Azole Chemistry. VIII.[1] Ring–Chain Tautomerism of Some 2-Mercaptoperimidine Derivatives

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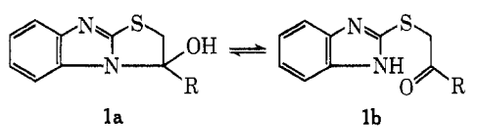
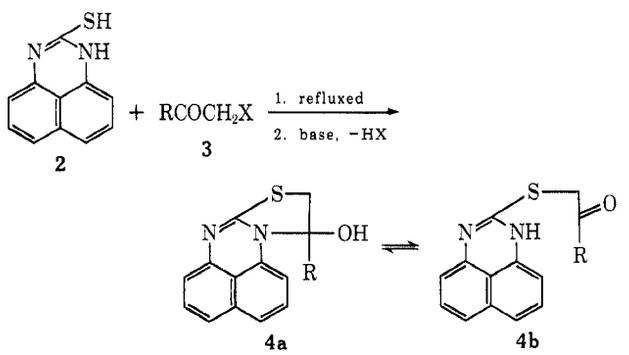
Reaction of α-halo ketones with 2-mercaptoperimidine affords carbinolamines and/or the tautomeric amino ketones. Inductive, conjugative, and steric effects on the ring–chain tautomeric equilibrium are discussed. The influence of basicity on ring–chain tautomerism is noted.

A recent investigation of the amino ketone carbinolamine ring–chain tautomerism for the products (**1a** ⇌ **1b**) obtained from the reaction of 2-mercaptobenzimidazole with α-halo ketones indicated the importance of inductive effects on the tautomeric process. Except for bulky (*e.g.*, **1**, R = diphenylmethyl) or conjugative (*e.g.*, **1**, R = aryl) groups, the tautomeric equilibrium is governed by the inductive effect of R.[2] We now report a study of ring–chain tautomerism of some 2-mercaptoperimidine derivatives. Although the latter heterocyclic system has a six-membered rather than a five-membered nitrogen-containing ring as in **1**, perimidines possess many of the properties characteristic of azoles.[3] Since the basicity of perimidine (pK_a = 6.39)[4] is different from that of benzimidazole (pK_a = 5.53),[5] it was also of interest to learn what effect basicity has on the ring–chain process.



1a **1b**

Treatment of 2-mercaptoperimidine (**2**) with a series of α-halo ketones (**3**) in either tetrahydrofuran or 2-butanone gave the hydrohalide salt of **4** in good yields



2 **3** **4a** **4b**

(see Table I for yields, melting points, and analytical data). The free base was obtained by exposure of the hydrohalide salt to triethylamine. Condensation of **2** with various α-halo acids has been shown to occur at the mercapto group.[6]

Solid-state spectra for **4** are those of the ring or chain forms, but not both, as ring–chain tautomerism does not occur in the solid state. Characteristic bands for **4a** appear in the region of 3600–2500 cm^{-1} and at 1125–1050 cm^{-1}, and are due to the hydrogen-bonded hydroxyl group stretch and to the carbon–oxygen stretching vibrations, respectively. A broad absorption (3600–2500 cm^{-1}) was also observed in the solid-state spectra of the β-keto sulfide **4b**, owing to the hydrogen-bonded NH stretch (free NH stretching at 3300–3270 cm^{-1} was noted in several instances). The carbonyl stretching absorption occurred at 1760–1660 cm^{-1}. Solution spectra showed similar bands for **4a** and/or **4b**.

The nuclear magnetic resonance (nmr) spectra were recorded in dimethyl sulfoxide-d_6 (Table I). Except for **4**, R = H, $COOC_2H_5$, the nmr spectra of **4a** ⇌ **4b** displayed a singlet signal for the methylene protons of **4b** and an AB quartet for the corresponding protons of **4a**. Where both ring and chain tautomers were present, the per cent of each tautomer was determined by repeated integration of the signals for the methylene protons. For **4b**, R = $COOC_2H_5$, a quartet (J = 14 Hz) was observed for the methylene protons of the SCH_2 group, and is due to possible restricted rotation. The carbonyl stretching frequency ($CHCl_3$) of **4b**, R = $COOC_2H_5$, was at an identical position with that of **1b**, R = $COOC_2H_5$ (1745 cm^{-1}). The carbonyl stretching absorption of **4a** would be expected to occur at a lower wavenumber than that of **4b**. For **4a**, R = H, the quartet for the methylene group is further split by the methine proton attached to the adjacent carbon.

The amount of chain tautomer increases with increasing electron-releasing ability of the R group for the series R = CH_3, C_2H_5, $CH(CH_3)_2$, and $C(CH_3)_3$. This trend is in agreement with results obtained for **1a** ⇌ **1b**, which demonstrated the control of the tautomeric equilibrium by the inductive effect of R for all but conjugative or very bulky substituents (*e.g.*, 1-adamantyl). Steric considerations can also account for the observed trend for these alkyl groups.

It was hoped that the study could be extended to **4**, R = CF_3, but basification of the hydrogen bromide adduct resulted in formation of 2,3-dihydro-1*H*-perimidin-2-one (**5**), an unusual example of a sulfur–carbon cleavage reaction. The mechanism for formation of **5** is unknown but it may occur *via* the chain tautomer (**4b** HBr) of the hydrohalide salt. Solid-state and solution infrared spectra, as well as nmr spectra for the hydrobromide salt of **4**, R = CF_3, clearly show the presence of only the ring tautomer, again in agreement with the results obtained for **1**, R = CF_3. If steric effects were important, there should be a considerable

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(2) H. Alper, E. C. H. Keung, and (in part) R. A. Partis, *J. Org. Chem.*, **36**, 1352 (1971).

(3) E. J. Browne, *Aust. J. Chem.*, **26**, 449 (1973), and references cited therein.

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(5) D. J. Brown, *J. Chem. Soc.*, 1974 (1958).

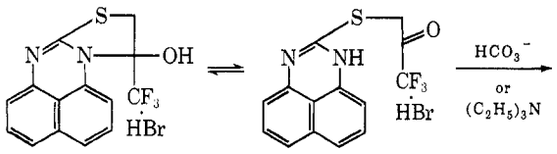
(6) H. S. Chaudhary and H. K. Pujari, *Indian J. Chem.*, **7**, 767 (1969).

TABLE I

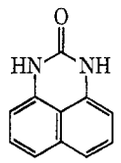
YIELDS, MELTING POINTS, NMR DATA, AND RING–CHAIN TAUTOMERIC RATIOS FOR **4a** ⇌ **4b**

R	Formula[a]	Yield,[b] %	Mp, °C	Time, hr	Nmr[d] Chain SCH_2 (J)	Nmr[d] Ring SCH_2 (J)[e]	% chain[f]
H	$C_{13}H_{10}N_2OS$	86	155 dec	12[c]		3.74[g] (6) 3.18[h] (12)	0
CH_3	$C_{14}H_{12}N_2OS$	76	124.5–126.5	37	4.07	3.46	33
C_2H_5	$C_{15}H_{14}N_2OS$	82	113–115	2.5	4.04	3.48 (11)	40
$CH(CH_3)_2$	$C_{16}H_{16}N_2OS$	73	188.5 dec	2.5	3.97	3.56	65
$C(CH_3)_3$	$C_{17}H_{18}N_2OS$	72	151 dec	15	4.33		100
$CO_2C_2H_5$	$C_{16}H_{14}N_2O_3S$	97	138.5 dec	0.25	3.65 (14)		100
1-Adamantyl	$C_{23}H_{24}N_2OS$	87	163 dec	12	4.27		100
C_6H_5	$C_{19}H_{14}N_2OS$	80	153 dec	12	4.71		100
p-$CH_3OC_6H_4$	$C_{20}H_{16}N_2OS$	89	155 dec	11.5	4.65		100
p-BrC_6H_4	$C_{19}H_{13}N_2OS$	86	167 dec	0.33	4.69		100

[a] All compounds except **4**, R = CH_3 (Calcd: N, 10.93. Found: N, 10.47.) and **4**, = R = H (Calcd: N, 11.56. Found: N, 10.93.) 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. [b] Based on hydrohalide adduct. [c] Reaction was run at room temperature. [d] Chemical shifts in parts per million based on tetramethylsilane. Dimethyl sulfoxide-d_6 was used as the solvent. [e] Coupling constants in cycles per second. [f] Accurate to within 3%. [g] Proton of methylene group cis to OH. [h] Proton of methylene group trans to OH.



4a HBr **4b** HBr



5

amount of chain tautomer for **4**, R = CF_3, since the steric effect of the trifluoromethyl group is between that of the isopropyl and *tert*-butyl groups.[7] The trifluoromethyl group of **4**, R = CF_3, makes the carbonyl carbon of **4b** more positive and therefore more susceptible to cyclization to **4a** by reaction with the amino group. The greater the electron-donating ability of R, for **4**, R = CH_3, C_2H_5, $CH(CH_3)_2$, and $C(CH_3)_3$, the less positive the carbonyl carbon of **4b**, and therefore the less the amount of ring tautomer.

The parent system **4**, R = H, is exceptional, since an aldehyde function (**4b**, R = H) would be expected to undergo cyclization more readily than a ketone carbonyl. A second exception occurs when a 1-adamantyl substituent is present (**4**, R = 1-adamantyl). Although the inductive effect of the 1-adamantyl group is estimated to be similar to that of a methyl group,[8] the steric effect of the 1-adamantyl group is expected to be substantial, and consequently only the chain tautomer **4b** is present in chloroform or dimethyl sulfoxide-d_6 solutions of **4**, R = 1-adamantyl.

Only the chain tautomer was observed for **4**, R = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4, and $COOC_2H_5$. Inductive effects are not important in these cases, as conjugation of the carbonyl group of the amino ketone with a benzene ring or with the carboethoxy group in **4b** would be destroyed on cyclization to **4a**.

Returning to the discussion of the results for **4**, R = CH_3, C_2H_5, and $CH(CH_3)_2$, it is true that, although the trends in the proportion of chain tautomer for these compounds and the same series for **1** are the same, the actual percentages are significantly different (Table II).

TABLE II

COMPARISON OF SOME OF THE DATA FOR **1** AND **4**

1 or **4**, R	% chain **1**	% chain **4**
CH_3	65	33
C_2H_5	71	40
$CH(CH_3)_2$	90	65

The difference in per cent chain isomer for **4**, R = CH_3, as compared to **1**, R = CH_3, may be due, at least in part, to the difference in basicity of the heterocyclic ring systems. Perimidine (pK_a = 6.39)[4] is a stronger base than benzimidazole (pK_a = 5.53).[5] Therefore, the tendency for the amino ketone **4b**, R = CH_3, to cyclize to **4a**, R = CH_3, would be enhanced relative to ring closure of **1b**, R = CH_3, to **1a**, R = CH_3. Consequently, the per cent chain of **4**, R = CH_3, is less than that for **1**, R = CH_3. The same rationale can be used to account for the results in the ethyl- and isopropyl-substituted derivatives of **1** and **4**. These studies indicate the importance of basicity in ring–chain tautomerism.

Experimental Section

α-Halo Ketones.—Ethyl bromopyruvate, 1-adamantyl bromomethyl ketone, chloro-2-propanone, 1-bromo-3,3,3-trifluoro-2-propanone, chloroethanal, 2-bromoacetophenone, and 2-bromo-4′-methoxyacetophenone were commercially available.

Bromination of pinacolone gave 1-bromo-3,3-dimethyl-2-butanone.[9] 1-Chloro-3-methyl-2-butanone[10] was prepared by reaction of dioxane dibromide with 3-methyl-2-butanone at room temperature. Bromination of 2-butanone in aqueous solution in the presence of potassium chlorate[11] gave 1-bromo-2-butanone.

General Procedure for the Reaction of 2-Mercaptoperimidine with α-Halo Ketones.—An equimolar amount of the heterocycle (recrystallized first from THF and pentane, and then from 2-butanone and pentane) and α-halo ketone (5–10 mmol) in tetrahydrofuran (THF) or 2-butanone (100–150 ml) was refluxed with

(7) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(8) See footnote 31 of ref 2.

(9) M. Charpentier-Morize, *Bull. Soc. Chim. Fr.*, 920 (1962).

(10) N. A. Oshueva and T. Temnikova, *J. Gen. Chem. USSR*, **29**, 3686 (1959).

(11) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

mechanical stirring. The reaction mixture was cooled to room temperature, the hydrohalide salt generally having precipitated out of solution. Soluble hydrohalide salts were precipitated by addition of pentane. The salt was filtered and dried. Conversion to the free base was accomplished by dissolving the salt in hot ethanol (95 or 100%), adding triethylamine until the solution was basic (pH usually 8–10), and, finally, pouring the solution into 1–4 volumes of ice water. This resultant mixture was allowed to stand undisturbed for 0.5–2 hr. Work-up was effected as follows in the individual cases.

A. R = C_6H_5.—The crystals were filtered and dissolved in hot benzene and Nuchar was added to effect partial decolorization. After filtration, the benzene filtrate was flash evaporated and petroleum ether (bp 30–60°) was then added to the residue. Slow crystallization occurred when the solution was kept in the refrigerator. The isolated solid was dissolved in the minimum amount of chloroform and chromatographed on Florisil. Elution with chloroform gave pure **4**, R = C_6H_5.

B. R = CH_3.—The product was extracted from the aqueous solution with methylene chloride, and the organic extract was dried over $MgSO_4$ and flash evaporated to an oil. The latter was covered with pentane (~125 ml) and kept overnight in the refrigerator. Pentane was decanted and the residue was treated with hot isooctane and filtered. The isooctane treatment was repeated until the filtrate was faint green in color. The product was then isolated by flash evaporation.

C. R = *p*-$CH_3OC_6H_4$.—The product was extracted from the aqueous solution with methylene chloride, and the organic extract was dried and flash evaporated. The residue was dissolved in the minimum amount of benzene and chromatographed on Florisil. Elution with chloroform gave pure β-keto sulfide.

D. R = 1-Adamantyl.—The crystals were filtered and dissolved in hot acetonitrile, and Nuchar was added to effect partial decolorization. The solution was filtered, the filtrate was evaporated, and acetone was then added to the residue to afford pure **4**, R = 1-adamantyl.

E. R = $CO_2C_2H_5$.—The aqueous solution was treated with methylene chloride, the layers were separated, and Nuchar was added to the organic extract. The solution was heated to boiling and filtered hot, and the filtrate was then flash evaporated. The residual oil was dissolved in chloroform and chromatographed on Florisil. Elution with chloroform gave a yellow oil. The latter was treated with a few milliliters of tetrahydrofuran, and addition of excess pentane resulted in crystallization.

F. R = H.—The crystals were filtered and dissolved in hot chloroform (Nuchar added), and the solution was filtered. Recrystallization from chloroform–pentane gave pure **4**, R = H.

G. R = $C(CH_3)_3$.—The crystals were treated with hot tetrahydrofuran (Nuchar added) and filtered, and the filtrate was concentrated to a few milliliters. Addition of pentane resulted in precipitation of impurities, which were removed by filtration. Evaporation of the filtrate gave the product. Analytically pure **4**, R = $C(CH_3)_3$, was obtained by repetition of this work-up procedure.

H. R = C_2H_5 or $CH(CH_3)_2$.—The aqueous solution was extracted with chloroform, the chloroform extract was flash evaporated, and the residue was chromatographed on Florisil. Elution with chloroform gave a new oil which, in the case of R = C_2H_5, was rechromatographed on alumina (neutral, Woelm activity grade I), whereby another oil was obtained on elution with chloroform. A few milliliters of tetrahydrofuran was added, and the product was crystallized on subsequent addition of pentane. Analytically pure material was obtained by recrystallization from tetrahydrofuran–pentane.

I. R = CF_3.—The crystals were filtered, treated with hot absolute methanol (Nuchar added), and filtered. The filtrate was flash evaporated until a green solid precipitated out of solution. The solution was filtered, and evaporation of the filtrate gave 2,3-dihydro-1*H*-perimidin-2-one: mp 301.5–303.0° after recrystallization from glacial acetic acid (lit.[12] mp 304–305°); nmr (DMSO-d_6) δ 6.50 (m, 2 H, ortho protons to nitrogen-bearing carbons), 7.20 (m, 4 H, meta and para protons), 10.1 (s, 2 H, NH); mass spectrum *m/e* 184, 166, 139, 128, 112, 92.

Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.29; H, 4.31; N, 14.94.

J. R = *p*-BrC_6H_4.—The crystals were filtered, dissolved in chloroform, and chromatographed on Florisil. Elution with chloroform gave **4**, R = *p*-BrC_6H_4.

Acknowledgments.—We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are indebted to Hoffmann-La Roche, Inc., for carrying out most of the microanalyses.

Registry No.—**2**, 30837-62-8; **3** (R = H, X = Cl), 107-20-0; **3** (R = CH_3, X = Cl), 78-95-5; **3** (R = CH_3CH_2, X = Br), 816-40-0; **3** (R = $CH(CH_3)_2$, X = Cl), 17687-63-7; **3** (R = $C(CH_3)_3$, X = Br), 5469-26-1; **3** (R = $CO_2C_2H_5$, X = Br), 70-23-5; **3** (R = 1-adamantyl, X = Br), 5122-82-7; **3** (R = Ph, X = Br), 70-11-1; **3** (R = *p*-$CH_3OC_6H_4$, X = Br), 2632-13-5; **3** (R = *p*-BrC_6H_4, X = Br), 99-73-0; **3** (R = CF_3, X = Br), 431-35-6; **4a** (R = H), 41367-08-2; **4a** (R = CH_3), 41367-09-3; **4b** (R = CH_3), 41367-10-6; **4a** (R = C_2H_5), 41367-11-7; **4b** (R = C_2H_5), 41367-12-8; **4a** (R = $CH(CH_3)_2$), 41367-13-9; **4b** (R = $CH(CH_3)_2$), 41367-14-0; **4b** (R = $C(CH_3)_3$), 41367-15-1; **4b** (R = $CO_2C_2H_5$), 41367-16-2; **4b** (R = 1-adamantyl), 41367-17-3; **4b** (R = C_6H_5), 41367-18-4; **4b** (R = *p*-$CH_3OC_6H_4$), 41367-19-5; **4b** (R = *p*-BrC_6H_4), 31797-11-2; **5**, 5157-11-9.

(12) F. Sachs, *Justus Liebigs Ann. Chem.*, **365**, 135 (1909).