

a 500-cc., two-necked flask under the column described above. A modified Hershberg stirrer was mounted in the second neck of the flask. The reaction mixture was stirred and heated in an oil-bath at 120–130° for thirty hours, while distillate was slowly taken off through the column jacketed at 65°. A total of 64 g. of distillate was collected. The residue was cooled in an ice-bath and worked up by the procedure described above under the condensation of methyl propionate with methyl benzoate.

Distillation of the reaction product through the spiral-packed column referred to above gave: (I) 8 g., probably methyl benzoate, b. p. 67–85° (9 mm.), (II) 47 g. methyl α -butyrylbutyrate, b. p. 85–90° (9–7 mm.), (III) 6 g. intermediate, (IV) 40 g. (41.3% on methyl benzoate) of methyl α -benzoylbutyrate, b. p. 115–120° (1 mm.), n_D^{25} 1.5215.

Summary

Sodium methoxide has been used to effect the acetoacetic ester type of condensation of several methyl esters. Procedures have been described for the self condensation of methyl propionate and of methyl n -butyrate to give good yields of β -ketoesters without the use of very large excesses of the esters. It has been found possible to effect satisfactory syntheses of methyl α -benzoylpropionate and of methyl α -benzoyl- n -butyrate by direct ester condensation.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Dialkylaminoalkyl Sulfides and Ethers Derived from Quinoline and Acridine Heterocycles

BY R. O. CLINTON AND C. M. SUTER

Although the literature contains references to a very large number of heterocyclic nitrogen compounds substituted by basic side chains linked to the nucleus by an imino ($-\text{NH}-$) group, few compounds of this type in which the linkage is oxygen or sulfur have been described. It was the purpose of the present study to determine the effect of replacement of the $-\text{NH}-$ by the $-\text{O}-$ or $-\text{S}-$ linkage upon the therapeutic activity of these compounds, particularly toward the malaria parasite.

The literature¹ describes several quinolines in which 2-dialkylaminoethoxy side chains are linked to the nucleus in the 2- or 4-position, and further substituents (*e. g.*, methyl, phenyl, carboxamide) appear in the quinoline ring. Bachman, *et al.*,² have reported the preparation of 3-amino-4-(3-diethylamino-2-hydroxypropylmercapto)-quinoline by the alkylation of the corresponding aminoquinolinethiol with 3-diethylamino-1,2-

TABLE I
7-CHLOROQUINOLINES

No.	4-Substituent	Max., $m\mu$	$\epsilon \times 10^{-3}$	Min., $m\mu$	$\epsilon \times 10^{-3}$
1	2-(2-Diethylamino-ethylmercapto)-ethoxy ^a	231	63.00	264	1.50
		305	9.49	307	9.18
		310	9.30		
2	4-Diethylamino-1-methylbutyloxy ^a	232	32.18	264	0.85
		310	6.66		
3	2-Diethylamino-ethylmercapto ^{a,b}	241	42.3	268	1.90
		332	17.59		
4	2-Di- n -hexylamino-ethylamino ^{a,c}	221	29.60	231	24.40
		235	25.25	245	15.72
		248	15.79	278	2.10
		326	18.15	330	16.24
		339	18.20		

(1) U. S. Patents 1,572,768 (Reissue 16,394), 1,688,469, 1,841,970, 1,860,286, 1,891,980; Bachman, *et al.*, *J. Org. Chem.*, **9**, 302 (1944).

(2) Bachman, Welton, Jenkins and Christian, *THIS JOURNAL*, **69**, 366 (1947).

5	4-Diethylamino-1-methylbutylmercapto ^a	241	36.80	275	19.65
		345	16.21	347	16.15
		349	16.20		
6	4-Diethylamino-1-methylbutylmercapto ^{a,e}	230	30.38	280	3.77
		315	9.98	320	9.90
		322	9.94		
7	4-Diethylamino-1-methylbutyl-amino ^{a,f}	220	32.25	231	18.05
		235	18.85	243	13.80
		256	16.28	280	1.85
		330	17.83	336	15.90
		343	19.45		
8	4-Diethylamino-1-methylbutyl-amino ^d	218	39.40	246	15.10
		255	17.91	275	1.33
		330	11.90		

6-CHLORO-2-METHOXYACRIDINES

9-Substituent

9	2-Diethylamino-ethylmercapto ^a	222	22.13	240	13.83
		275	68.97	310	1.01
		381	14.13	404	3.77
		445	5.58		
10	4-Diethylamino-1-methylbutylmercapto ^a	225	19.31	240	13.76
		276	64.26	315	0.83
		376	12.40	406	4.10
		445	5.79		
11	4-Diethylamino-1-methylbutyl-amino ^{a,g}	220 (?)	...	242	10.19
		280	55.07	318	2.69
		344	4.99	364	1.26
		424	9.40	436	8.65
		444	8.87		

^a In 0.01 *N* hydrochloric acid. ^b Inflection at 380–385 $m\mu$, $\epsilon = 450$. ^c Huber, Bair and Laskowski, *THIS JOURNAL*, **67**, 1619 (1945). ^d In 0.01 *N* sodium hydroxide. ^e Inflection at 375–380 $m\mu$, $\epsilon = 900$. ^f These values agree well with those reported by Drake, *et al.*, *THIS JOURNAL*, **68**, 1214 (1946). ^g Cf. Scudi and Jelinek, *J. Biol. Chem.*, **152**, 27 (1944).

epoxypropane. In addition, several quinolyl sulfides of related types are listed by Wiselogle,³

(3) Wiselogle, "Survey of Antimalarial Drugs," Vol. II, Part 2, pp. 1107–1108 (1946).

TABLE II
 BASES AND DERIVATIVES

Compound	Base			Analyses, %	
	B. p., °C.	Mm.	Formula	Calcd.	Found
2-(2-Diethylaminoethylmercapto)-quinoline	113	0.05	C ₁₅ H ₂₀ N ₂ S
2-(3-Diethylaminopropylmercapto)-4-methylquinoline	169	0.40	C ₁₇ H ₂₄ N ₂ S	N, 9.71	9.67
4-(2-Diethylaminoethylmercapto)-3,6-dimethylquinoline ^a	150	0.06	C ₁₇ H ₂₄ N ₂ S	N, 9.71	9.73
7-Chloro-4-(2-diethylaminoethylmercapto)-quinoline ^f	140	0.34	C ₁₅ H ₁₉ ClN ₂ S	N, 9.50	9.23
4-(2-Diethylaminoethylmercapto)-3,8-dimethylquinoline	152-155 ^f	0.26
7-Chloro-4-(3-diethylaminopropylmercapto)-quinoline ⁱ	140	0.04	C ₁₆ H ₂₁ ClN ₂ S	N, 9.07	8.90
7-Chloro-4-(3-N-piperidylpropylmercapto)-quinoline ⁱ	152	0.03	C ₁₇ H ₂₁ ClN ₂ S	N, 8.73	8.44
7-Chloro-4-(4-diethylaminobutylmercapto)-quinoline	146	0.02	C ₁₇ H ₂₃ ClN ₂ S	N, 8.68	8.66
7-Chloro-4-(5-isopropylaminopentylmercapto)-quinoline ^m	C ₁₇ H ₂₃ ClN ₂ S	N, 8.68	8.64
7-Chloro-4-(4-diethylamino-1-methylbutylmercapto)-quinoline	182	0.45	C ₁₈ H ₂₅ ClN ₂ S	C, 64.16	64.45
7-Chloro-4-(3-diethylaminopropylmercapto)-3-methylquinoline	176	0.47	C ₁₇ H ₂₃ ClN ₂ S	N, 8.68	8.64
7-Chloro-4-(2-diethylaminoethoxy)-quinoline ^a	C ₁₅ H ₁₉ ClN ₂ O	N, 10.05	9.96
7-Chloro-4-(4-diethylamino-1-methylbutyloxy)-quinoline	160 ^f	0.25
7-Chloro-4-(2-(2-diethylaminoethylmercapto)-ethoxy)-quinoline ^r	186-188 ^f	0.08

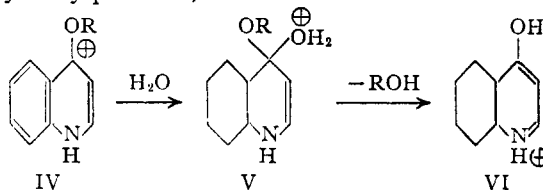
a number of which were originally prepared in the present work. A few acridyl sulfides, analogous to those presently described, have been prepared by Das-Gupta.⁴

In the present work a series of quinolines and acridines substituted by ω -dialkylaminoalkylmercapto side chains has been prepared by reaction between a sodio- ω -dialkylaminoalkanethiol and a suitable nitrogen heterocyclic chloro compound. These syntheses offered little difficulty, and the desired products were usually isolated readily in high yields by distillation or crystallization.⁵

The synthesis of the oxygen-linked side chains from a sodio- ω -tertiary-aminoalcoholate and a nitrogen heterocyclic chloro compound⁶ (e. g., 4-chloroquinoline) gave excellent yields of crude products; purification proved difficult, however, since distillation even in high vacuum at comparatively low temperatures brought about partial thermal cleavage of the oxygen linkage. The oxygen linkage was also readily cleaved by acids, the ease of cleavage being related to the type of nitrogen heterocyclic nucleus and the type of basic side chain. It is apparent that these com-

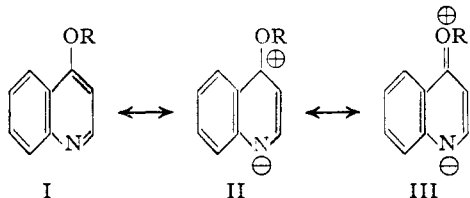
pounds can exist as resonance hybrids (I-III) and that the hybrid forms II and III are vinylogs of an imino ether rather than the normal phenolic ether type.

Hydrolytic cleavage in acid solution probably involves the attack of a water molecule on IV, the proton-coupled form of II, to give V, with subsequent release of an alcohol molecule to yield the hydroxyquinoline, VI.



The hybrid form III will not undergo cleavage, since it merely forms an oxonium salt in acid solution. For the 9-dialkylaminoalkoxyacridines the nuclear increase in resonance energy involving the third ring, and consequent stabilization of the forms analogous to II and III, decreases the stability of the oxygen-linked side chain compounds to the point at which they will undergo hydrolytic cleavage even with weak acids at room temperature within a few hours. A similar situation prevails with the corresponding sulfur-linked side chain compounds, although to a lesser degree because of the increased resonating property of the sulfur atom as compared with the oxygen atom, and consequent greater stabilization of the form corresponding to III.

It is interesting to note that in the corresponding imino-linked series the quinoline compounds are stable in acid solution for an indefinite period, whereas an acridine such as quinacrine does hydrolyze slowly under these conditions. This increased resistance of the imino-linked series toward hydrolytic cleavage is readily related to the greater stabilization of the resonance forms analogous to III, this stability being greater in the quinolines than in the acridines. Reaction rate



(4) Das-Gupta, *J. Indian Chem. Soc.*, **20**, 137 (1943); *C. A.*, **37**, 6665 (1943).

(5) Gilman and co-workers (*THIS JOURNAL*, **67**, 1845 (1945)) have reported that the treatment of 2-chloroquinoline with 2-diethylaminoethanethiol or the corresponding 3-propane analog, in an ethanolic solution of sodium ethoxide, results in the formation of the corresponding bis-(diethylaminoalkyl)-disulfides and not the expected quinolyl sulfides. This discrepancy with the present work cannot be explained.

(6) The converse reaction between the nitrogen heterocyclic hydroxy compound and an ω -dialkylaminoalkyl halide leads exclusively to N-substitution in most cases. cf. U. S. Patent 1,941,312

TABLE II (Continued)

Base			Dipicrate			Salt					
Analyses, %	Calcd.	Found	M. p., °C.	Analyses, %	Calcd.	Found	M. p., °C.	Calcd.	Analyses, %	Calcd.	Found
S, 12.31	11.72		148-150 ^a	S, 6.55	6.75		106.5-107.5 ^b	N, 6.13	5.92	S, 7.02	7.21
.....	...		130-131	S, 4.20	3.99		198-201 ^{c,d}	N, 7.76	7.67	Cl, 19.63	19.67
S, 11.12	11.00		164-165	S, 4.20	4.05		210-212.5 ^e	N, 7.76	7.80	Cl, 19.63	19.70
C, 61.10	61.31		213-214 ^d	N, 3.72 ^g	3.68		153.5-157.5 ^b				
H, 6.50	6.73										
.....	...		177-179	S, 4.20	4.31		188-190 ^c	N, 7.76	7.56	S, 8.87	8.86
S, 10.38	10.50		215-216	S, 4.18	4.33		175-178 ^c	S, 8.40	8.60	Cl, 18.57 ^h	18.53
S, 9.99	10.31		238-240 ^d	S, 4.11	4.40		227-228 ^{b,d}	S, 6.20	6.43
S, 9.93	9.96		195-196 ^d	S, 4.10	4.40	
S, 9.93	9.92		185-186	S, 4.10	4.13		224.8-225.4 ^e	N, 7.08	6.90	Cl, 17.91 ^h	17.63
H, 7.48	7.51		175-176	Cl, 4.46	4.44	
S, 9.93	9.95		196-197 ^d	S, 4.10	4.11		193-196 ^{c,d}	N, 7.08	7.10	Cl, 17.91 ^h	17.78
Cl, 12.72	12.44		211-212 ^d	N, 11.40 ^p	11.46		172-174 ^c	N, 7.97	7.76	Cl, 20.16 ^h	19.81
.....	...		188-189	Cl, 4.55	4.55		112-114 ^{d,q}	Cl, 6.91	6.94
.....	...		178-179	S, 4.02	4.04		103-105 ^r	N, 4.71	4.47	Cl, 5.96	5.98

^a This compound was exceptional in that it formed only a monopicate. ^b Diphosphate. ^c Dihydrochloride. ^d With decomposition. ^e Chloroquinoline: ref. 13. ^f M. p. 15-16° (from Skellysolve A). ^g Basic nitrogen by titration with perchloric acid in glacial acetic acid. ^h Calcd.: H₂PO₄, 39.9. Found: H₂PO₄, 40.5. ⁱ With extensive decomposition, see text. ^j M. p. 20-21° (from Skellysolve A). ^k Ionic halogen only. ^l M. p. 46-48° (from Skellysolve A). ^m M. p. 39° (from Skellysolve A-Skellysolve B, 10:1). ⁿ M. p. 34.5-35.0° (from Skellysolve B). The compound crystallized from dilute alcohol as a hydrate, m. p. 62-63°, which effloresced slowly at 25° and under conditions of low humidity to give the anhydrous form. ^p Nitro nitrogen by titanous chloride titration. ^q Citrate. ^r Side chain: Clinton, *et al.*, THIS JOURNAL, 67, 594 (1945). ^s Dihydriodide.

measurements on these three types of compounds would undoubtedly furnish interesting results.

A representative number of the compounds prepared in the present work were also investigated spectrophotometrically. These data and data on certain analogous imino-linked compounds are given in Table I.⁷

From these data it is readily apparent that the substitution of oxygen for the imino-linkage causes a pronounced hypsochromic and hypochromic effect coupled with diminution in the number of principal maxima. These effects are the result of the decreased number of resonance forms involved in the proton-coupled form of the molecule, as compared with a compound such as no. 7 (Table I). As would be expected,⁸ the higher inherent resonance energy of the sulfur atom as compared to the oxygen atom produces a large bathochromic and hyperchromic effect (compare nos. 2 and 5), and indeed the principal maxima are further into the visible than those observed with the corresponding imino-linked compounds if weighting effects are taken into account. This indicates that the resonance hybrids, VII-VIII, possess a higher potential energy than the corresponding imino-linked compounds. This effect, how-

ever, is not nearly so apparent in the acridine series, in which the resonance of the acridine nucleus contributes a much larger part of the total resonance energy. Diminution in number of principal maxima in the sulfur-linked series is here again evident, however.

As would be expected, the use of aqueous base as solvent produces the normal hypsochromic shift (compare nos. 5, 6 and 7, 8), although the data available are insufficient to indicate possible isobestic points. Certain anomalies are also apparent, *e. g.*, the disappearance of the twinned principal maxima in nos. 2 and 3, although this effect may be only apparent, due to lack of sufficient resolution.

A number of the compounds prepared in the present work were screened against Avian malaria with negative results. However, in screening tests against certain other organisms, including in particular *Brucella abortus*, some of the compounds proved highly active *in vitro*.⁹

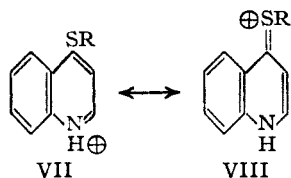
Experimental¹⁰

Sulfur-linked Side Chains.—These compounds were prepared by the reaction between a sodio-dialkylamino-alkanethiol and a nitrogen heterocyclic chloro compound in absolute alcohol solution. Examples of this method follow; most of the compounds prepared are described and characterized in Table II. The yields in all cases were nearly quantitative. All but one of the thiols used in the present work have been previously described.¹¹

(9) Private communication from Drs. C. A. Lawrence and E. W. Dennis.

(10) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(11) Albertson and Clinton, THIS JOURNAL, 67, 1222 (1945); Clinton and Salvador, *ibid.*, 68, 2076 (1946); Laskowski and Clinton, *ibid.*, 69, 519 (1947).



(7) The authors are indebted to Dr. Galen Ewing and staff for the spectra determinations.

(8) Cf. McMurry, J. Chem. Phys., 9, 241 (1941).

5-Isopropylaminopentanethiol.—This compound was prepared from 5-isopropylaminopentyl chloride hydrochloride by methods previously described.¹¹ 5-Isopropylaminopentylisothiuronium chloride hydrochloride (94% yield) formed rosetts of white needles from absolute alcohol-acetone, m. p. 149–151°.

Anal. Calcd. for $C_9H_{13}Cl_2N_2S$: N, 15.21; Cl, 25.66. Found: N, 15.48; Cl, 25.40.

The isothiuronium salt was converted in 73% yield to the thiol: colorless oil, b. p. 94.0° at 8 mm., n_D^{20} 1.4682.

Anal. Calcd. for $C_9H_{13}NS$: N, 8.68. Found: N, 8.52.

The picrolonate formed large, blunt yellow needles from alcohol, m. p. 175–177°.

Anal. Calcd. for $C_{19}H_{27}N_5O_5S$: basic nitrogen, 3.29. Found: basic nitrogen, 3.27.

7-Chloro-4-(2-diethylaminoethylmercapto)-quinoline.—Ten and one-tenth grams of 2-diethylaminoethanethiol was added in one portion to a warm solution of 1.75 g. of sodium in 50 ml. of absolute alcohol, contained in a 250-ml., three-necked flask equipped with a reflux condenser, mechanical stirrer and dropping funnel. The solution was heated under reflux with stirring and there was added dropwise during twenty minutes a solution of 15.0 g. of 4,7-dichloroquinoline¹² in 100 ml. of absolute alcohol. There was an almost immediate precipitation of sodium chloride. The mixture was refluxed and stirred for an additional four hours, cooled, and then filtered. After removal of the alcohol *in vacuo* the residual orange oil was distilled *in vacuo*.

4-(2-Diethylaminoethylmercapto)-3,8-dimethylquinoline.—The reaction between sodio-2-diethylaminoethanethiol and 4-chloro-3,8-dimethylquinoline¹³ was carried out as described above. The crude product, after removal of the alcohol *in vacuo*, was dissolved in 5% hydrochloric acid and the solution was made neutral to congo red by the addition of solid sodium acetate. The mixture was extracted thoroughly with ether to remove any unreacted chloroquinoline, the aqueous layer made strongly basic with 35% sodium hydroxide solution, and the precipitated oil extracted with ether. After drying and removal of the ether *in vacuo* the residual oil¹⁴ was dissolved in alcohol and treated with somewhat more than two equivalents of picric acid in alcoholic solution. The resulting dipicrate crystallized from glacial acetic acid-alcohol solution in long, feathery, canary-yellow needles.

The dipicrate was reconverted to the base with 10% hydrochloric acid-ethyl acetate, etc., in the usual manner, and the recovered base was treated in acetone solution with an excess of ethereal anhydrous hydrogen chloride (15% by weight). Crystallization from absolute alcohol-ethyl acetate-ether gave short, pale yellow needles of the dihydrochloride.

The dihydrochloride loses one hydrogen chloride molecule on prolonged heating at 100° *in vacuo*.

6-Chloro-9-(2-diethylaminoethylmercapto)-2-methoxyacridine.—Fifty-three and two-tenths grams of 2-diethylaminoethanethiol was added to a solution of 9.2 g. of sodium in 1000 ml. of absolute alcohol. One hundred eleven and two-tenths grams of 6,9-dichloro-2-methoxyacridine was added to the resulting warm solution in one portion, and the heterogeneous mixture was refluxed and stirred for seven hours. Solution of the dichloroacridine was complete after about two hours; sodium chloride precipitation was rapid. After filtration the filtrate was concentrated *in vacuo* to a volume of 500–600 ml., made turbid by the addition of water, and cooled in ice. The mixture

readily crystallized on scratching, and further dilution with water precipitated the base completely. After thorough drying the base was crystallized twice from Skellysolve B at –50°, to give a nearly quantitative yield of product as small yellow needles, m. p. 57–58°.

Anal. Calcd. for $C_{20}H_{23}ClN_2OS$: N, 7.47; Cl, 9.46. Found: N, 7.44; Cl, 9.40.

The monohydrochloride was precipitated from an acetone solution of the base by the addition of exactly a one mole proportion of concentrated hydrochloric acid; yellow needles, m. p. 200.5° (dec.).

Anal. Calcd. for $C_{20}H_{23}ClN_2OS \cdot HCl$: N, 6.81; Cl, 17.24. Found: N, 6.71; Cl, 17.02.

Attempts to prepare the dihydrochloride gave an orange-red crystalline product of m. p. 218–200° (dec.), containing varying amounts of water and more than two moles of hydrogen chloride (compare ref. 4).

6-Chloro-9-(4-diethylamino-1-methylbutylmercapto)-2-methoxyacridine.—This compound was prepared by a method analogous to the above procedure. The free base could not be obtained crystalline. The monohydrochloride formed orange-yellow needles, m. p. 167–168°.

Anal. Calcd. for $C_{25}H_{29}ClN_2OS \cdot HCl$: N, 6.18; S, 7.07. Found: N, 5.81; S, 6.93.

Oxygen-Linked Side Chains.—These compounds were prepared by the reaction between a sodium alcoholate and a nitrogen heterocyclic chloro compound in toluene solution. An example is given in detail below; most of the compounds prepared appear in Table II.

7-Chloro-4-(4-diethylamino-1-methylbutyloxy)-quinoline.—Sixty-three and six-tenths grams of redistilled 4-diethylamino-2-pentanol was added in one portion to a refluxing, stirred suspension of 6.9 g. of sodium in 100 ml. of dry toluene. After three hours the sodium had completely reacted. There was then added, in one portion, 59.4 g. of dry 4,7-dichloroquinoline, and the resulting clear solution was refluxed and stirred for twenty-four hours. The cooled mixture was filtered, and after removal of toluene *in vacuo* the residual oil was dissolved in 400 ml. of cold 4 N hydrochloric acid. The clear solution was neutralized to congo red by the addition of solid sodium acetate and extracted twice with ether. The aqueous layer was made strongly basic with 35% sodium hydroxide solution and the precipitated oil taken up in ether. After drying, the ether was removed *in vacuo* and the residual oil distilled up to a bath temperature of 150° at 0.20 mm. to remove the excess of 4-diethylamino-2-pentanol. The residual crude base was converted to the dipicrate by treatment with excess picric acid in alcohol solution.

The dipicrate was reconverted to the base by means of cold 10% hydrochloric acid-ethyl acetate, and after recovery from the hydrochloric acid solution the base was treated in absolute alcohol solution with a slight excess of citric acid monohydrate. The citrate formed rosetts of white needles from absolute alcohol-ethyl acetate.

6-Chloro-9-(2-diethylaminoethoxy)-2-methoxyacridine was obtained in good yield in the above manner. A small amount of acridone (insoluble in toluene) also was formed in the reaction. The dried crude product was crystallized twice from Skellysolve B at –20°, forming bright yellow needles, m. p. 60.5–61.5°.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2$: N, 7.81; Cl, 9.88. Found: N, 7.81; Cl, 9.67.

Summary

There have been described a number of quinolines and acridines substituted by basic side chains linked to the nucleus by oxygen or sulfur. The spectroscopic relation of these compounds to the analogous imino-linked series, and their hydrolytic cleavage has been investigated.

RENSSELAER, NEW YORK

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(12) Surrey and Hammer, *THIS JOURNAL*, **68**, 113 (1946).

(13) Steck, Hallock and Holland, *ibid.*, **68**, 129, 132 (1946). The authors are indebted to Dr. Edgar Steck for a supply of this material.

(14) When an attempt was made to distill this oil at 175° (bath) and 0.06 mm., extensive decomposition ensued, with distillation of a mixture of solid and a mobile, low boiling compound.