] Several of these papers have reported investigations of inductive and resonance effects of various aromatic substituents on the position of the tautomeric equilibrium.[6,7,12,14,15] In addition, Dorman[10] has shown that 2-alkyl-4,5-dimethyl-6-phenyltetrahydro-2*H*-1,3,4-oxadiazines exist in equilibrium with their γ-hydroxyhydrazone chain tautomers, the proportion of chain form increasing with an increase in the size of the 2-alkyl group. There have been no systematic studies, to our knowledge, of the effect of various simple aliphatic and cycloalkyl substituents on the position of a ring–chain tautomeric equilibrium. This paper reports on such a study our intention being to determine what factors (steric or inductive or both) control the equilibrium process.

The system chosen for investigation was 3-hydroxy-3-substituted 2,3-dihydrothiazolo[3,2-*a*]benzimidazole



**1a** **1b** (1)

(**1a**, R′ = H) which can exist in equilibrium with its open-chain amino ketone tautomer **1b** (R′ = H). The nuclear magnetic resonance spectra (nmr) of most derivatives of this system are very simple with the signal for the methylene protons of **1b** appearing as a singlet while that given by **1a** is an AB quartet.[16] The infrared spectra (ir) are also generally easy to interpret (indicating presence or absence of C=O, N–H, O–H, and C–O stretching). The parent heterocycle (**1**, R = R′ = H) exists solely as the cyclic carbinolamine both in the solid state and in solution. Solid-state infrared studies have shown 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole to exist as the ring tautomer (**1a**, R = $CH_3$, R′ = H), but nmr spectra of dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) solutions indicate a 1:2 mixture of **1a** and the chain tautomer **1b**, respectively.[13]

## Experimental Section

**General Comments.**—Melting points were determined on a Fisher-Johns or Gallenkamp apparatus and are uncorrected. Elemental analyses were carried out by A. Bernhardt, 5251 Elbach Uber Engelskirchen, Fritz-Pregl-Strasse, West Germany, and Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on Perkin-Elmer 457 and 521 spectrophotometers; the wavelength readings were calibrated with a polystyrene film. Nmr spectra were determined on a Varian A-60 or HA-100 spectrophotometer. Tetramethylsilane was used as internal standard.

**α-Halo Ketones.**—Chloro-2-propanone, 1,3-dichloro-2-propanone, 1-adamantyl bromomethyl ketone, 1-bromo-3,3,3-trifluoro-2-propanone, and ethyl bromopyruvate were commercial products. We are grateful to Professor V. Rosnati of the Istituto di Chimica Industriale dell'Universita di Milano for a generous gift of 1-chloro-3-phenylmercapto-2-propanone.

1-Bromo-2-butanone was prepared by bromination of 2-butanone in aqueous solution in the presence of potassium chlorate.[17] 1-Bromo-3,3-dimethyl-2-butanone[18] was obtained by bromination of pinacolone at room temperature. Chlorination of methyl cyclopropyl ketone according to Kosower and coworkers[19] gave chloromethyl cyclopropyl ketone. In our hands, chlorination of methyl isopropyl ketone with sulfuryl chloride failed to give any 1-chloro-3-methyl-2-butanone.[20] The desired chloro ketone could be obtained, however, by reaction of isobutyryl chloride with diazomethane.[21] Also prepared by diazomethane treatment of acid chlorides were chloromethyl cyclohexyl ketone,[22] 1-chloro-

(1) For a preliminary communication of this work, see H. Alper, *Chem. Commun.*, 383 (1970).
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4,4-dimethyl-2-pentanone,[23] 1,1,1,3-tetrachloro-2-propanone,[24] and 1-chloro-3,3-diphenyl-2-propanone.[25]

**General Procedure for Reaction of 2-Mercaptobenzimidazole with α-Halo Ketones.**—An equimolar mixture of 2-mercaptobenzimidazole (recrystallized from 95% ethanol) and α-halo ketone (8–30 mmol) in 2-butanone (40–200 ml) was refluxed with stirring for 2–8 hr. The reaction mixture was cooled and the precipitated hydrohalide salt of 1 isolated by suction filtration. The salt was then converted to the free base by (a) dissolving the salt in water and basifying with a saturated sodium bicarbonate solution, or by (b) suspending the salt in 95% ethanol, heating the mixture to reflux, adding triethylamine, and pouring the resulting basic solution into 4–6 vol of water. The latter procedure was used for those salts which were insoluble in water. Recrystallization from acetonitrile, aqueous ethanol, or acetone gave pure 1. The melting points and analyses of these compounds are listed in Table I.

TABLE I

CONDENSATION PRODUCTS FROM REACTIONS OF 2-MERCAPTOBENZIMIDAZOLE AND 2-MERCAPTO-5-NITROBENZIMIDAZOLE WITH α-HALO KETONES

| 1a ⇄ 1b | | Registry no. | | | |
|---|---|---|---|---|---|
| R | R′ | 1a | 1b | Mp, °C | Molecular formula[a] |
| $CH_2CH_3$ | H | 27784-37-8 | 27784-38-9 | 94.0–96.0 | $C_{11}H_{12}N_2OS$ |
| $CH(CH_3)_2$ | H | 27784-39-0 | 27784-40-3 | 109.0–111.0 | $C_{12}H_{14}N_2OS$ |
| $C(CH_3)_3$ | H | 27784-41-4 | 26559-22-8 | 104.5–105.5 | $C_{13}H_{16}N_2OS$ |
| $CH_2C(CH_3)_3$ | H | 27784-43-6 | 27932-06-5 | 116.0–117.0 | $C_{14}H_{18}N_2OS$ |
| $CH_2SC_6H_5$ | H | 27784-44-7 | 27784-45-8 | 138.0–139.0 dec | $C_{16}H_{14}N_2OS_2$ |
| $CH_2Cl$ | H | 27784-46-9 | 27784-47-0 | 181.0–184.0 dec | $C_{10}H_9ClN_2OS$ |
| $CH(C_6H_5)_2$ | H | 27784-48-1 | 27784-49-2 | 150.0–152.0 | $C_{22}H_{18}N_2OS$ |
| $CF_3$ | H | 26559-21-7 | 27784-51-6 | 138.0–139.0 | $C_{10}H_7F_3N_2OS$ |
| $COOC_2H_5$ | H | 27784-52-7 | 27784-53-8 | 124.0–125.5 | $C_{12}H_{12}N_2O_3S$ |
| Cyclopropyl | H | 27784-54-9 | 27784-55-0 | 131.0–132.0 | $C_{12}H_{12}N_2OS$ |
| Cyclohexyl | H | 27784-56-1 | 27784-57-2 | 155.0–156.0 | $C_{15}H_{18}N_2OS$ |
| 1-Adamantyl | H | 27784-58-3 | 27932-07-6 | 188.5–190.5 | $C_{19}H_{22}N_2OS$ |
| $CH_3$ | $NO_2$ | 27784-59-4 | 27784-60-7 | 122.0–124.0 | $C_{10}H_9N_3O_3S$ |
| $CF_3$ | $NO_2$ | 27784-61-8 | 27784-62-9 | 206.5–208.5 | $C_{10}H_6F_3N_3O_3S$ |

[a] All compounds except one gave C, H, and N analysis within 0.4 of the calculated values and the analytical data were made available to the editors and referees. The exception is $C_{10}H_9N_3O_3S$. Calcd: C, 47.80; H, 3.62; N, 16.73. Found: C, 48.27; H, 3.99; N, 16.53.

The same general procedure was applied to the reaction of 2-mercapto-5-nitrobenzimidazole (recrystallized from 50% aqueous ethanol) with chloro-2-propanone and 1-bromo-3,3,3-trifluoro-2-propanone. The melting points and analyses of the products are given in Table I.

## Results and Discussion

Condensation of 2-mercaptobenzimidazole with a series of α-halo ketones in 2-butanone gave **1** (R′ = H; R groups listed in Table I). The position of condensation of 2-mercaptobenzimidazole and α-halocarbonyl compounds has been established as occurring at the mercapto group.[13,26] The infrared spectra were recorded as potassium bromide disks and in chloroform or dimethyl sulfoxide solutions (Table II). The spectra of the KBr disks indicate the presence of either tautomer **1a** or **1b** but not both as ring–chain tautomerism occurs only in solution or in the liquid or gaseous states. Tautomer **1a** shows broad absorption in the region of 3300–2500 $cm^{-1}$ due to the O–H stretch of the hydrogen-bonded hydroxyl group and a sharp, usually intense band in the region of 1182–1068 $cm^{-1}$ for the C–O stretch of a tertiary alcohol. The spectrum of the amino ketone tautomer **1b** also exhibits broad absorption in the region of 3200–2500 $cm^{-1}$ due to the hydrogen-bonded N–H stretch but in addition a strong band, due to carbonyl stretching, appears at 1747–1693 $cm^{-1}$. We have observed, in all instances, that the occurrence of tautomer **1b** in the solid state indicates that this will be the *only* tautomer present in solution. If the carbinolamine **1a** is the tautomer present in the solid state, then solution studies will show the presence of only tautomer **1a** or a mixture of ring and chain tautomers. Similar ir bands occur for **1a** and **1b** in both chloroform and dimethyl sulfoxide with the appearance of free N–H or O–H stretching absorptions in addition to, or in place of, the corresponding hydrogen-bonded stretch.

The nmr spectra were recorded for DMSO-$d_6$ solutions of **1**. Unfortunately, any study of solvent effects on the equilibrium **1a** ⇄ **1b** is generally limited by low solubility of **1** in less polar solvents [certain derivatives were sufficiently soluble in deuteriochloroform ($CDCl_3$) for nmr purposes]. The position of the singlet for the methylene protons of **1b** and the center of the AB quartet for the corresponding protons of **1a** are given in Table II ($J_{AB}$ = 11–13 cps). The relative amounts of ring and chain tautomers, where applicable, were evaluated by careful and repeated integration of the appropriate nmr signals of the two forms. The results obtained for the series, methyl, ethyl, isopropyl, and *tert*-butyl (Table II), indicate that the equilibrium shifts to the chain form with increasing steric bulk of R.[27] However, the data could also be interpreted as the chain tautomer being more favored as the electron-donating ability of the alkyl group increases. Alternatively, the equilibrium may be controlled by both inductive and steric effects. Results obtained with some of the other substituents demonstrate the importance of inductive effects in these systems.

The group, $CH_2SC_6H_5$, probably has a steric effect[28] similar to that of an isopropyl group.[29] Consequently, these should be approximately 90% **1b** (R = $CH_2S$-$C_6H_5$, R′ = H) present in DMSO-$d_6$ solution if the tautomerism is governed by steric effects. However, the $CH_2SC_6H_5$ group is electron attracting thus favoring an increased proportion of ring tautomer (41% observed). Similarly, the steric effect of a trifluoromethyl group is between that of the isopropyl and *tert*-butyl groups indicating that the chain form should be predominant for **1** (R = $CF_3$, R′ = H). The latter, in fact, exists only as the ring tautomer in the solid state and in chloroform or DMSO solution in agreement with its powerful electron-withdrawing ability. The cyclohexyl group, although sterically larger than the isopropyl group, shows a small amount of ring form **1a** in solution in agreement with the smaller electron-donating properties of a cyclohexyl compared to an isopropyl group. The chloromethyl group is sterically not much larger than a methyl substituent but has considerable electron-withdrawing character.[28] As another illustration of the extent of inductive control of the tautomeric equilib-

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(27) The proportion of chain tautomer for **1** (R = $CH_3$, R′ = H) was redetermined and found to be slightly less than the originally reported value of 66.7%.[13] We had hoped to be able to study the compound **1** (R = $CD_3$, R′ = H) in order to determine deuterium isotope effects. Reaction of 1-chloro-3,3,3-trideuterio-2-propanone with 2-mercaptobenzimidazole gave the hydrochloride salt of **1**. However, basification with triethylamine in dry acetonitrile resulted in H–D exchange.

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(29) Based on a comparison of steric substituent constants for $CH_3OCH_2$, $CH_3SCH_2$, and $C_6H_5OCH_2$.[28]

TABLE II

PERTINENT IR AND NMR DATA AND RING–CHAIN TAUTOMERIC RATIOS FOR **1a** ⇄ **1b**

| 1a ⇄ 1b | | Ir[a] | | Nmr[d] | | | |
|---|---|---|---|---|---|---|---|
| R | R′ | KBr, ν[b] | Solution,[c] ν | Solvent[e] | Chain, $SCH_2$ | Ring, $SCH_2$ ($J$)[f] | % chain |
| $CH_3$ | H | | | | | | 65[g] |
| $CH_2CH_3$ | H | 3200–2700 (OH), 1081 (CO) | C, 3660 (OH, free), 3545 (OH, bonded), 3454 (NH, free), 3300–3200 (NH, bonded), 1710 (C=O), 1110 (CO) | D | 4.33 | 3.92 (12) | 71 |
| $CH(CH_3)_2$ | H | 3300–2700 (OH), 1068 (CO) | D, 3200–2780 (OH, NH), 1705 (C=O) | D | 4.44 | 3.83 (12) | 90 |
| $C(CH_3)_3$ | H | 3100–2600 (OH), 1712 (C=O) | C, 3455 (NH, free), 3307 (NH, bonded), 1705 (C=O) | C | 4.45 | | 100 |
| | | | | D | 4.62 | | 100 |
| $CH_2C(CH_3)_3$ | H | 3100–2600 (NH), 1710 (C=O) | C, 3450 (NH, free), 3320–3160 (NH, bonded), 1712 (C=O) | D | 4.30 | | 100 |
| $CH_2SC_6H_5$ | H | 3100–2600 (OH), 1129 (CO) | C, 3670 (OH, free), 3561 (OH, bonded), 3456 (NH, free), 3300–3100 (NH, bonded), 1719 (C=O), 1126 (CO) | D | 4.52 | 4.08 (11) | 59 |
| $CH_2Cl$ | H | 3200–2600 (OH), 1132 (CO) | A, 3450 (NH, free), 3140–2780 (OH, NH, bonded), 1720 (C=O), 1138 (CO) | [h] | | | |
| $CH(C_6H_5)_2$ | H | 3300–2700 (NH), 1718 (C=O) | C, 3450 (NH, free), 3305 (NH, bonded), 1720 (C=O) | C | 4.15 | | 100 |
| | | | | D | 4.45 | | 100 |
| $CF_3$ | H | 3100–2550 (OH), 1182 (CO) | C, 3100–2600 (OH), 1188 (CO) | D | | 4.38 (13) | 0 |
| $COOC_2H_5$ | H | 3100–2600 (NH), 1747 (C=O) | C, 3480 (NH, free), 3300–3150 (NH, bonded), 1740 (C=O) | C | 4.09 | | 100 |
| | | | | D | 4.17 | | 100 |
| Cyclopropyl | H | 3100–2560 (NH), 1693 (C=O) | C, 3460 (NH, free), 3290 (NH, bonded), 1698 (C=O) | D | 4.47 | | 100 |
| Cyclohexyl | H | 3200–2700 (OH), 1071 (CO) | D, 3465 (NH, free), 3300–2800 (OH, NH, bonded), 1705 (C=O) | D | 4.42 | 3.86 (12) | 85 |
| 1-Adamantyl | H | 3100–2600 (NH), 1705 (C=O) | C, 3445, (NH, free), 3300–3160 (NH, bonded), 1685 (C=O) | C | 4.41 | | 100 |
| | | | | D | 4.56 | | 100 |
| $CH_3$ | $NO_2$ | 3200–2700 (OH), 1082 (CO) | D, 3420 (NH, free), 3200–2660 (OH, NH, bonded), 1710 (C=O) | D | 4.44 | 3.04 (12) | 79 |
| $CF_3$ | $NO_2$ | 3200–2600 (OH), 1193 (CO) | D, 3200–2600 (OH), 1198 (CO) | D | | 4.42 (12) | 0 |

[a] Data given in units of $cm^{-1}$. [b] Type of stretching vibration. [c] A = acetonitrile, C = chloroform, D = dimethyl sulfoxide. Reliable C–O stretching values could not be obtained in dimethyl sulfoxide due to background solvent absorption in the C–O stretching region. [d] Chemical shifts in ppm. Spectra measured within 10 min of preparing the solutions do not change when measured again 24 hr later [except for **1** (R = $CH_2Cl$, R′ = H)]. [e] C = chloroform-*d*, D = dimethyl sulfoxide-$d_6$. [f] Coupling constants in cycles per second. [g] Previously reported as 66.7% with identical ir and nmr data (ref 13). [h] In both DMSO-$d_6$ and acetonitrile-$d_3$, the signals for the protons of the $-SCH_2-$ group of the ring and chain tautomers and the $-CH_2Cl$ group of the chain tautomer appeared in the region of 4.0–4.5 ppm and could not be reliably assigned.

rium, infrared studies indicate the ring tautomer **1a** (R = $CH_2Cl$, R′ = H) to be the major tautomer in solution (acetonitrile). Unfortunately, proton magnetic resonance spectra did not afford a value for the ring–chain tautomer ratio for **1** (R = $CH_2Cl$, R′ = H) because the signals for the $-SCH_2-$ of the ring and chain tautomers and for the $-CH_2Cl$ of the chain tautomer were not well separated in either DMSO-$d_6$ or acetonitrile-$d_3$. Furthermore, the heterocycle reacted with DMSO-$d_6$.[30] Attempts to prepare **1** (R = $CCl_3$, R′ = H) by reaction of 1,1,1,3-tetrachloro-2-propanone with 2-mercaptobenzimidazole failed as reaction of the trichloromethyl group occurred on basification of the hydrochloride salt of **1** (R = $CCl_3$, R′ = H) with triethylamine in 95% ethanol.

An exception to the above results occurs for **1** [R = $CH_2C(CH_3)_3$, R′ = H]. The steric substituent constant of the neopentyl group is more negative than the value reported for the *tert*-butyl group while the electron-releasing ability of the latter is greater than that of the neopentyl group.[28] Hence, if inductive effects alone controlled the equilibrium, one would expect approximately 10–15% ring tautomer to be present in solution. The total absence of ring tautomer may be due to the steric effect becoming substantial for groups larger than *tert*-butyl. In this case, severe repulsion between one of the substituent methyl groups and a hydrogen of the $-SCH_2-$ group may occur in the ring form. This steric strain is relieved, of course, in the amino ketone tautomer. The diphenylmethyl group **1** [R = $CH(C_6H_5)_2$, R′ = H] is essentially the same size as the neopentyl group[28] and gives the same results as neopentyl although it has greater electron-withdrawing properties. Weber[31] has reported $\sigma^n$ values for *m*-1-adamantyl and *p*-1-adamantyl groups of −0.121 and −0.131, respectively, from which one can estimate the $\sigma^*$ value of 1-adamantyl to be roughly comparable to that of a methyl group. No steric substituent constant for 1-adamantyl has been published, but it is reasonable to assume that the steric effect of this group is substantial, and thus **1** (R = 1-adamantyl,

(30) The reaction of a number of α-halo ketones with DMSO to form α-keto aldehydes has been reported: N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, **79**, 6562 (1957). The tautomer **1b** (R = $CH_2Cl$, R′ = H) also gives the keto aldehyde (a singlet at 9.67 ppm due to the aldehydic proton begins to appear within a few minutes after dissolving the heterocycle in DMSO-$d_6$).

(31) J. Weber, Dissertation, Aachen, Germany, 1966, p 51. We thank Professor P. v. R. Schleyer for informing us of these data.

R′ = H) exists solely as the chain tautomer in the solid state and in solution.

The results for the cyclopropyl substituent appear surprising on first inspection. Cyclopropyl is both sterically small and inductively slightly electron withdrawing,[32] and thus one would predict a ring–chain tautomer ratio similar to that for **1** (R = $CH_3$, R′ = H). However, the conjugative ability of a cyclopropyl group is well documented.[33] Cyclopropyl–carbonyl conjugation in the chain form is destroyed on forming the carbinolamine and thus **1** (R = cyclopropyl, R′ = H) exists solely as the chain tautomer both in the solid state and in solution, conjugation being the driving force for chain tautomer stabilization. Similarly, **1** (R = $COOC_2H_5$, R′ = H) exists only as the amino ketone in solution. These results are further supported by earlier work[34] on **1** [R = *p*-$XC_6H_4$– (where X = H, Cl, Br, $NO_2$, $OCH_3$), R′ = H] where, in all cases, **1b** was the only tautomer present in solution. Here, the aromatic ring can conjugate with the carbonyl group of the amino ketone.

The results previously obtained for **1** (R = R′ = H)[13] cannot be applied to the study reported herein since an aldehyde such as **1b** is substantially more susceptible to condensation with an amino group than a ketone, thus giving the ring tautomer **1a**.

It was also of interest to determine whether or not a strongly electron-attracting group on the benzene ring would have an effect on the ring–chain tautomeric equilibrium; *i.e.*, would a compound existing solely as the ring tautomer for **1** (R′ = H) be a mixture of tautomers when R′ = $NO_2$? 2-Mercapto-5-nitrobenzimidazole was treated with chloro-2-propanone and 1-bromo-3,3,3-trifluoro-2-propanone to give **1** (R = $CH_3$ or $CF_3$, R′ = $NO_2$). Consider **2a** and **2b** as resonance contributors to **1a**.[35] If **2b** makes an important contribution to **1a**, then the positive nitrogen of **2b** would favor opening of the thiazolidine ring. Table II shows that for **1** (R = $CH_3$, R′ = $NO_2$), the presence of the nitro group exerts a modest shift to the chain tautomer from **1** (R = $CH_3$, R′ = H). However, the presence of a nitro group on the benzene ring has no effect on the tautomeric equilibrium of the trifluoromethyl compound, thereby indicating the powerful inductive control by the substituent in the 3 position.

In summary, the results obtained from this investigation lead to the following conclusions: (a) for R groups of steric bulk up to *tert*-butyl, ring–chain tautomerism of **1** is controlled predominantly, if not exclusively, by the inductive effects of the substituent (*e.g.*, if R is electron releasing, the carbonyl carbon of **1b** becomes more negative thus making it less susceptible to ring formation by reaction with the amino group; the reverse argument applies when R is electron withdrawing); (b) for very bulky groups, *e.g.*, neopentyl and diphenylmethyl, steric effects become important; (c) any group having conjugative properties will result in the heterocyclo existing solely as **1b**.

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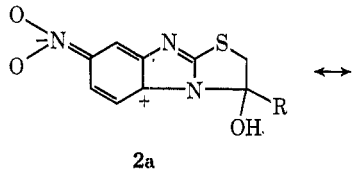
(32) Y. E. Rhodes, Fourteenth Annual Report on Research under Sponsorship of the Petroleum Research Fund, 1969, p 70.

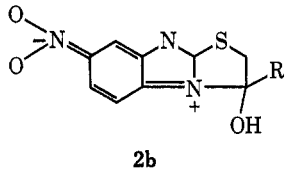
(33) (a) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967); (b) J. C. Bourmanne, G. Leroy, and J. Weiler, *Tetrahedron*, **26**, 2281 (1970).

(34) H. Alper and A. E. Alper, *J. Org. Chem.*, **35**, 835 (1970).

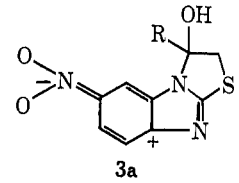
(35) The nitrogen on the carbon atom meta to the nitro group may also be involved in the tautomeric process but, in any case, the same arguments apply as per **2a** ↔ **2b**.



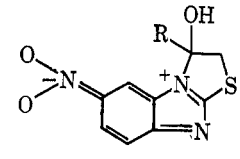
**2a**



**2b**



**3a**



**3b**