267 (4.21), 303 (4.46), 309 (4.27), and 339 (3.33), and in the visible (ϵ) at 652 (3.81), 684 (333), 718 (339), and 807 (130) with shoulders at 602 (270), 670 (342), and 763 (147). The n.m.r. spectrum had a sharp singlet at 2.33 τ attributed to the 2-hydrogen and was otherwise consistent with structure IV.

Anal. Calcd. for $C_{10}H_5Br_3$: C, 32.91; H, 1.38; Br, 65.70. Found: C, 33.00; H, 1.23; Br, 66.12.

1,3-Dibenzoyloxy-5-chloroazulene (V).—To a solution of 70 mg. (0.19 mmole) of 1,3-dibenzoyloxyazulene[18] and 10 ml. of methylene chloride was added 26 mg. (0.2 mmole) of N-chlorosuccinimide and the mixture was allowed to stand overnight in a refrigerator. Ether was then added and the whole was washed with water. The residue from the dried organic solution was chromatographed on Florisil. Benzene eluted a pale yellow fraction and a band which was originally green changed to blue-green. The latter material was removed with methylene chloride and removal of the solvent left a green residue which crystallized when triturated with ether and afforded 55 mg. (72%) of green needles, m.p. 122–129°. Recrystallization from ether gave 24 mg. of chartreuse needles, m.p. 132–133°. A second crop amounted to 10 mg., m.p. 126–129.5° (total yield, 44%). A cyclohexane solution exhibited maxima in mμ in the ultraviolet (log ϵ) at 237 (4.58), 281 (4.69), and 379 (3.93), and in the visible (ϵ) a broad peak at 683 (380) with a broad shoulder at 728 (340).

Anal. Calcd. for $C_{24}H_{15}O_4Cl$: C, 71.56; H, 3.75. Found: C, 71.63; H, 3.73.

The Synthesis and Chemistry of Certain 2-Substituted 5,6-Dihydroimidazo-, -oxazolo-, and -thiazolo[*ij*]quinolines

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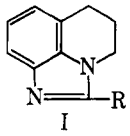
Received March 27, 1963

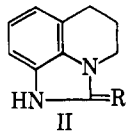
Isosteric 2-substituted 5,6-dihydroimidazo-, -oxazolo-, and -thiazolo[*ij*]quinolines were synthesized and examined for their chemical and physical properties. The 2-oxo and 2-thioxo derivatives are neutral compounds, but the 2-imino derivatives are of sufficient basic character to form salts and otherwise to become involved in reactions with acidic reagents. The infrared absorption peaks due to the substituents were determined. On the basis of infrared and ultraviolet spectral studies, the imidazoquinolines were assigned the tautomeric *exo* double bond structure (II). The ultraviolet studies also allowed a determination of important chromophores in these systems.

In a previous publication,[1] the synthesis and chemistry of 2-substituted 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolines (I) was discussed. Included as part of

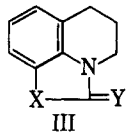


I

that work was an investigation of the ultraviolet spectra of the title compounds. On the basis of certain chemical and spectral characteristics, the authors concluded that the 2-hydroxy and the 2-mercapto derivatives existed in the cyclic urea form (II), which



II



III

is tautomeric with the structure usually assigned to the 5,6-dihydroimidazo[4,5,1-*ij*]quinolines (I). As an extension of that work, it was necessary to prepare those compounds (III) where X and Y are the same or different and are chosen from O, S, or NH in order to observe the chemical and spectra similarities and differences in the three (III, X = O, S, NH) isosteric families under consideration. As will be seen later, this work confirms the cyclic urea structure (II) reported[1] earlier for the 2-hydroxy and 2-mercapto derivatives. Furthermore, the data obtained in this work indicate an exo-imino structure for the 2-amino derivative. The imidazo[*ij*]quinolines, therefore, will hereafter be referred to in light of structure II.

(1) A. Richardson, Jr., and E. D. Amstutz, *J. Org. Chem.*, **25**, 1138 (1960).

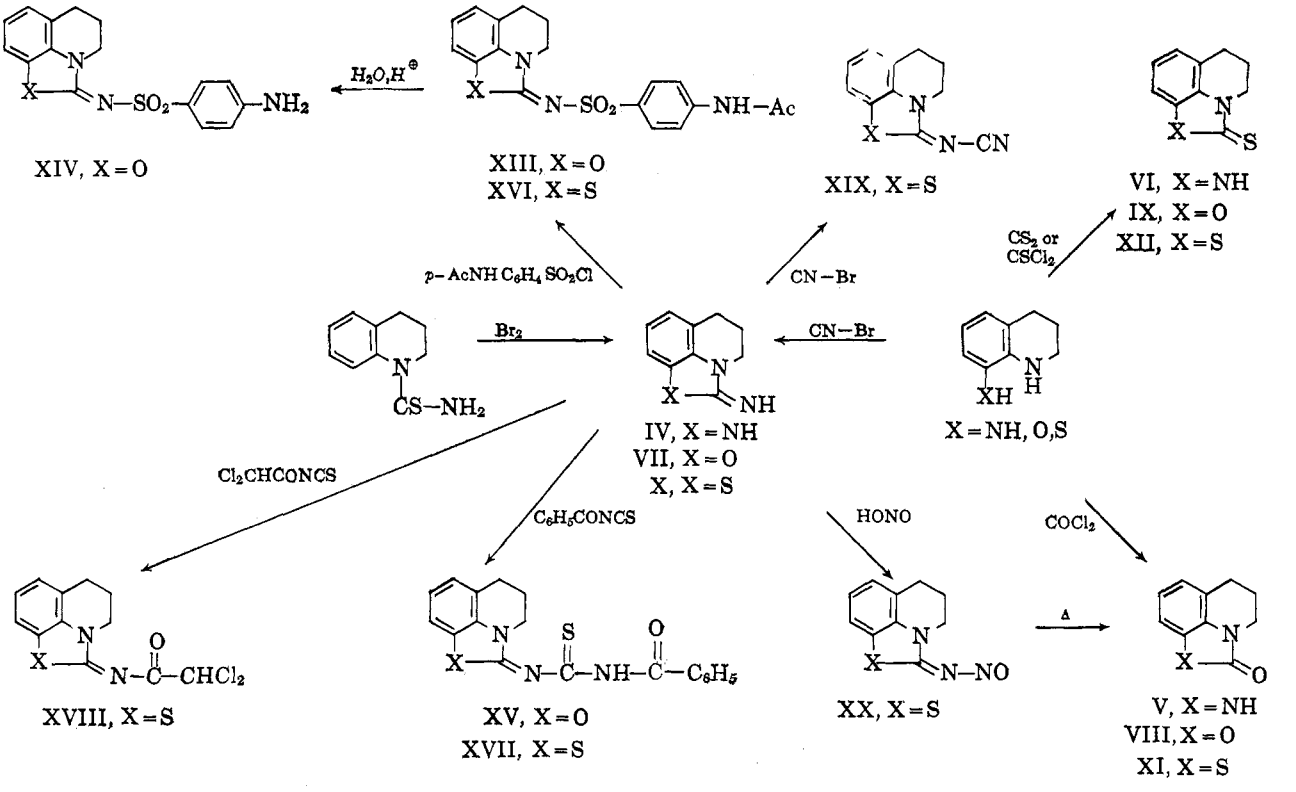
The 2-imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]-quinoline (IV) was prepared by condensing 8-amino-1,2,3,4-tetrahydroquinoline with cyanogen bromide in an aqueous medium. No difficulties were encountered during this procedure. Although the product was first isolated as a hydrobromide salt, the base was readily obtained by treatment of the salt with aqueous sodium hydroxide solution. The corresponding 2-oxo (V) and 2-thioxo (VI) derivatives were described earlier.[1]

The 2-imino-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VII) was prepared by condensing 8-hydroxy-1,2,3,4-tetrahydroquinoline with cyanogen bromide in an aqueous medium. The product separated as the hydrobromide salt, and the base, an oil, was obtained by treatment of this salt with aqueous sodium hydroxide solution. The corresponding 2-oxo (VIII) and 2-thioxo (IX) derivatives were prepared by treating 8-hydroxy-1,2,3,4-tetrahydroquinoline with phosgene and thiophosgene, respectively.

The basic character of the imino group of VII was exemplified by the reactions of that compound with certain other reagents. The imino compound reacted with *p*-acetamidobenzenesulfonyl chloride to yield the corresponding sulfonimido derivative (XIII). Compound XIII was subsequently hydrolyzed to form 2-(*p*-aminobenzenesulfonimido)-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (XIV). In another reaction, the imine (VII) was condensed with benzoyl isothiocyanate to yield 2-[(N-benzoylthiocarbamyl)imino]-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (XV) which was deep yellow in color. Attempts to N-nitrosate VII in aqueous media failed.

The 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (X) was prepared *via* an adaptation of the

SCHEME I



method of König, *et al.*[2] The procedure involved a bromine cyclization of 1-thiocarbamyl-1,2,3,4-tetrahydroquinoline and the product was isolated as the hydrobromide salt. The base was obtained as a low-melting solid by treatment of the salt with aqueous sodium hydroxide solution. The 2-oxo analog (XI) was prepared by a modification of König's method.[2] In this procedure, the 2-imino compound (X) was nitrosated in a mixture of dimethylformamide and glacial acetic acid. The N-nitrosoimino derivative (XX) was subsequently refluxed in xylene, whereupon it lost nitrogen and was converted to XI.

In order to synthesize 2-thioxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XII) it was necessary first to prepare 8-mercapto-1,2,3,4-tetrahydroquinoline. This compound has been described by Ushenko,[3] who prepared it by the hydrolysis of XI in alcoholic potassium hydroxide. In the work reported here, 2-nitrosoimino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XX), in hot alcoholic potassium hydroxide, conveniently was hydrolyzed to 8-mercapto-1,2,3,4-tetrahydroquinoline. The product was an oil which was characterized as the hydrochloride salt. The 2-thioxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XII) was prepared by condensing 8-mercapto-1,2,3,4-tetrahydroquinoline with either carbon disulfide or thiophosgene. The yield of XII by either procedure was low, but with thiophosgene it was nearly twice that obtained *via* carbon disulfide.

The 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (X) was reacted successfully with several reagents to yield imino-substituted derivatives. Nitrous acid yielded a solid N-nitrosoimino derivative (XX), which was employed as an intermediate during this work. With *p*-acetamidobenzenesulfonyl chloride or benzoyl isothiocyanate, the imine (X) formed 2-(*p*-acetamidobenzenesulfonimido)- (XVI) and 2-[(N-benzoylthiocarbamyl)imino]-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XVII), respectively. These results were analogous to those obtained with the corresponding iminoöxazoloquinoline (VII). When the imine (X) was condensed with dichloroacetyl isothiocyanate, the desired dichloroacetylthiocarbamylimino compound was not obtained. Instead, acylation of the imine occurred and the 2-dichloroacetylimino derivative (XVIII) was isolated. Treatment of the imine (X) with cyanogen bromide in benzene formed the corresponding 2-cyanimino derivative (XIX).

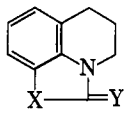
The three isosteric families under consideration exhibited very similar physical and chemical properties. In the imidazoquinoline and thiazoloquinoline families the melting points of the derivatives increased in the order: 2-imino, 2-oxo, 2-thioxo. The 2-imino and 2-oxo derivatives in the oxazoloquinoline family were oils. The 2-thioxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]-quinoline, however, was a solid and, therefore, it too was the highest melting compound of the three (VII, VIII, IX) members of the oxazoloquinoline family under discussion. Also consistent was the fact that in each family the 2-oxo and the 2-thioxo derivatives were insoluble in aqueous solutions of acid or bases. The 2-imino derivatives, however, were of sufficient basicity to allow salt formation and reactions with other acidic reagents. Spectral data, presented earlier[1] and also in the next section, show that the imidazoquinolines (IV, V, VI) exist in the *exo* double bond form; thus, all of the compounds discussed here are represented by structure III.

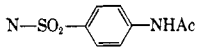
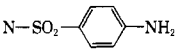
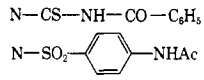
Scheme I will serve to illustrate and summarize the chemistry of the three ring systems under discussion.

(2) W. König, W. Kleinst, and J. Götze, *Ber.*, **64**, 1664 (1931).
(3) I. K. Ushenko and V. A. Portnyagina, *Ukr. Khim. Zh.*, **21**, 744 (1955); *Chem. Abstr.*, **50**, 16753[f] (1956).

TABLE I

FUSED HETEROCYCLIC [*ij*] QUINOLINES



Compound no.	X[a]	Y	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	$\mu_{C=Y}$
IV	NH	NH	201–202	69.33	69.03	6.40	6.60	24.26	24.19	
V	NH	O	210–211[b]	68.98	68.96	5.79	5.88	16.09	16.30	5.91
VI	NH	S	214.5–215.5[c]	63.14	63.25	5.31	5.40	14.72	14.68	8.23
VII	O	NH	254–256[d]	47.07	47.00	4.35	4.58	10.98	10.88	5.91[e]
VIII	O	O	Oil[f]	68.56	68.22	5.18	5.27	8.00	7.79	5.62
IX	O	S	136.5–137.5	62.80	62.78	4.74	4.54	7.32	7.11	8.51
X	S	NH	343–345[g]	44.28	44.35	4.09	4.09	10.33	10.09	6.21[h]
XI	S	O	75.5–76.0[i]	62.80	62.57	4.74	4.78	7.33	7.13	5.99
XII	S	S	123.5–125.5	57.94	57.83	4.38	4.10	6.76	6.59	8.85
XIII	O		316–317 dec.	58.21	58.67	4.61	4.56	11.31	11.06	
XIV	O		245–247	58.34	58.51	4.59	4.50	12.76	12.51	
XV	O		127–128 dec.	64.08	64.00	4.48	4.48	12.45	12.23	
XVI	S		276–277	55.77	55.55	4.42	4.60	10.84	10.72	
XVII	S	N—CS—NH—CO—C_6H_5	182–183 dec.	61.16	60.97	4.28	4.21	11.89	11.67	
XVIII	S	N—CO—$CHCl_2$	167–168	47.85	47.70	3.35	3.48	9.30	9.06	
XIX	S	N—CN	162–164	61.37	61.52	4.21	4.25	19.52	19.57	
XX	S	N—NO	147 dec.	Not analyzed						

[a] Ultraviolet and infrared spectra indicate the imidazoquinolines are in the form where X = NH. [b] Reported m.p. 213–214°. See ref. 1. [c] Data from original sample as reported in ref. 1. [d] Melting point and analysis are of the hydrobromide salt. Free base is an oil which forms a picrate which melts at 229–230°. [e] $\mu_{C=Y}$ for the hydrobromide salt, 5.85. [f] B.p. 128–130° (0.5 mm.); $n^{25}D$ 1.5857. [g] Melting point and analysis are of hydrobromide salt reported to melt at 328° (see ref. 2). Free base melts at 56–58° and forms a picrate which melts at 250–251°. [h] $\mu_{C=Y}$ for the hydrobromide salt, 6.10. [i] Reported m.p. 77° (see ref. 2).

Discussion of the Spectra

Infrared and ultraviolet absorption spectra were taken on these compounds in an attempt to determine the structures of certain of the compounds and also to record the absorption peaks of the 2-substituents where possible. The infrared absorption peaks are listed in Table I, while the ultraviolet absorption spectra are found in Figures 1–4. The structures of the oxazoloquinolines and of the thiazoloquinolines are fixed; however, the imidazoquinolines, IV, V, and VI, are theoretically able to exist in two tautomeric forms (I and II). By a comparison of the infrared and ultraviolet spectra of the imidazoquinolines in question, with those of the oxazolo-, thiazolo- and other imidazoquinolines, some conclusions may be drawn regarding the predominant tautomeric structure of IV, V, and VI.

Intense carbonyl peaks were found at 5.62 μ and 5.99 μ in the infrared absorption spectra of 2-oxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VIII) and 2-oxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XI), respectively. A similarly intense peak was found at 5.91 μ in the spectrum of 2-oxo-5,6-dihydro-1*H*,4H-imidazo[4,5,1-*ij*]quinoline (V). There was no such peak found in the spectrum of the other imidazoquinolines discussed here or in the spectrum of 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline itself. From the intensity of the peak at 5.91 μ, one would conclude that 2-oxo-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (V) is predominantly or entirely in keto form (II, R = O).

The determination of the absorption peaks due to thiocarbonyl groups was less conclusive, since the thiocarbonyl absorption is characteristically sensitive to the nature of the molecule containing that functional group. After a process of careful comparison of the spectra of other members of the same family, the bands at 8.51 μ and 8.85 μ were chosen as the bands representing the thiocarbonyl group in 2-thioxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (IX) and 2-thioxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XII), respectively. The absence of any absorption in the 4-μ region of the spectrum of 2-thioxo-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (VI) is an indication that VI exists in the thioketo form (II, R = S). By a process of comparison and elimination, the peak at 8.23 μ in the spectrum of VI was considered to be the thiocarbonyl absorption peak of VI. The choice of the thiocarbonyl peaks in these three compounds is also in agreement with reported observations[4–7] of the infrared absorption due to the thiocarbonyl group. In addition, the ratio of the wave number of a carbonyl peak to the wave number of the corresponding thiocarbonyl peak was reported[5–7] to be in the range of 1.14–1.6 and is quite often close to 1.5. In the three series discussed here, those ratios are 1.39, 1.52, and 1.48 for the imidazoquinoline, oxazoloquinoline, and thiazoloquinoline series, respectively. The thioxo derivatives (VI, IX, XII) also exhibit very strong bands in the 7-μ region. The imidazoquinoline derivative (VI) exhibits such a band at 6.82 μ, while

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 355–357.

(5) R. Mecke, R. Mecke, and A. Lüttringhaus, *Z. Naturforsch.*, **10b**, 367 (1955).

(6) R. Mecke, Jr., and R. Mecke, Sr., *Ber.*, **89**, 343 (1956).

(7) R. Mecke, R. Mecke, and A. Lüttringhaus, *ibid.*, **90**, 975 (1957).

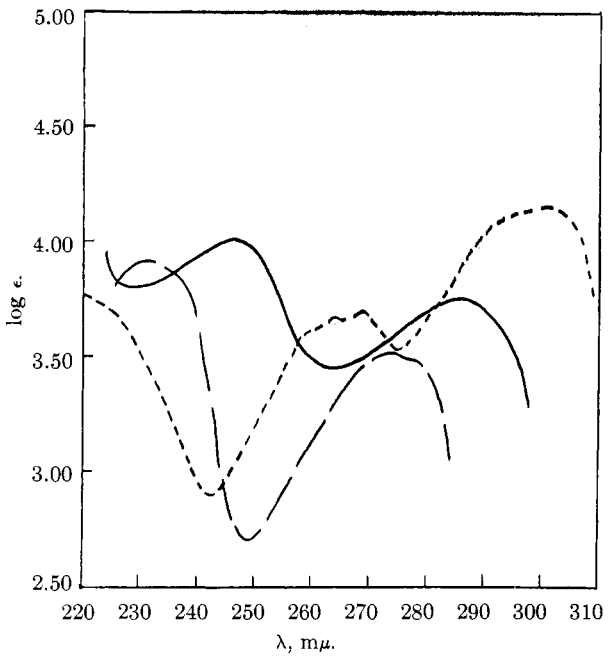


Fig. 1.—Ultraviolet absorption spectra of 2-substituted 5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinolines: ———, VII; — — —, VIII; - - - - -, IX.

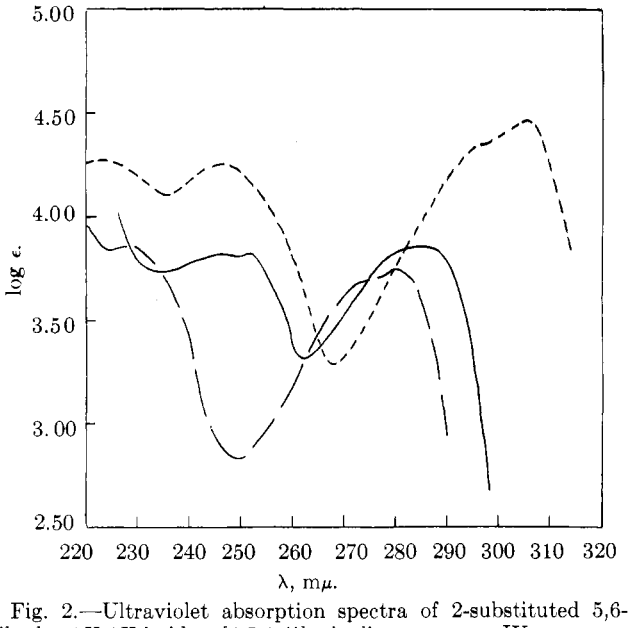


Fig. 2.—Ultraviolet absorption spectra of 2-substituted 5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinolines: ———, IV; — — —, V; - - - - -, VI.

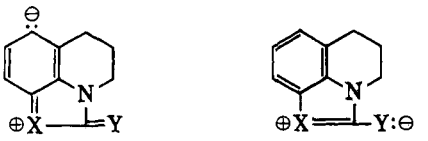
the corresponding oxazoloquinoline (IX) and thiazoloquinoline (XII) exhibit similar bands at 7.04 μ and 7.31 μ, respectively. These bands have been assigned to the infrared absorption of the C–N group in the thioxo derivatives. Such an assignment is in agreement with previously reported[4] work.

The imine peaks are at 5.91 μ and 6.21 μ for 2-imino-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VII) and 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (X), respectively. It is interesting that the imine peak of the hydrobromide salt of each of these compounds is shifted hyposchromically. That for the oxazoloquinoline salt is at 5.85 μ, while the corresponding peak for the thiazoloquinoline salt is at 6.10 μ. It was not possible to determine the imine peak in the spectrum of 2-imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (IV). The infrared spectrum of that compound is too complex in the imine–amine absorption regions to allow proper interpretation. In this case, the ultraviolet absorption spectrum was employed for a determination of structure.

Figures 1, 2, and 3 indicate the ultraviolet absorption spectra of the imino, oxo, and thioxo derivatives of 5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline, 5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline, and 5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline, respectively. For purposes of comparison, the spectra of the 8-substituted-1,2,3,4-tetrahydroquinolines are included in Figure 4. The ultraviolet absorption bands of 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline and its 2-methoxy derivative were reported earlier.[1] In general, the absorption maximum in a given family of compounds, including the starting materials, increases in wave length as the substituent varies from oxygen to nitrogen to sulfur. This same phenomenon is also generally observed if one holds the substituent constant and proceeds from the oxazoloquinoline family to the imidazoquinoline family to the thiazoloquinoline family; *i.e.*, from oxygen to nitrogen to sulfur. As might, therefore, be predicted, 2-oxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VIII) has the lowest wave-length absorption maximum, while 2-thioxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XII) exhibits the highest wave-length absorption maximum of the nine isosteres (IV–XII) under consideration.

A comparison of the absorption curves for 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline and its 2-methoxy derivative[1] with those of 2-oxo- and 2-imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (Figure 2) may shed some light on the structure of the 2-imino derivative (IV). 2-Methoxy-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline exhibits an absorption spectrum similar to 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline itself. Furthermore, 2-oxo-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (V) has an absorption spectrum which is unlike the spectra of these representative imidazoquinolines. The spectrum of the oxo compound (V) is more like that of 8-amino-1,2,3,4-tetrahydroquinoline. This similarity is expected since the infrared analysis, discussed above, indicates a phenyleneurea structure (II, R = O) for the compound. The absorption spectrum of 2-imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (IV) is also similar to those of the oxo compound (V) and 8-amino-1,2,3,4-tetrahydroquinoline, and it also differs from the spectra of the representative imidazoquinolines. On the basis of ultraviolet absorption, then, the exo-imino structure (II, R = NH) was assigned to 2-imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]-quinoline (IV).

Although a number of contributors to the resonance hybrid are possible, a consideration of the effects of variations in X and Y (III) on the ultraviolet absorption maxima was of value in determining the important chromophores involved in these isosteres. The ring hetero atom, X, is capable of donating electrons to the aromatic ring and/or to the *exo* double bond system involving Y. The resulting contributors to the hybrid are illustrated in part by IIIa and IIIb shown. If one considers IIIa to be a major contributor to the hybrid involving X and the aromatic ring, then the



IIIa IIIb

effect of X on the absorption spectra is nicely explained. As X becomes less electronegative, its unshared electrons become more capable of conjugating with the ring to form a system such as IIIa; thus, IIIa becomes a lower energy system, exhibiting a longer wave-length absorption maximum. This effect is illustrated by the ultraviolet spectra in Figures 1, 2, and 3. When Y is held constant, the oxazoloquinolines (X = O) generally produce the shortest wave-length maxima, while the imidazoquinolines (X = NH) and the thiazoloquinolines (X = S) produce increasingly longer wave-length maxima.

The effect of variations in Y can be similarly explained if one considers IIIb to be a major contributor to the hybrid involving Y. From a consideration of both IIIa and IIIb, one can see that Y and the aromatic ring compete for the unshared electrons on X. The effect of Y, and therefore the effect of chromophore IIIb, is to tend to prohibit the formation of chromophore IIIa. As Y becomes less electronegative, however, the contribution of IIIb decreases and less energy is required to form IIIa. This effect of Y can be observed in the ultraviolet absorption spectra (Figures 1, 2, and 3). When X is held constant, one will observe that the oxo derivatives (Y = O) exhibit the shortest wave length maxima, while the imino (Y = NH) and the thioxo (Y = S) derivatives exhibit increasingly longer wavelength maxima.

The ultraviolet absorption spectra show that as X and/or Y become less electronegative, the absorption maxima are shifted bathochromically. These data support IIIa and IIIb as major contributions to the hybrid. These structures serve to illustrate and explain what appear to be important electronic properties of the isosteric systems discussed here.

Experimental[8]

All melting points and boiling points are uncorrected. Yields, in most cases, correspond to the quantity of analytically pure product isolated. Few attempts were made to vary reaction conditions to improve the yield. The infrared spectra were obtained using a Perkin-Elmer, Model 21, infrared spectrophotometer. All of the infrared spectra were taken *via* potassium bromide plates, except for compounds VII, VIII, and X whose spectra were determined on the undiluted oils in sodium chloride cells. The ultraviolet spectra were obtained using a Cary ultraviolet spectrophotometer. Solutions of the compounds in alcohol were employed in obtaining the ultraviolet spectra.

2-Imino-5,6-dihydro-1*H*,4*H*-imidazo[4,5,1-*ij*]quinoline (IV).—A slurry of 14.0 g. (0.094 mole) of 8-amino-1,2,3,4-tetrahydroquinoline[1] in 150 ml. of water was stirred under an atmosphere of nitrogen. To the mixture was added 10.0 g. (0.094 mole) of cyanogen bromide (Eastman) in small portions. During the addition, the mixture warmed and became slightly colored while a solid separated which was assumed to be the hydrobromide salt. After all the cyanogen bromide had been added, the mixture was stirred for 4 hr. at room temperature. It was allowed to stand under a nitrogen atmosphere overnight, and was then filtered. The solid which separated was slurried in 10% aqueous sodium hydroxide. The product was then filtered, washed with water, dried, and recrystallized from hot toluene. The product separated as colorless needles which weighed 6.5 g. (40%) and melted at 201–202°. A picrate formed which darkened without melting below 320°.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.33; H, 6.40; N, 24.26. Found: C, 69.03; H, 6.60; N, 24.19.

2-Imino-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VII).—Cyanogen bromide (Eastman) and 8-hydroxy-1,2,3,4-tetrahydroquinoline[9] were condensed by the procedure outlined for IV. The base was an oil; therefore, the hydrobromide salt first obtained (39%) was recrystallized from ethanol–ether and analyzed. This salt melted at 254–256°. A picrate formed which melted at 229–230°.

Anal. Calcd. for $C_{10}H_{10}N_2O$ HBr: C, 47.07; H, 4.35; N, 10.98. Found: C, 47.00; H, 4.58; N, 10.88.

2-Oxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (VIII).—A slurry of 14.9 g. (0.10 mole) of 8-hydroxy-1,2,3,4-tetrahydroquinoline[9] in 150 ml. of glacial acetic acid was stirred and treated dropwise with a solution of 9.9 g. (0.10 mole) of phosgene in 50

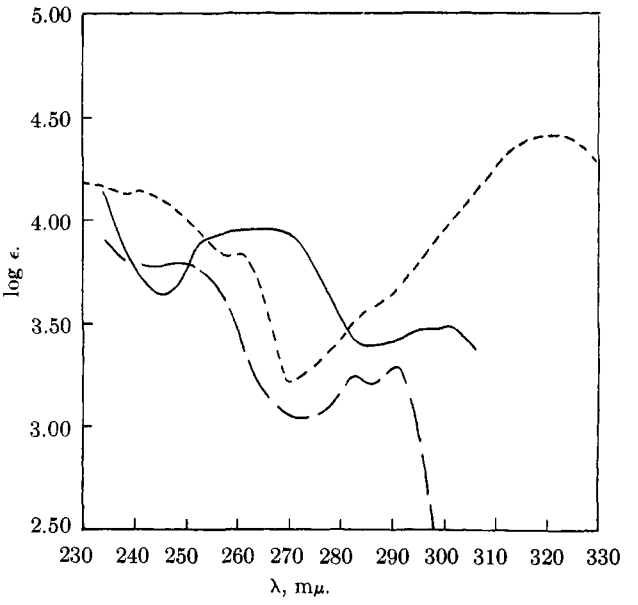


Fig. 3.—Ultraviolet absorption spectra of 2-substituted 5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinolines: ———, X; — — —, XI; - - - -, XII.

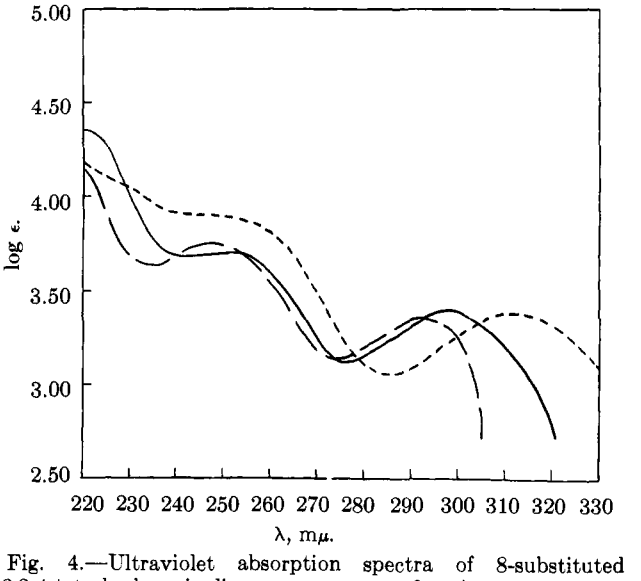


Fig. 4.—Ultraviolet absorption spectra of 8-substituted 1,2,3,4-tetrahydroquinolines: ———, 8-amino-1,2,3,4-tetrahydroquinoline; — — —, 8-hydroxy-1,2,3,4-tetrahydroquinoline; - - - - -, 8-mercapto-1,2,3,4-tetrahydroquinoline.

(8) Compounds V and VI were prepared according to the methods described in ref. 1. Compounds X and XI were prepared according to the methods described in ref. 2.

(9) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

ml. of benzene. The mixture warmed slightly and the original solid dissolved. Before all the phosgene had been added, a new solid began to separate. The mixture was stirred for 2.5 hr. after all the phosgene had been added. It was then refluxed for 1.5 hr., cooled, and filtered. The solid which was collected (6.4 g.) melted at 219–221° and did not depress the melting point of authentic 8-hydroxy-1,2,3,4-tetrahydroquinoline hydrochloride prepared by treating an alcoholic solution of 8-hydroxy-1,2,3,4-tetrahydroquinoline with an alcoholic solution of hydrogen chloride.

The acetic acid filtrate was condensed *in vacuo* on a steam bath. The oily residue was treated first with aqueous sodium bicarbonate until neutral, and then with 10% sodium hydroxide until slightly alkaline. It was extracted with ether, dried over magnesium sulfate, filtered, and distilled. The product boiled at 128–130° (0.5 mm.); however, it appeared to be slightly cloudy.

This distillate was chromatographed on alumina with a mixture of methylene chloride and low boiling (40–60°) petroleum ether. Initially, a 10% solution of methylene chloride was used, but this was gradually increased to 100% as the elution continued. The clear fractions of eluted oil were then combined. The product weighed 2.2 g. (19% based on unrecovered 8-hydroxy-1,2,3,4-tetrahydroquinoline), $n^{25}D$ 1.5857, and formed no picrate.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.22; H, 5.27; N, 7.79.

2-Thioxo-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (IX).—A solution of 19.5 g. (0.130 mole) of 8-hydroxy-1,2,3,4-tetrahydroquinoline[9] and 26.5 g. (0.260 mole) of triethylamine in 200 ml. of absolute ether was cooled in an ice bath and stirred. To this was added a solution of 15.0 g. (0.130 mole) of thiophosgene (Matheson Coleman and Bell) in 150 ml. of ether, dropwise. A solid separated immediately. After complete addition of the thiophosegene, the mixture was gently refluxed for 1 hr. It was then cooled and filtered. The solid which separated was washed twice with 500-ml. portions of water, dried, and recrystallized from benzene–petroleum ether. The pale yellow solid weighed 10.6 g. (43%) and melted at 135–137°.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.79; H, 4.74; N, 7.32. Found: C, 62.98; H, 4.63; N, 6.98.

2-Nitrosoimino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XX).—A slurry of 27.1 g. (0.10 mole) of 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline hydrobromide (X) was made in 125 ml. of glacial acetic acid and 125 ml. of dimethylformamide. This mixture was stirred and treated in small portions with a solution of 6.9 g. (0.10 mole) of sodium nitrite in 20 ml. of water. The reaction was followed with starch–iodide paper. An orange solid formed during the nitrosation. The mixture was stirred for 2 hr. after the last addition of the sodium nitrite solution. An equal volume of water was added, with stirring, and the orange solid which separated was filtered, washed with water, and dried. The product weighed 17.9 g. (82%) and melted at 147° with vigorous decomposition (lit.[2] m.p. 154° dec.).

8-Mercapto-1,2,3,4-tetrahydroquinoline.—A solution of 14.0 g. (0.25 mole) of potassium hydroxide in 200 ml. of absolute ethanol was refluxed. To the solution was added 17.9 g. (0.082 mole) of 2-nitrosoimino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XX) in small portions. The material effervesced, lost its color and dissolved. After approximately half of the nitroso compound had been added, a solid began to separate. From this point, small portions of ethanol were added to maintain the fluidity of the mixture; approximately 50 ml. of ethanol was required.

The mixture was refluxed for 4.5 hr. after the complete addition of the nitroso compound. The mixture was cooled and filtered. The filtrate was evaporated *in vacuo* on the steam bath and the oily residue was dissolved in an equal volume of water. Acidification of the solution to pH 2 with concentrated aqueous hydrochloric acid caused an oil to separate. This oil was extracted with ether. The solution was dried over magnesium sulfate, filtered, and distilled. A nearly colorless oil was collected at 134–136° (2.5 mm.) [lit.[3] b.p. 139–140° (5–6 mm.)]. Higher boiling fractions were very dark in color and were not collected.

The product weighed 5.5 g. (41%), $n^{25}D$ 1.6375. It formed a picrate which melted at 124° and a hydrochloride which melted at 183–184° dec.

Anal. Calcd. for $C_9H_{11}NS\cdot HCl$: C, 53.59; H, 5.50; N, 6.94. Found: C, 53.83; H, 5.81; N, 6.69.

2-Thioxo-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XII). Method A.—A solution of 3.3 g. (0.02 mole) of 8-mercapto-1,2,3,4-tetrahydroquinoline and 1.5 g. (0.02 mole) of carbon disulfide in 25 ml. of absolute ethanol was refluxed for 3 days. The solvent was removed *in vacuo* and an olly residue remained. This residue was triturated with ether and the solid which remained was recrystallized from absolute ethanol. The yellow needles which separated weighed 0.3 g. (7.2%) and melted at 123.5–125.5°.

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.76. Found: C, 57.83; H, 4.10; N, 6.59.

Method B.—A solution of 5.5 g. (0.033 mole) of 8-mercapto-1,2,3,4-tetrahydroquinoline and 6.7 g. (0.066 mole) of triethylamine in 55 ml. of ether was cooled in an ice bath. It was stirred and treated dropwise with a solution of 3.8 g. (0.033 mole) of thiophosgene (Matheson Coleman and Bell) in 40 ml. of ether. An additional 50 ml. of ether was introduced after the complete addition of the thiophosgene and the slurry was stirred at room temperature for 10 min. The mixture was then refluxed for 10 min., cooled and filtered. The solid which separated was slurried in water and made alkaline with 10% sodium hydroxide solution. It was filtered, washed with water, dried and recrystallized from ethanol. More of the same product was obtained by evaporating the original ethereal filtrate and working up the residue in a similar fashion. Both fractions were combined and recrystallized three times from ethanol (charcoal employed). The product formed pale yellow prisms which weighed 0.9 g. (13%) and melted at 125.0–127.5°.

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.76. Found: C, 57.92; H, 4.20; N, 6.77.

2-(*p*-Acetamidobenzenesulfonimido)-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (XIII).—A 10.0-g. (0.0392 mole) quantity of 2-imino-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline hydrobromide (VII) was shaken with 10% aqueous sodium hydroxide. The free base which separated as an oil was extracted with ether and dried over magnesium sulfate. The mixture was then filtered into 75 ml. of pyridine. It was stirred and treated dropwise with a solution of 9.2 g. (0.0392 mole) of *p*-acetamidobenzenesulfonyl chloride (Eastern) in 50 ml. of pyridine. The turbid mixture was heated on a steam bath, whereupon the ether evaporated and a clear solution remained. This solution was heated on a steam bath for 18 hr., during which time a solid separated. The mixture was cooled and poured into three times its volume of water. The solid which separated was quite intractable and was purified by triturating with boiling ethanol. The product weighed 2.1 g. (14%) and melted at 316–317° dec.

Anal. Calcd. for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31. Found: C, 58.67; H, 4.56; N, 11.06.

2-(*p*-Aminobenzenesulfonimido)-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (XIV).—A slurry of 1.7 g. (0.0046 mole) of 2-(*p*-acetamidobenzenesulfonimido)-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]-quinoline (XIII) in 50 ml. of 4 *N* aqueous hydrochloric acid and 25 ml. of ethanol was refluxed for 4 hr. The mixture was filtered and 0.7 g. of starting material was recovered as undissolved solid. The filtrate was diluted with an equal volume of water and made alkaline with concentrated aqueous ammonia. The solid which separated was recrystallized twice from ethanol to yield 0.1 g. (7%) of colorless needles which melted at 245–247°.

Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.51; H, 4.50; N, 12.51.

2-[(N-Benzoylthiocarbamyl)imino]-,5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline (XV).—A 13.0-g. (0.05 mole) quantity of 2-imino-5,6-dihydro-4*H*-oxazolo[5,4,3-*ij*]quinoline hydrobromide (VII) was slurried with aqueous 10% sodium hydroxide. The base was extracted with ether and dried over magnesium sulfate.

In the meantime, 3.8 g. (0.05 mole) of ammonium isothiocyanate was dissolved in 100 ml. of dry acetone and this solution was treated dropwise with 7.0 g. (0.05 mole) of benzoyl chloride. The resulting mixture, which contained a colorless solid, was stirred and refluxed for 5 min. The benzoyl isothiocyanate thus formed was not isolated but was used in the next step.

The ethereal solution of 2-imino-5,6-dihydro-4*H*-oxazolo-[5,4,3-*ij*]quinoline (VII) was filtered and added dropwise to the benzoyl isothiocyanate solution at a rate such that a gentle reflux was maintained. After complete addition of the imine, the mixture was refluxed for 0.5 hr., cooled, and poured onto cracked ice. The yellow solid which separated was filtered, washed with water, triturated with ethanol, and recrystallized from benzene. The deep yellow product weighed 6.1 g. (36%) and melted at 127–128° dec.

Anal. Calcd. for $C_{18}H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45. Found: C, 64.00; H, 4.48; N, 12.23.

2-(*p*-Acetamidobenzenesulfonimido)-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XVI).—A 5.4-g. (0.02 mole) quantity of 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline hydrobromide (X) was shaken with 10% aqueous sodium hydroxide and the free base was extracted with ether and dried over magnesium sulfate. It was then filtered into 75 ml. of pyridine. To this mixture was added a solution of 4.7 g. (0.02 mole) of *p*-acetamidobenzenesulfonyl chloride (Eastman) in 25 ml. of pyridine. A solid separated immediately and the liquid phase became orange. The mixture was heated on a steam bath for 1 hr., during which time the ether phase evaporated and the pyridine phase became colorless. It was then cooled and filtered. The solid which separated was the hydrochloride salt of the imine. The filtrate was treated with 10% aqueous sodium hydroxide and the solid which separated weighed 0.7 g. (9%). It was combined with the product obtain by repetition of this reaction, and recrystallized twice from dimethylformamide and water, whereupon it melted at 276–277°.

Anal. Calcd. for $C_{18}H_{17}N_3O_3S_2$: C, 55.77; H, 4.42; N, 10.84. Found: C, 55.55; H, 4.60; N, 10.72.

2-[(N-Benzoylthiocarbamyl)imino]-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XVII).—A 15.0-g. (0.055 mole) quantity of 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline hydrobromide (X) was slurried with 10% aqueous sodium hydroxide. The base was extracted with ether and dried over magnesium sulfate. This solution was then filtered into a dropping funnel and it was added dropwise to a solution of benzoyl isothiocyanate (0.06 mole) in acetone, prepared as described for the synthesis of XV. The rate of addition was such that a gentle reflux was maintained. After the complete addition of the imine, the mixture was refluxed for 15 min., cooled, and poured onto ice.

The ether layer was separated and retained. The aqueous phase was extracted several times with ether, and all the extracts were combined and diluted with a twofold volume of low boiling petroleum ether. The material which separated was recrystallized twice from benzene as yellow prisms which weighed 3.7 g. (19%) and melted at 182–183° dec.

Anal. Calcd. for $C_{18}H_{15}N_3OS_2$: C, 61.16; H, 4.28; N, 11.89. Found: C, 60.97; H, 4.21; N, 11.67.

2-Dichloroacetimido-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XVIII).—A solution of 4.4 g. (0.058 mole) of ammonium thiocyanate in 75 ml. of dry acetone was treated with 8.5 g. (0.058 mole) of dichloroacetyl chloride. A colorless solid separated immediately. This mixture was stirred and treated dropwise with a solution of 11.0 g. (0.058 mole) of 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (X) in 100 ml. of acetone. The reaction mixture warmed only slightly during the addition of the imine. After the addition of the imine was complete, the mixture was refluxed for 15 min., cooled, and poured onto ice. The solid which separated was decolorized and recrystallized twice from ethanol. The colorless product weighed 1.1 g. (6.3%) and melted at 167–168°.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2OS$: C, 47.85; H, 3.35; N, 9.30. Found: C, 47.70; H, 3.48; N, 9.06.

2-Cyanimino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline (XIX).—A 7.2-g. (0.027 mole) quantity of 2-imino-5,6-dihydro-4*H*-thiazolo[5,4,3-*ij*]quinoline hydrobromide (X) was slurried in 10% aqueous sodium hydroxide. The free base was extracted with benzene, dried over magnesium sulfate and filtered. The solution was stirred and treated first with 2.6 g. (0.026 mole) of triethylamine and then with 2.7 g. (0.026 mole) of cyanogen bromide (Eastman) in small portions. The mixture was refluxed for 2 hr. after the last addition of the cyanogen bromide, cooled, and filtered. The solid which separated was washed with benzene, dried, and then washed with water and dried. Meanwhile, the benzene filtrate was treated with low boiling petroleum ether and the solid which separated was collected. Both of these solids proved to be identical by a mixture melting point. After recrystallization from ethanol, the product weighed 0.8 g. (15%) and melted at 162–164°.

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.52; H, 4.25; N, 19.57.

5,6-Dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline.—A solution of 10.0 g. (0.0675 mole) of 8-amino-1,2,3,4-tetrahydroquinoline[1] in 50 ml. of formic acid was refluxed for 17 hr. The solution was cooled and made slightly alkaline with dilute aqueous ammonia. The mixture was extracted with ether, dried over magnesium sulfate, filtered, and the solvent was evaporated. The oil which remained was triturated with petroleum ether (75–90°), whereupon it crystallized. It was filtered and dried for 22 hr. at 40° (0.2 mm.). The product weighed 5.0 g. (44%) and melted at 76–77°.[10]

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.91; H, 6.37; N, 17.71. Found: C, 76.16; H, 6.72; N, 17.63.

Acknowledgment.—The author wishes to express his thanks to Mrs. Janice Hall and Mr. William F. Boyd, who ran the infrared and ultraviolet spectra, and to Mr. Michael Gordon and Mr. Raymond Snider, who performed the microanalyses. The author also appreciates the kind advice offered by his colleagues, Mr. Frank P. Palopoli, Dr. Albert A. Carr, and Dr. Frederick J. McCarty, during the preparation of this manuscript.

(10) This product was slightly hygroscopic; thus, the lower melting point previously reported (see ref. 1) may have been due to hydration of the sample.

Reactions of Aromatic Thiols with Oxazolines

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Received April 4, 1963

N-Arylmercaptoalkyl amides are obtained in high yield by reaction of aromatic thiols with oxazolines. Structural proof is presented and a reaction mechanism is proposed.

Goldberg and Kelly[1] have shown that N-(2-hydroxyethyl)thiobenzamide results from the reaction of hydrogen sulfide with 2-phenyl-2-oxazoline, the sulfur becoming bonded to what was initially C-2 of the oxazoline ring. Fry[2] and others[3] have reported that thio acids, RCOSH, on reaction with oxazolines yield derivatives resulting from attack at position 5 of the ring. It became of interest to us, as a continuation of our investigation of the chemistry of oxazolines,[4] to determine the behavior of these heterocyclics toward other sulfur compounds. The results of studies with aromatic thiols are reported here.

A reaction occurs on heating a mixture of 2-ethyl-4,4-dimethyl-2-oxazoline and benzenethiol as indicated by a rise in the reflux temperature. Distillation gives a 1:1 product in 98% yield. This was proved to be N-(2-phenylmercapto-1,1-dimethylethyl)propionamide (I). A benzamide derivative II is obtained by the reaction of benzenethiol with 2-phenyl-4,4-dimethyl-2-oxazoline,

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