Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.53; H, 6.17; N, 4.23.

d-1-(β-Phenylisopropyl)-4-carbethoxy-2,3-dioxopyrrolidine. The compound was prepared by the one-step procedure previously described.[5a] From 78 g. (0.58 mole) of *d*-β-phenylisopropylamine, 90 g. (59% yield) of the 4-carbethoxy-2,3-dioxopyrrolidine was obtained. After recrystallization from an ethanol-water mixture white needles were obtained, m.p. 115–116°, $[\alpha]_D = +75.48°$ (c 4.0, 95% ethanol).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.55; H, 6.81.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY LEHIGH UNIVERSITY]

Study of the Synthesis and Chemistry of the 5,6-Dihydroimidazo[ij]quinoline Series[1]

ALFRED RICHARDSON, JR.,[2] AND E. D. AMSTUTZ

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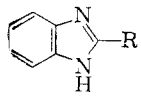
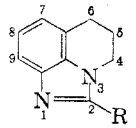
A series of 2-substituted 5,6-dihydroimidazo[ij]quinolines has been synthesized by the condensation of 8-amino-1,2,3,4-tetrahydroquinoline with carboxylic acids or their derivatives. These condensations may lead directly to the final product or to amides which may be subsequently cyclized. In general, the amino-amides are obtained and isolated in the case of substituted or unsubstituted aromatic acid chlorides. Attempts to form 2-substituted imidazo[ij]quinolines from 8-amino-1,2-dihydroquinoline led only to 8-amidoquinolines. Certain pyridoquinoxalines were synthesized from 8-amino-1,2,3,4-tetrahydroquinoline and benzoin-type compounds. The spectra of the dihydroimidazo[ij]quinolines are similar to those of the benzimidazoles.

In view of the fairly wide range of physiological activities shown by benzimidazole (I.R = H) and its derivatives, it was of interest to prepare a series of derivatives of the related 5,6-dihydroimidazo-[ij]quinolines (II). This paper describes the synthetic methods employed in the preparation of a variety of new members of this virtually unexplored group.



I



II

The first synthesis of a 5,6-dihydroimidazo-[ij]quinoline was realized by Kunckell,[3] who condensed 8-amino-6-bromo-1,2,3,4-tetrahydroquinoline with acetic acid. The product he obtained was 8-bromo-2-methyl-5,6-dihydroimidazo[ij]quinoline. Other earlier workers[4–12] synthesized compounds in this series where the 2-substituent was an alkyl group sometimes containing hydroxyl groups or aromatic residues. The diamine usually was 8-amino-1,2,3,4-tetrahydroquinoline, although at times, an 8-amino-1,2,3,4-tetrahydroquinoline was employed which contained substituents on the aromatic ring.[6–9] In most cases, the appropriate diamine was heated with the corresponding acid in the absence of solvent,[4–9] although a few members of the series were synthesized by condensing an 8-amino-1,2,3,4-tetrahydroquinoline with aliphatic aldehydes and ketones.[10–12]

Although simple amidines are readily hydrolysed in aqueous acid,[13] the dihydroimidazoquinolines, which are essentially cyclic amidines, are stable in a refluxing 4*N* hydrochloric acid medium and many can be prepared by its use. This inertness toward acid hydrolysis is apparently due to a resonance stabilization of the benzimidazole system.

Tables I and II list the dihydroimidazo[ij]-quinolines and benzimidazoles synthesized during this research, while the condensation procedures are discussed in detail in the paragraphs which follow.

Condensations with carboxylic acids.[16] The methods used in condensing 8-amino-1,2,3,4-tetrahydroquinoline with carboxylic acids were either to reflux in 4*N* hydrochloric acid or to heat the reactants without a solvent. Other methods which were attempted without success were heating in

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(3) F. Kunckell, *Ber. Dtsch. Pharm. Ges.*, **20**, 198, 215 (1910); *Chem. Abstr.*, **5**, 8718 (1911).

(4) S. J. Hazlewood, G. Hughes, and F. Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 462 (1938).

(5) H. R. Ing and R. S. Cohen, *J. Chem. Soc.*, 2195 (1931).

(6) R. C. Elderfield and G. L. Kreuger, *J. Org. Chem.*, **17**, 358 (1952).

(7) R. C. Elderfield, F. J. Kreysa, J. H. Dunn, and D. D. Humphreys, *J. Am. Chem. Soc.*, **70**, 40 (1948).

(8) E. Bamberger and P. Wulz, *Ber.*, **24**, 2070 (1891).

(9) H. R. Snyder and N. R. Easton, *J. Am. Chem. Soc.*, **68**, 2641 (1946).

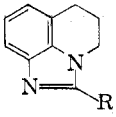
(10) R. C. Elderfield and E. F. Claflin, *J. Am. Chem. Soc.*, **70**, 2953 (1952).

(11) R. C. Elderfield and F. J. Kreysa, *J. Am. Chem. Soc.*, **70**, 44 (1948).

(12) H. J. Barber and W. R. Wragg, *J. Chem. Soc.*, 610 (1946).

(13) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).

TABLE I. 2-SUBSTITUTED 5,6-DIHYDROIMIDAZO[ij]QUINOLINES

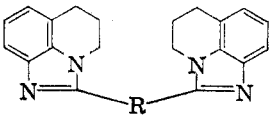


No.	R	Method[a]	Yield, %	M.P.°		Analyses, C	H	N	Picrate, M.P.°
III	H—	B; 14 hr.	50	58–60[b]	Known				225
IV	CH_3—	B; 24 hr.	35	128[c]					
		B[i]; 4 hr.	35	119					
		C; 3 hr.	17	128	Known				237–238
V	$HOCH_2$	A; 24 hr.	74	185[d]	Known				216
VI	$HSCH_2$	A; 24 hr.	39	160–161	Calcd.:[j]	64.71	5.88	13.73	215–216
					Found:	65.20	5.51	13.63	dec.
VII	$HSCH_2CH_2$—	A; 24 hr.	63	oil	Calcd.:[u]	48.30	3.84	15.66	190
					Found:	48.40	4.14	15.35	
VIII[e]	$HOCH_2CH_2CH$—$_2$	A[m]; 24 hr.	85	128–130	Calcd.:	72.22	7.41	12.96	157
					Found:	72.30	7.20	12.90	
IX	$CH_3CO_2CH_2CH_2CH_2$—	E; 17 hr.	56	47–49	Calcd.:	69.74	7.04	10.84	144–145
					Found:	69.85	7.12	10.84	
X[f]	Cyclohexyl-	D[n]; 6.5 hr.	67	93–95	Calcd.:	74.38	8.59	10.84	183–184
					Found:	74.80	8.50	10.97	
XI	HO—[g]	C[o]; 1 hr.	75	213–214	Calcd.:	68.94	5.80	16.07	None
					Found:	68.65	6.02	15.73	
XII	HS—[g]	B[p]; 24 hr.	32	214.5–215.5	Calcd.[k]:	63.14	5.31	14.72	None
					Found:	63.25	5.40	14.68	
XIII	Cl—	F	60	75–76	Calcd.:	62.32	4.72	14.53	175 dec.
					Found:	62.60	4.55	14.50	
XIV	C_6H_5—	D[q]; 12 hr.	Quant.	80–82	Calcd.:	82.05	5.98	11.97	196–197
		D[r]; 1–2 hr.	43	80–82	Found:	81.90	6.02	12.07	
XV	3,4,5-Trimethoxyphenyl	C; 24 hr.	62	181–182	Calcd.:	70.37	6.17	8.64	208–210
		D[q]; 2 hr.	Quant.	179–180	Found:	70.50	6.22	8.70	
XVI	4-Nitrophenyl-	D[q]; 2 hr.	35	179–180	Calcd.:	68.82	4.66	15.05	214–215
		D[s]; 5 hr.	43	176–179	Found:	68.70	4.52	15.35	
XVII[h]	β-Naphthyl-	C; 18 hr.	51	206–207	Calcd.:	84.51	5.63	9.86	221–222
					Found:	84.30	5.88	10.00	
XVIII[i]	γ-Pyridyl-	A; 24 hr.	14	142.5	Calcd.:	76.60	5.53	17.90	183–185
		C; 24 hr.	62	142.5	Found:	76.38	5.76	17.70	
XIX	p-$H_2NC_6H_4SCH_2$—	A; 69 hr.	53	92–94	Calcd.:	69.10	5.82	14.21	169
					Found:	69.40	5.80	14.30	
XX	β-Indolyl-CH_2—	A; 69 hr.	10.3	232–233	Calcd.:	79.40	5.98	14.61	211–213
					Found:	79.15	6.01	14.23	
XXI[l]	CH_3O—	G; 5.5 hr.	Quant.	oil	Calcd.[w]:	48.91	3.64	16.79	154–155
					Found:	48.90	3.67	16.45	

[a] Method A: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid were refluxed in 4N hydrochloric acid. Neutralization with dilute ammonium hydroxide afforded the product which was recrystallized from aqueous alcohol. Method B: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid were refluxed or heated over a free flame until effervescence ceased. The product was extracted with alcohol and recrystallized from aqueous alcohol. Method C: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the acid chloride were refluxed in benzene-pyridine. The solvent was evaporated, the residue slurried with ammonium hydroxide, and the product recrystallized from aqueous alcohol. Method D: The amide intermediate was cyclodehydrated by heating with an appropriate reagent as listed elsewhere in the table. Evaporation of the solvent followed by neutralization of the residue with dilute ammonium hydroxide gave the product which was recrystallized from aqueous alcohol. Method E: A solution of the carbinol in acetyl chloride was allowed to stand at room temperature. The solution was poured onto ice, neutralized with dilute ammonium hydroxide, and the product extracted with ether. Method F: The hydroxy compound (XI) was refluxed in phosphorus oxychloride for 1.5 hours. The solution was poured onto ice and neutralized with dilute ammonium hydroxide. The product was recrystallized from aqueous alcohol. Method G: The chloro compound was refluxed with a 9M excess of sodium methoxide in methanol. The solution was cooled, filtered and evaporated. The residue was extracted with ether and the product obtained by evaporating the dried ethereal solution. [b] Hazlewood, *et al.*[4] erroneously reported a melting point of 148°. [c] Hazlewood, *et al.*[4] reported a melting point of 128°. [d] Hazlewood, *et al.*[4] reported a melting point of 183°. [e] Hydrochloride, m.p. 255°. [f] Melting point and analyses are for the monohydrate. [g] Although the product is shown here in the imidol form, the authors believe an equilibrium exists and that the amide or urea form predominates. Refer to section on the discussion of the spectra. [h] Hydrochloride, m.p. 250° dec. [i] Hydrochloride, m.p. 256–258°. [j] Sulfur analysis: Calcd.: 15.69. Found: 15.18. [k] Sulfur analysis: Calcd.: 16.88. Found: 16.65. [l] Acetic anhydride was employed. [m] The reactant was γ-butyrolactone. [n] The amide was cyclized using a 9 mole excess of phosphorus pentoxide and 19 mole excess of phosphorus oxychloride in refluxing xylene. [o] The 8-amino-1,2,3,4-tetrahydroquinoline was dissolved in glacial acetic acid, treated with an equivalent quantity of phosgene in chlorobenzene, and refluxed. [p] The 8-amino-1,2,3,4-tetrahydroquinoline was treated with an equivalent of carbon disulfide in ethanol, refluxed until the evolution of hydrogen sulfide ceased, and cooled, whereupon the products separated. [q] The amide was cyclized *via* a 9-mole excess of phosphorus pentoxide in refluxing benzene. [r] The amide was cyclized in refluxing phosphorus oxychloride. [s] The amide was cyclized by employing a 9-mole excess of phosphorus pentachloride in phosphorus oxychloride under reflux. [t] Hydrochloride, m.p. 212–214°. [u] Analysed as the monopicrate.

TABLE II

A. 2,2′-Bis(5,6-Dihydroimidazo[ij]quinolines)



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XXII	No. Bridge[f]	H;[h] 16 hr.	very low	261–262	Calcd.:	76.40	5.79	17.81	210
		B;[h] 0.5 hr.	11	259–260	Found:	76.90	5.56	17.60	
XXIII	—CH_2—	B;[i] 0.5 hr.	11	262–263	Calcd.:	77.74	6.23	16.03	245–246
					Found:	77.40	6.22	15.80	
XXIV	—CH_2CH_2—	A; 48 hr.	24	256–258	Calcd.:	77.16	6.48	16.36	dwmb 350
		A; 65 hr.	73	255–256	Found:	77.40	6.60	16.35	
XXV	—$CH_2CH_2CH_2$—	A; 48 hr.	32	198[e]	Calcd.:	70.37	7.21	14.27	268 dec.
		A; 65 hr.	61	198[e]	Found:	70.60	7.38	14.08	
XXVI	—$CH_2CH_2CH_2CH_2$—	B; 0.5 hr.	5.4	217–218	Calcd.:	77.79	7.10	15.11	dwmb 300
		A; 48 hr.	70	215	Found:	77.50	7.29	15.00	
XXVII	—CH=CH—[d]	A; 48 hr.	11	318–320[c]	Calcd.:	70.19	6.43	14.88	dwmb 360
					Found:	70.55	6.56	14.74	
XXVIII	—CH_2OCH_2—	A; 5 days	61	171–172	Calcd.:	73.72	6.19	15.62	254 dec.
					Found:	73.80	6.30	15.60	
XXIX[g]	—CH_2SCH_2—	A; 48 hr.	47	190–193[e]	Calcd.:	67.31	6.17	14.27	247 dec.
		A; 113 hr.	26	194[e]	Found:	67.75	6.30	14.28	
XXX	—$CH_2CH_2SCH_2CH_2$—	I.	65	139.5–140.0	Calcd.:	71.58	6.53	13.91	228 dec.
					Found:	71.20	6.65	13.48	
XXXI	—CH_2—CH(OH)—	A; 72 hr.	14	225.0–225.5[e]	Calcd.:	70.17	6.43	14.88	dwmb 360
					Found:	70.80	6.43	14.28	
XXXII	$HOCH_2$—	A; 24 hr.	1.5	280–283[j]	Known				252–253 dec.
XXXIII	$HSCH_2$—	A; 13.5 hr.	36	164–166[k]	Calcd.:	58.49	4.93	17.05	192–194
					Found:	58.40	4.97	16.85	
XXXIV	$HOCH_2CH_2CH_2$—	A;[l]	8.6	165–166	Calcd.:	68.16	6.87	15.90	None
					Found:	68.20	7.01	15.83	

[a] Methods A–F are listed in footnote *a* of Table I. The benzimidazoles were prepared from *o*-phenylenediamine instead of 8-amino-1,2,3,4-tetrahydroquinoline. Method H: Equivalent quantities of 8-amino-1,2,3,4-tetrahydroquinoline and the corresponding amide were refluxed in ethylene glycol. The solution was cooled, diluted with water, and the product recrystallized from methanol. Method I: The β-mercaptoethyl compound VII was placed under vacuum at room temperature until effervescence ceased. The residue was recrystallized from ethanol-water. [b] The notation "dwmb" indicates, "darkens without melting below." [c] As a dihydrate. [d] Product assumed to be the *trans* isomer. [e] As a monohydrate. [f] Product is 2,2′-bis(5,6-dihydroimidazo[ij]quinoline). Starting material was ammonium oxalate hydrate. [g] Sulfur analysis: Calcd.: 8.18, found, 7.91. [h] Ammonium oxalate employed instead of oxamide or oxalic acid. [i] Malonamide employed instead of malonic acid. [j] Bistozycki and Przeworski[14] reported a melting point of 171–172°, however ultraviolet confirmed the benzimidazole structure. [k] Hughes and Lions[15] reported a melting point of 158°. [l] The diamine was condensed with γ-butyrolactone.

4*N* hydrochloric acid in a sealed tube at 165° and heating in polyphosphoric acid.

The most successful method by far was refluxing with 4*N* hydrochloric acid, which is a modification of the Phillips[17] benzimidazole synthesis. A disadvantage of this method for dihydroimidazoquinoline formation is that while it is generally applicable to the synthesis of aliphatic substituted compounds, it is usually unsuccessful in the synthesis of aromatic-, heterocyclic-, or unsaturated aliphatic-substituted products. In this connection, it is interesting to note that thiophenoxyacetic acid, *p*-aminobenzoic acid, and *N*-phenylgycine yielded no product, but *p*-aminothiophenoxyacetic acid and indole-3-acetic acid (vinylog of *N*-phenylglycine) each formed the desired product (XIX and XX, respectively).

Decarboxylation of the acid played an important hindering role in some condensations. Thus, picolinic, nicotinic, isonicotinic, and β-(2-pyridyl)acrylic acids were observed to decarboxylate as evidenced by a strong pyridine-like odor during the work-up. In addition, benzylamine was isolated when a condensation of α-aminophenylacetic acid with 8-amino-1,2,3,4-tetrahydroquinoline was attempted. In contrast to the lack of reactivity of glycine, both glycollic acid and thioglycollic acid con-

(14) A. Bistozycki and G. Przeworski, *Ber.*, **45**, 3483 (1912).

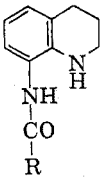
(15) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N.S. Wales.* **71**, 209 (1938); *Chem. Abstr.* **32**, 5830 (1948).

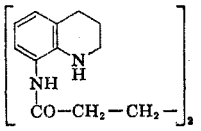
(16) Those acids which yielded no product in all attempted condensations with 8-amino-1,2,3,4-tetrahydroquinoline are: acrylic, aspartic, chloroacetic, cyclohexanecarboxylic, diethylacetic, fumaric, glutamic, glycine, isobutyric, levulinic, maleic, malonic, oxalic, trimethylacetic, *p*-aminobenzoic, benzoic, α-naphthoic, *p*-nitrobenzoic, terephthalic, 3,4,5-trimethoxybenzoic, imidazole-2-carboxylic, nicotinic, picolinic, thiophene-2-carboxylic, α-aminophenylacetic, cinnamic, dibenzylacetic, α-naphthylacetic, *N*-phenylglycine, β-(2-pyridyl)acrylic, thiophenoxyacetic.

(17) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

TABLE III

8-*N*-ACYLAMINO-1,2,3,4-TETRAHYDROQUINOLINES



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XXXV	CH_3—	A	16	116.5–117.5	Calcd.:	69.45	7.41	14.72	233–234[b]
					Found:	69.65	7.21	14.65	
XXXVI		A	11	235 dec.	Calcd.:	71.05	7.44	13.75	
		A[f]	29	235 dec.	Found:	70.70	7.47	13.10	
XXXVII	Cyclohexyl-	B	80	184–186	Calcd.:	74.42	8.53	10.85	183–184
		A	49	191.0–191.5	Found:	74.70	8.79	11.25	
XXXVIII[c]	$C_6H_5CH_2$—	A	17	171–172	Calcd.:	76.69	6.77	10.53	152–153
					Found:	76.55	6.99	10.21	dec.
XXXIX[c]	C_6H_5—	B	59	186–187	Calcd.:	76.19	6.35	11.11	not formed
XL[d]	3,4,5-Trimethoxyphenyl-	A	35	182–183	Found:	76.35	6.41	11.18	
		B	37	223–225	Calcd.:	66.67	6.43	8.19	not formed
					Found:	66.45	6.33	8.08	
XLI[e]	4-Nitrophenyl-	A	90	210–212	Calcd.:	64.65	5.05	14.14	170–172
		B[g]	20	191–194	Found:	64.55	4.98	14.10	

[a] Method A: The 8-amino-1,2,3,4-tetrahydroquinoline was treated with an equivalent of the acid chloride in benzene at room temperature. The mixture was allowed to stand overnight and was then filtered. The solid was slurried with dilute ammonium hydroxide and recrystallized from methanol or methanol-water. Method B: a modification of Method A. A small amount of pyridine was added to the mixture. [b] Formed the picrate of 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV). [c] *N*-Nitroso derivative, m.p. 145–150°. [d] *N*-Nitroso derivative, m.p. 160°. [e] *N*-Nitroso derivative, m.p. 165–170°. [f] The mixture was refluxed for 5 hr. [g] The mixture was refluxed overnight.

densed readily with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid to yield the corresponding 2-hydroxymethyl- (V), and 2-mercaptomethyl-5,6-dihydroimidazo[ij]quinoline (VI). The next higher homolog of the latter compound, 2-(β-mercaptoethyl)-5,6-dihydroimidazo[ij]quinoline (VII) was synthesized in an analogous manner from β-mercaptopropionic acid. This product was an oil, the only liquid product observed during the course of this work. Upon continued standing or with heating under vacuum, the β-mercaptoethyl compound yielded a solid in addition to hydrogen sulfide. This solid was β,β′-bis-2-(5,6-dihydroimidazo[ij]quinolyl)ethyl sulfide (XXX) which may have formed by an addition of a second molecule of VII to 2-vinyl-5,6-dihydroimidazo[ij]quinoline, which should be the initial product.

A convenient synthesis of 2-mercapto-5,6-dihydroimidazo[ij]quinoline (XII) involved the condensation of 8-amino-1,2,3,4-tetrahydroquinoline with carbon disulfide in refluxing ethanol.

Another interesting condensation, which led to 2-(γ-hydroxypropyl)-5,6-dihydroimidazo[ij]quinoline (VIII), involved the condensation of γ-butyrolactone with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid. That this reaction first involved a hydrolysis of the lactone to γ-hydroxybutyric acid was shown by the inability of γ-butyrolactone to condense with 8-amino-1,2,3,4-tetrahydroquinoline hydrochloride when the reactants were heated without a solvent.

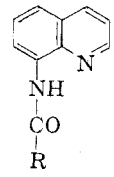
Dibasic acids such as succinic, glutaric, and adipic acids condensed readily forming the expected bisdihydroimidazo[ij]quinolines when refluxed with 8-amino-1,2,3,4-tetrahydroquinoline in 4*N* hydrochloric acid. The series was further extended by the condensations of diglycollic and thiodiglycollic acids to form the corresponding bismethyl ether (XXVIII) and bismethyl sulfide (XXIX). Malic acid condensed with 8-amino-1,2,3,4-tetrahydroquinoline in refluxing 4*N* hydrochloric acid to yield two products. One of them was the expected α-hydroxy-2,2′-ethylenebis- (XXXI), and the other was 2,2′-vinylenebis(5,6-dihydroimidazo-[ij]quinoline) (XXVII). The fact that maleic and fumaric acids did not yield any condensed products indicates that the unsaturated compound (XXVII) was formed from the carbinol (XXXI) by the elimination of water. Thiomalic acid formed only XXVII.

Condensations with acid chlorides. Tables III and IV list the 8-*N*-acylaminotetrohydroquinolines and 8-*N*-acylaminoquinolines synthesized during the course of this work and are found below.

Acid chlorides were successfully condensed with 8-amino-1,2,3,4-tetrahydroquinolines in many cases

TABLE IV

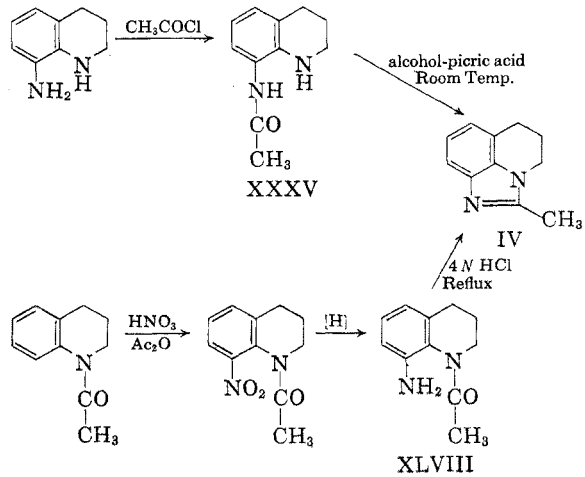
8-*N*-ACYLAMINOQUINOLINES



No.	R	Method[a]	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XLII	H—	C	Quant.	152–154	Calcd.:	69.77	4.65	16.27	140
					Found:	69.90	4.96	16.78	
XLIII	CH_3—	A	85	100–101[d]	Calcd.:	70.94	5.42	15.05	196–197
					Found:	71.05	5.43	14.80	
XLIV	C_6H_5—	A	49	91–92[e]	Calcd.:	77.42	4.84	11.29	189–190
					Found:	77.40	5.15	11.28	
XLV	3,4,5-Trimethoxyphenyl-	A	18	134	Calcd.:	67.46	5.33	8.28	195–198
		B[e]	62	132–133	Found:	67.30	5.28	8.27	
XLVI	4-Nitrophenyl-	A	93	182–183[b]	Calcd.:	65.53	3.75	14.33	155–156
					Found:	65.65	3.64	14.38	

[a] See footnote *a* in Table III for Methods A and B. Method C: A solution of 8-amidoquinoline in 85% formic acid was refluxed overnight. The solution was cooled and made alkaline with dilute ammonium hydroxide. The solid was recrystallized from methanol-water. [b] Gorvin[19] reported a melting point of 188°. [c] Hall[20] claimed to have synthesized this compound but reported no physical properties. [d] Ochiai *et al.*[21] reported a melting point of 102–103°. [e] The mixture was refluxed for 3 hr.

and were especially useful in the synthesis of aromatic- and heterocyclic-substituted dihydroimidazo[ij]quinolines which could not be attained *via* the corresponding carboxylic acid.[18] In refluxing benzene or benzene-pyridine, the desired product was sometimes attained directly (IV, XV, and XVII), while at room temperature the amide intermediate was isolated exclusively. That the acyl group was located on the primary nitrogen of 8-amino-1,2,3,4-tetrahydroquinolines was shown by the fact that the amides readily formed a solid *N*-nitroso derivative with nitrous acid. In addition, 8-benzamidotetrahydroquinoline (XXXIX) formed a precipitate with benzenesulfonyl chloride in an alkaline medium and another with nickel chloride–carbon disulfide reagent, both reactions being indicative of a free secondary amino function. It was further found that 8-benzamido-1-benzoyltetrahydroquinoline (XLVII) did not react with nitrous acid, thus ruling out the possibility of *N*-nitrosation of an amide function. Conclusive proof of the reactive nitrogen in 8-amino-1,2,3,4-tetrahydroquinoline was attained by the synthesis of both of the isomeric, monoacetylated 8-amino-1,2,3,4-tetrahydroquinoline derivatives (XXXV and XLVIII). One isomer (XXXV) was synthesized by treating a benzene solution of 8-amino-1,2,3,4-tetrahydroquinoline with acetyl chloride in a procedure identical with that employed in the synthesis of some of the 8-amidotetrahydroquinolines described above. The product was a solid with an analysis corresponding to a monoamide of 8-amino-1,2,3,4-tetrahydroquinoline. It could not be diazotized, but formed an alkali insoluble solid with benzenesulfonyl chloride. An absorption spectrum (λ-max, log ϵ: 251, 3.91; 306, 3.52 mμ) was typical of an 8-acylaminotetrahydroquinoline. In alcoholic picric acid solution, it formed the picrate of 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV), which indicates the ease of cyclization of the amide which has been assigned structure XXXV. The other isomer, 8-amino-1-acetyltetrahydroquinoline (XLVIII) was synthesized by reduction of 8-nitro-1-acetyltetrahydroquinoline either catalytically or with iron and acetic acid. It (XLVIII) was an oil which had the correct analysis for a monoamide of 8-amino-1,2,3,4-tetrahydroquinoline and could be diazotized and coupled with β-naphthol.



(18) Where the desired product could be obtained through the acid as well as *via* the acid chloride, it was observed (Table I) that generally, the acid chloride led to a better yield of the dihydroimidazo[ij]quinoline.

(19) J. H. Gorvin, *J. Chem. Soc.*, 61 (1946).

(20) D. M. Hall, *J. Chem. Soc.*, 1603 (1948).

(21) E. Ochiai, J. Haginiwa, and K. Komatsu, *J. Pharm. Soc., Japan*, **70**, 372 (1950), *Chem. Abstr.*; **45**, 2476a (1951).

Treatment with refluxing 4*N* hydrochloric acid for two hours caused cyclization to 2-methyl-5,6-dihydroimidazo[ij]quinoline (IV). An absorption spectrum (λmax, log ε: 257, 4.11; 282.7, 3.74 mμ) was different from that of XXXV, and the amide did not cyclize in alcoholic picric acid solution, but formed a picrate of the desired product as indicated by the analysis. These results leave no doubt that the reactive nitrogen in 8-amino-1,2,3,4-tetrahydroquinoline, is the primary nitrogen.

Occasionally it was necessary to treat an amide separately with a cyclizing agent to form the desired dihydroimidazoquinoline. Thus, 8-(4′-nitrobenzamido)tetrahydroquinoline (XLI) could be cyclized to 8-(4′-nitrophenyl)-5,6-dihydroimidazo-[ij]quinoline (XVI) by phosphorus pentoxide in refluxing benzene, or better, by phosphorus oxychloride. This amide could not be ring-closed by heating under vacuum above its melting point or by employing polyphosphoric acid at 80°. In the only attempt at cyclization of 3′,4′,5′-trimethoxybenzamidotetrahydroquinoline (XL), a nearly quantitative yield of product (XV) was obtained by the use of phosphorus pentoxide in refluxing benzene. A nearly quantitative yield of the desired ring-closed product (XIV) was also obtained when 8-benzamidotetrahydroquinoline (XXXIX) was treated under the same conditions. The latter could also be cyclized in refluxing phosphorus oxychloride to give a 43% yield of the product, although no cyclized product was obtained when this amide was heated under vacuum above its melting point. The most difficult amide to cyclize was 8-cyclohexylcarboxamidotetrahydroquinoline (XXXVII). This compound failed to lose the elements of water when heated above its melting point under vacuum, when treated with polyphosphoric acid at 80°, when refluxed with phosphorus pentoxide in benzene, or when refluxed with phosphorus pentachloride in phosphorus oxychloride. It did ring-close (X), however, when refluxed with phosphorus pentoxide and phosphorus oxychloride in xylene.

A most interesting application of these methods was the use of phosgene. When 8-amino-1,2,3,4-tetrahydroquinoline was heated with phosgene in an acetic acid-chlorobenzene solution, a 75% yield of 2-hydroxy-5,6-dihydroimidazo[ij]quinoline resulted (XI). Like the 2-mercapto compound (XII) the product appeared to exist mainly as the keto form since the absorption spectrum (Figure V) resembled that of 8-amino-1,2,3,4-tetrahydroquinoline which is essentially an *N*-substituted phenyleneurea. By refluxing the 2-hydroxy compound (XI) in phosphorus oxychloride for one to two hours, the corresponding 2-chloro-5,6-dihydroimidazo[ij]quinoline (XIII) was formed in 60% yield. In addition, 2-methoxy-5,6-dihydroimidazo-[ij]quinoline (XXI) formed quantitatively when the chloro compound (XIII) was treated with sodium methoxide.

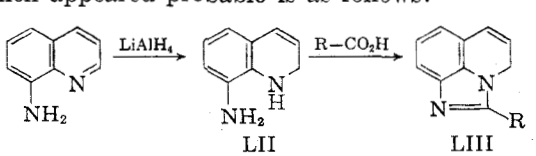
The use of dibasic acid chlorides was generally unsuccessful, although in two cases, a characterizable product was isolated. Adipyl chloride formed *N*,*N*′-bis[8′-(1′,2′,3′,4′-tetrahydroquinolyl)]adipamide (XXXVI) at room temperature and at reflux temperature in benzene. As the corresponding tetramethylenebisdihydroimidazoquinoline (XXVI) formed readily with adipic acid in 4*N* hydrochloric acid, no attempt was made to ring-close this amide. Oxalyl chloride produced only a pyridoquinoxaline (XLIX) with 8-amino-1,2,3,4-tetrahydroquinoline.

Other dibasic acid chlorides were not successfully condensed with 8-amino-1,2,3,4-tetrahydroquinoline; thus, terephthalyl chloride formed an intractable product, while reactions with fumaryl, maleyl, chloroacetyl, diethylcarbamyl, and β-diethylaminopropionyl chlorides all led to tars.

Condensations with amides. The use of amides proved fruitful in the synthesis of 2,2′-bis(5,6-dihydroimidazo[ij]quinoline) (XXII) and 2,2′-methylenebis(5,6-dihydroimidazo[ij]quinoline) (XXIII) where other methods failed. Because oxamide is probably the immediate precursor to the former product, ammonium oxalate was employed with success in ethylene glycol or in the absence of solvent, as it decomposes to oxamide above 150°. The products were best synthesized by heating the required reactant with an equivalent quantity of 8-amino-1,2,3,4-tetrahydroquinoline in the absence of solvent. Under these conditions, both ammonium oxalate and malonamide formed the desired products (XXII and XXIII respectively). When ethylene glycol was employed as a high boiling solvent, ammonium oxalate formed the desired product (XXII) in a very low yield while malonamide formed a small amount of a high-melting, unidentified product. Benzamide did not condense in ethylene glycol or in the absence of solvent.

Condensations with benzoins. Hazlewood[4] found that benzoin condensed with 8-amino-1,2,3,4-tetrahydroquinoline to form the disubstituted pyridoquinoxaline (L) and we were likewise successful with anisoin in obtaining LI. Pyridoin, however, did not give any recognizable product and decomposition was obvious.

Imidazo[ij]quinolines. A route to this series which appeared probable is as follows:

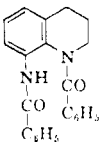
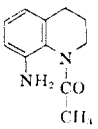
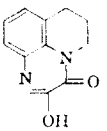
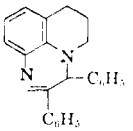
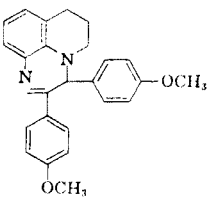


LII LIII

The required intermediate, 8-amino-1,2-dihydroquinoline (LII), is not a known compound, and attempts were made to synthesize it *via* a lithium aluminum hydride reduction of 8-aminoquinoline. A green-yellow oil formed whose elemental analysis was close to that calculated for the desired product. The compound formed a picrate which

TABLE V

MISCELLANEOUS COMPOUNDS

No.	Structure	Yield, %	M.P.°		Analyses C	H	N	Picrate, M.P.°
XLVII[a,d]		84	155–157	Calcd.: Found:	77.52 78.05	5.62 5.71	7.86 7.92	Not formed
XLVIII		77	oil	Calcd.[c]: Found:	48.68 48.60	4.10 4.00	16.71 16.60	205
XLIX[a,e]		low	258–260	Calcd.: Found:	65.35 65.45	4.95 5.26	13.86 13.67	Not formed
L		28	148.0–148.5[b]					150–151 dec.
LI[f]		30	148–149	Calcd.: Found:	78.10 78.20	6.30 6.40	7.28 7.12	166

[a] Refer to method B and footnote *g* of Table III for experimental details. [b] Hazlewood, *et al.*[4] reported a melting point of 146°. [c] Analyzed as the monopicrate, $C_{17}H_{17}N_5O_8$. [d] Two moles of benzoyl chloride were employed per mole of 8-amino-1,2,3,4-tetrahydroquinoline. [e] Oxalyl chloride was condensed with 8-amino-1,2,3,4-tetrahydroquinoline. [f] The method of Hazlewood, *et al.*[4] was employed. The appropriate benzoin was heated with 8-amino-1,2,3,4-tetrahydroquinoline over a free flame until effervescence ceased. The product was extracted with ethanol and recrystallized from ethanol or ethanol-water.

TABLE VI

ABSORPTION MAXIMA OF 2-SUBSTITUTED 5,6-DIHYDROIMIDAZO[ij]QUINOLINES

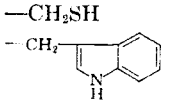
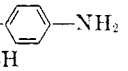
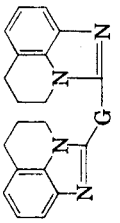
—R	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε
—H	—	—	257	3.78	274	3.65	283.1	3.59
—CH_3	—	—	255.2	3.73	273.6	3.63	282.4	3.62
—CH_2OH	—	—	259	3.83	276	3.77	285	3.63
—CH_2SH	—	—	—	—	—	—	282	4.14
	225	4.37	258	4.06	274.6	4.10	283.5	4.08
—CH_2—S—  —NH_2	—	—	265	4.21	—	—	—	—
—CH_2CH_2SH	222.2	4.06	256.7	3.86	275	3.77	284	3.72
—$CH_2CH_2CH_2OH$	—	—	256	3.85	274	3.79	282.8	3.77
—$CH_2CH_2CH_2OCOCH_3$	—	—	256	3.86	274	3.79	283	3.73
Cyclohexyl	—	—	256.5	3.69	274.5	3.64	283.2	3.67
—OH	225–234	3.82	—	—	—	—	284	3.76
—OCH_3	—	—	242.5	3.72	275	3.58	282	3.63
—SH	225	4.27	247.6	4.26	—	—	304.8	4.47
—Cl	—	—	256.0	3.88	275.0	3.82	283.5	3.78
C_6H_5	—	—	240	4.19	—	—	290	4.22
p-NO_2—C_6H_4—	—	—	240–248	4.10	—	—	337.5	4.20
3,4,5-Trimethoxyphenyl	222–225	4.55	252.5	4.07	—	—	298	4.35
β-Naphthyl	—	—	243	4.69	280	435	308	4.36
4-Pyridyl	—	—	250.7	3.95	—	—	306	4.21

TABLE VII

ABSORPTION MAXIMA OF 2,2′-BIS(5,6-DIHYDROIMIDAZO[ij]QUINOLINE) COMPOUNDS



No	G—	Present	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε	max λ (mμ)	log ε
					240.8	4.39	264	4.22	327.5	4.41	368	3.13	387	3.45	409	3.63	435	3.53
	—CH_2—		—	—	258	4.14	276	4.11	284.8	4.09	360	3.12	—	—	—	—	—	—
	—CH_2CH_2—		221	4.34	258	4.16	275.3	4.13	284	4.09	—	—	—	—	—	—	—	—
	—$(CH_2)_3$—		—	—	256.5	4.18	274.9	4.14	283.5	4.09	—	—	—	—	—	—	—	—
	—$(CH_2)_4$—		—	—	256.6	4.13	275	4.07	284	4.04	—	—	—	—	—	—	—	—
	—CH_2OCH_2—		222	4.33	261.3	4.18	274	4.15	—	—	—	—	—	—	—	—	—	—
	—CH_2SCH_2—		222	4.37	265	4.14	280	4.17	—	—	—	—	—	—	—	—	—	—
	—CH_2—$CH(OH)$—		—	—	259	4.18	276	4.17	284	4.09	—	—	—	—	—	—	—	—
	—$CH_2CH_2SCH_2CH_2$—		221	4.38	258.5	4.17	275.5	4.15	284.4	4.10	—	—	—	—	—	—	—	—
	—CH=CH—		—	—	251	4.08	—	—	285	3.56	360	4.40	277	4.42	396	4.34	—	—

reverted to the picrate of 8-aminoquinoline upon recrystallization. When refluxed with formic or acetic acid, the corresponding 8-aminoquinolines resulted (XLII and XLIII respectively). No 2-substituted imidazo[ij]quinolines (LIII) were isolated nor were any of the corresponding 5,6-dihydro derivatives (II) found; the latter would most certainly have formed were there any 8-amino-1,2,3,4-tetrahydroquinolines present.

The spectra of the 5,6-dihydroimidazo[ij]quinolines. The compounds in this series exhibited spectra which were characteristic of the benzimidazoles and could often be identified through their spectra. Tables VI and VII list the absorption maxima of the compounds described in this paper. Fig. 1 illustrates the similarity of the spectrum of 5,6-dihydroimidazo[ij]quinoline (III) to that of benzimidazole, while the other figures indicate the effect of the 2-substituent upon the spectrum of the parent compound (III).

The difference in the spectra of the parent compound (III) and the 2-alkyl substituted compounds was negligible. Alkyl groups with substituents further removed from the heterocyclic system than

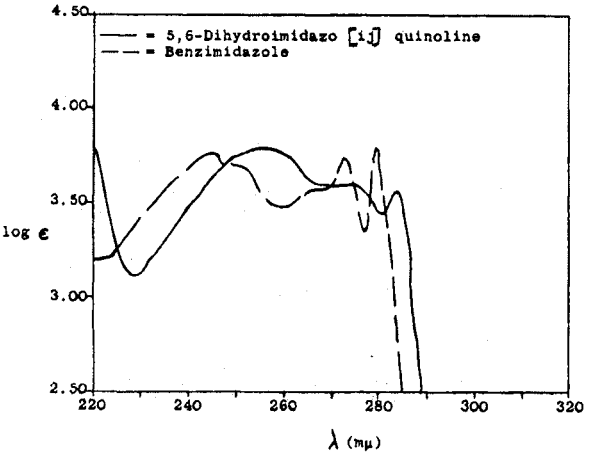


Fig. 1. Absorption maxima of 5,6-dihydroimidazo[ij]-quinoline as compared with benzimidazole

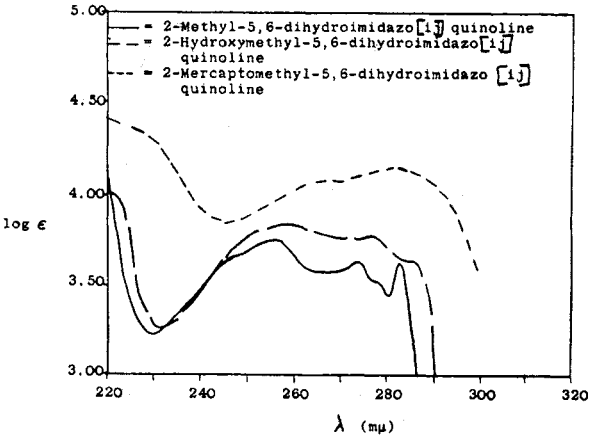


Fig. 2. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

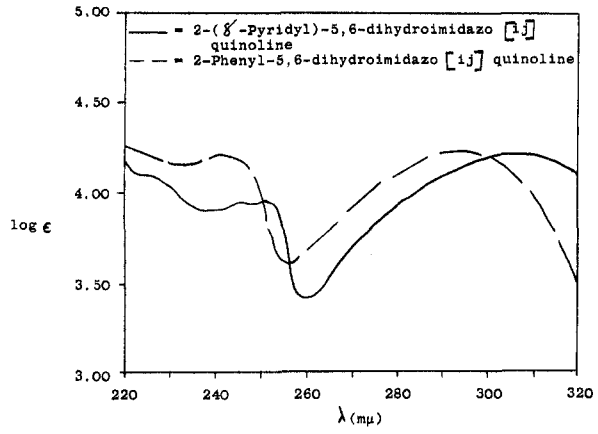


Fig. 3. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

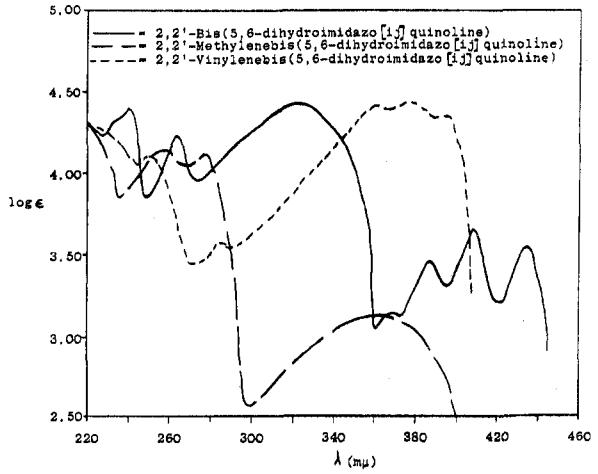


Fig. 4. Absorption maxima of 2-substituted 5,6-dihydroimidazo[ij]quinolines

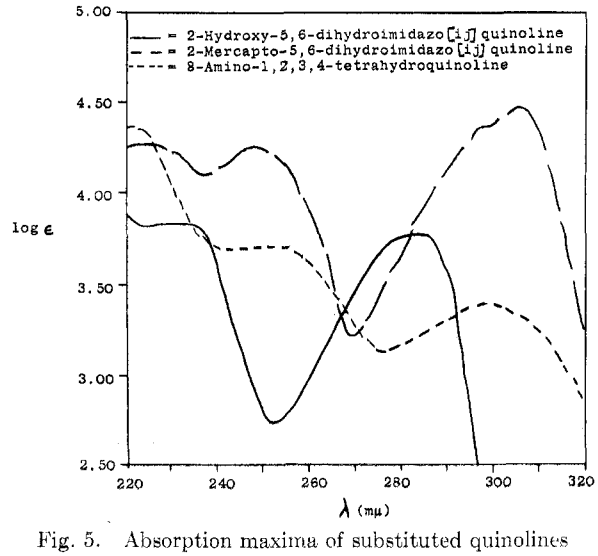
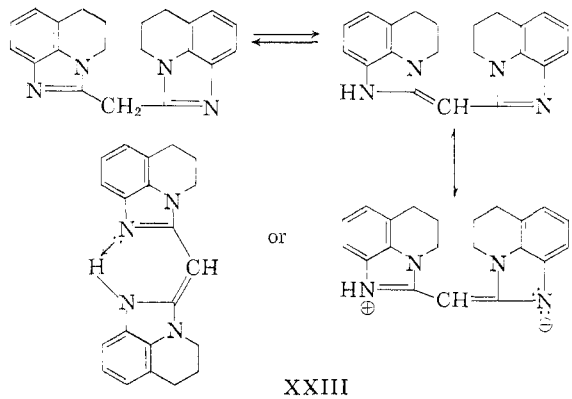


Fig. 5. Absorption maxima of substituted quinolines

one methylene group likewise had a negligible effect upon the resultant spectrum. A definite effect was noted, however, where α-substituted alkyl groups were present in the 2-position of the dihydroimidazo[ij]quinoline nucleus. In certain cases [2-hydroxymethyl- (V), 2-mercaptomethyl- (VI), 2-(3'-indolylmethyl)- (XX) and 2-(*p*-aminothiophenoxymethyl - 5,6 - dihydroimidazo[ij]quinoline (XIX)], the effect may have been merely inductive as the fine structure disappeared and a broad maximum resulted, while in others, the effect appeared to be mesomeric in nature. The latter appeared to be important in the case of the 2-aromatic or 2-heterocyclic substituted compounds as well as in the case of certain bisdihydroimidazo-[ij]quinolines capable of conjugation through the bridge (XXII, XXIII, and XXVII). Furthermore, as the aromatic or heterocyclic substituent was increasingly capable of accepting a negative charge, the long wave length maximum shifted bathochromically. One of the major contributors to the excited state may therefore be:

A unique compound is 2,2'-methylenebis(5,6-dihydroimidazo[ij]quinoline) (XXIII). Although this molecule exhibited a typical spectrum in the ultraviolet, it also absorbed in the visible (Figure IV). For this to occur, a conjugation of the heterocyclic groups through the methylene group is necessary. Such a conjugation may be brought about by an initial tautomerism of a methylene hydrogen; furthermore, the charged species which appears to be responsible for the long wave length absorption may be stabilized by a cyclization which would result in the formation of hydrogen bonded six-membered ring. The resulting system is distinctly reminiscent of the pyrromethenes.



XXIII

A comparison of the spectra of the 2-hydroxy- (XI) and 2-mercapto- (XII) compounds with those of 2-methoxy-5,6-dihydroimidazo[ij]quinoline (XXI) and 8-amino-1,2,3,4-tetrahydroquinoline revealed that these substances exist primarily in the corresponding keto forms.

Pharmacological results. To date, eight of the substituted dihydroimidazo[ij]quinolines (VI, VII, VIII, XV, XVII, XVIII, XXIV, XXVI) have

been screened for pharmacological activity. One of those examined, 2-mercaptomethyl-5,6-dihydroimidazo[ij]quinoline (VI) was active toward dextran edema; however, the remaining seven compounds displayed no pharmacological activity.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Commercial intermediates were used without further purification. Yields correspond to the amount of pure product obtained.

Starting materials. The 8-aminoquinoline (m.p. 63–64°) was produced by an iron and acetic acid reduction of the 8-nitro compound[22] or in 67% yield from oxine[23] employing a reaction ratio of 1:2:10 of oxine, ammonium sulfite, and ammonia. When the amount of sodium in the sodium-alcohol reduction of 8-aminoquinoline[4] was increased to 14–15 g.-atoms per mole of 8-aminoquinoline, the yield rose to 84% of pure 8-amino-1,2,3,4-tetrahydroquinoline, b.p. 145° at 2 mm. Isonicotinyl chloride was obtained from the acid with thionyl chloride in 88% yield, b.p. 95–96° at 25 mm, by an adaptation of Koo's method.[24]

Directions for the methods used in the preparation of the dihydroimidazo[ij]quinolines and related compounds are to be found as footnotes to the appropriate table.

8-Nitro-1-acetyl-1,2,3,4-tetrahydroquinoline. A solution of 1-acetyltetrahydroquinoline (6.7 g. 0.0382 mole) in 10 ml. of acetic anhydride was cooled and treated cautiously with a solution of 3.6 g. (0.04 mole) of 70% nitric acid in 10 ml. of acetic anhydride. After 0.5 hr. in an ice bath, the red mixture was allowed to stand at room temperature overnight (12 hr.). The solution was poured onto ice. The oil which separated was extracted with ether and the ethereal solution was washed with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent yielded 7.3 g. (89%) of the product as a red oil, which, on acid hydrolysis afforded the known 8-nitro-1,2,3,4-tetrahydroquinoline, m.p.: 82–84° (lit.,[25] m.p. 82–83°).

8-Amino-1,2-dihydroquinoline (LII). A slurry of 6.5 g. (0.174 mole) of lithium aluminum hydride in 150 ml. of absolute diethyl ether was heated to boiling with stirring. To the slurry was added 5.0 g. (0.0347 mole) of 8-aminoquinoline (Eastman) dissolved in 50 ml. of absolute diethyl ether. The mixture was refluxed for 24 hr. during which time the initially blood-red slurry became lighter and a yellow solid remained. The slurry was cooled to 0° and water was added cautiously with stirring under a nitrogen atmosphere until hydrolysis was complete. The mixture was filtered, the filtrate dried over magnesium sulfate, and the solvent evaporated and the residue distilled. The green-yellow oil boiled at 157–160° (6 mm.).

Anal. Calcd. for: $C_9H_{10}N_2$: C, 73.94; H, 6.91; N, 19.17. Found: C, 73.10; H, 6.71; N, 18.50–18.63.

A picrate formed as golden-brown needles which melted at 204–205° and showed no depression in melting point when admixed with authentic 8-aminoquinoline picrate. In another experiment, an orange picrate formed which melted at 192–194° and showed a depression of 20° when admixed with 8-aminoquinoline picrate. When the orange picrate was recrystallized from 95% ethanol, however, golden-brown needles resulted which melted at 200–201° and proved to be 8-aminoquinoline picrate by a mixture melting point.

Condensation of certain acids with 8-amino-1,2-dihydroquinoline. A. Formic acid. A solution of 1.1 g. (0.0075 mole) of 8-amino-1,2-dihydroquinoline in 25 ml. of 85% formic acid was refluxed overnight (13–17 hr.). The orange solution was cooled and made alkaline with dilute ammonium hydroxide, whereupon a silvery solid separated which was filtered, washed with water, and recrystallized from methanol to yield colorless needles which melted at 148.0–148.5°. A mixture melting point with authentic 8-formamidoquinoline (XLII) showed no depression, and an analysis and ultraviolet spectrum confirmed the 8-formamidoquinoline structure.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.77; H, 4.65; N, 16.27. Found: C, 69.90; H, 4.96; N, 16.78.

B. Acetic acid. Reaction with acetic acid afforded only 8-acetamidotetrahydroquinoline, m.p. 100–101° (lit.,[21] m.p. 102–103°).

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Preparation of 5,6-Dihydro-1,3-thiazines and 2-Thiazolines from Mercaptoalcohols and Nitriles[1]

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Treatment of certain mercaptoalcohols with nitriles in cold concentrated sulfuric acid results in a one-step nuclear synthesis of dihydro-1,3-thiazines and 2-thiazolines. This ring closure has been found to be applicable to a wide variety of nitriles.

Earlier methods of synthesis of dihydro-1,3-thiazines and 2-thiazolines have been extensively reviewed by Elderfield[2] and Kuhn and Drawert[3]

(1) Presented before the 15th Annual Southwest Regional meeting of the American Chemical Society, Baton Rouge, La., December 3–5, 1959.

(2) R. C. Elderfield and E. E. Harris, *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, 1957, p. 604.

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