Synthesis of 5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolines and Some Related Ring Systems

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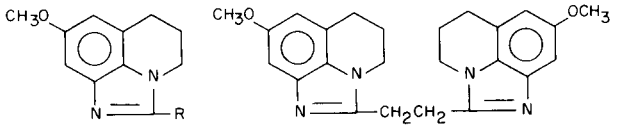
Reduction of amides of 8-amino-6-methoxyquinoline over platinum oxide in glacial acetic acid at room temperature affords 2-substituted-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]-quinolines (I). The method could not be utilized for urea or carbamate derivatives of 8-amino-6-methoxyquinoline. 2-Amino derivatives of I were prepared through the chloro compound obtained from 5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, (IV). Several related ring systems have also been prepared.

Derivatives of 8-amino-6-methoxyquinoline are known to be potent agents in the therapy of malaria, and to have activity against various other parasitic infections. Recently both imidazoles and imidazoheterocyclic systems have shown a variety of pharmacological activities. We were prompted therefore to investigate the derivatives of 5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline (I) (R=H) a system combining these elements.

Though the first imidazo[*i,j*]quinoline was described in 1891 (1) there has been little activity in this general area and virtually none involving the 8-methoxy derivatives. The early work has been summarized by Mosby (2), while the most recent investigations are those of Richardson (3,4).

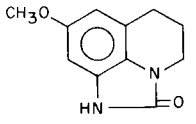
The early studies involved heating an 8-amino-1,2,3,4-tetrahydroquinoline with an acid anhydride or fusion with a carboxylic acid. Richardson achieved greater success by heating the acid and amine in 4*N* hydrochloric acid under reflux; however, the shortcomings of this method, particularly its failure with aromatic, heterocyclic, or unsaturated aliphatic acids, was evident.

The ready availability of 8-amino-6-methoxyquinoline and several observations in the literature which appeared to be pertinent led us to attempt the development of a generally useful synthetic route to I directly from the completely aromatic precursors. Snyder (5) had noted that hydrogenation of 8-amino-5-anilino-6-methoxyquinoline at room temperature in acetic acid over platinum oxide at 3 atmospheres gave a product believed to be 7-anilino-5,6-dihydro-8-methoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline. Elderfield (6) later observed a similar conversion of 8-amino-6,7-dimethoxyquinoline in acetic acid upon hydrogenation over palladium at 500 lb pressure and 140-160° for 5 hours. Barber and Wragg (7) observed that reduction of 8-amino-6-methoxyquinoline in ethyl acetate over Raney nickel at 110°/40 atmospheres gave 40% of I (R=CH_3) together with the desired



I

III



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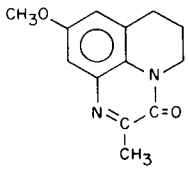

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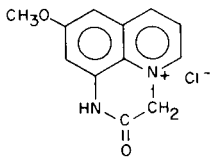

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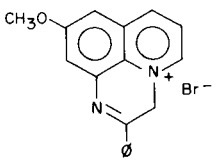

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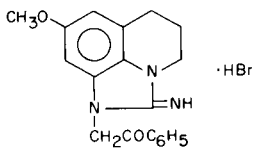

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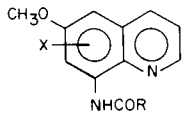
TABLE I

8-Aminoquinoline-amides (a)

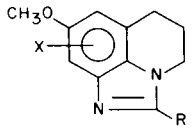


R	X	Yield purified, %	Mp, °C	Crystallization Solvent	Formula	Analyses Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
CF_3	H	46 (b)	138-139	EtOH	$C_{12}H_9F_3N_2O_2$	53.33	53.40	3.36	3.58	10.37	10.97
CH_2Cl	H (13)	70	110-112	EtOH	$C_{12}H_{11}ClN_2O_2$						
CH_3	2-CH_3 (15)	59	113-115	*n*-Heptane	$C_{13}H_{14}N_2O_2$	67.80	67.99	6.13	6.26	12.23	12.18
CH_3	5-OCH_3	52 (c)	225-227	2-PrOH	$C_{13}H_{14}N_2O_3 \cdot HCl$	55.22	55.48	5.35	5.60	9.91	9.90
$CH_2CH_2CO_2H$	H	71 (d)	153-155	2-PrOH	$C_{14}H_{14}N_2O_4$	61.31	61.51	5.15	5.28	10.22	10.06
2-Thienyl	H	23	146-148	EtOH	$C_{15}H_{12}N_2O_2S$	63.36	63.37	4.26	4.48	9.86	9.78
2-Furoyl	H	81 (e)	158-159	EtOH	$C_{15}H_{12}N_2O_3$	67.15	67.31	4.51	4.58	10.44	10.57
3-Pyridyl	H	36	172-173	2.PrOH	$C_{16}H_{13}N_3O_2$	68.80	68.80	4.69	4.69	15.05	14.97
$CH_2N(C_2H_5)_2$	H (13)	63	$b_{3.7}$ 230		$C_{16}H_{21}N_3O_2$						
C_6H_5	H	74 (e)	156-158	EtOH	$C_{17}H_{14}N_2O_2$						
$CH_2C_6H_5$	H	40	118.5-120.5	EtOH	$C_{18}H_{16}N_2O_2$	73.95	74.08	5.52	5.38	9.59	9.43
$CH(OCOCH_3)C_6H_5$	H	31	138-140.5	EtOH	$C_{20}H_{18}N_2O_4$	68.56	68.46	5.18	5.20	7.99	8.02
$(CH_2)_{10}CH_3$	H	48 (e)	55-58	*n*-Heptane	$C_{22}H_{32}N_2O_2$	74.12	74.29	9.05	9.12		

(a) The amides were prepared according to the method described in the experimental section for 8-acetamido-6-methoxyquinoline when not indicated otherwise in the footnotes. (b) Amide prepared in pyridine with trifluoroacetic anhydride at room temperature, F, Calcd. 21.10; Found, 21.35. (c) Amide prepared in chloroform under reflux 2 hours with acetic anhydride. Hydrochloride salt prepared in chloroform with gaseous hydrogen chloride. (d) Reaction run under reflux in benzene for 2 hours with succinic anhydride. (e) Amide prepared in pyridine with acid chloride on the steam bath for 1 hour.

TABLE II

5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolines



R	X	Yield Purified, %	Mp, °C	Crystallization Solvent	Formula	Analyses Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	H	48	89-91.5	C_6H_6-Petr Et_2O	$C_{11}H_{12}N_2O$	70.18	70.62	6.43	6.40	14.89	14.85
CH_2OH	H	21	190-192	2-PrOH	$C_{12}H_{14}N_2O_2$	66.02	66.02	6.46	6.31	12.83	12.91
CH_3	7-NH_2	17.5	169-170	C_6H_6	$C_{12}H_{15}N_3O$	66.34	66.56	6.96	6.84	19.34	19.43
CH_3	4-CH_3	48	140-142	*n*-Heptane	$C_{13}H_{16}N_2O$	72.19	72.27	7.47	7.47	12.97	13.01
CH_3	8-OCH_3	13	161-163	---	$C_{13}H_{16}N_2O_2$	67.21	66.84	6.94	7.06	12.06	12.14
$CH_2CH_2CO_2H$	H	31	221.5-223.5	EtOH	$C_{14}H_{16}N_2O_3$	64.60	64.55	6.20	6.18	10.77	10.84
$CH_2N(C_2H_5)_2$	H	53	78-81	*n*-Heptane	$C_{16}H_{23}N_3O$	70.29	70.21	8.48	8.46	15.37	15.49
C_6H_5	H	45	237-238	2-PrOH	$C_{17}H_{16}N_2O$·HCl	67.88	68.18	5.70	5.57	9.32	9.20
$CH_2C_6H_5$	H	48	94.5-97	$(iPr)_2O$	$C_{18}H_{18}N_2O$	77.67	77.46	6.52	6.69	10.07	9.93
$CHOHC_6H_5$	H	44	230.5-236	$(CH_3)_2NCHO$	$C_{18}H_{18}N_2O_2$	73.45	73.56	6.16	6.26	9.52	9.69
$(CH_2)_{10}CH_3$	H	52	67.5-72.5	*n*-Heptane	$C_{22}H_{34}N_2O$	77.14	77.18	10.01	10.11	8.18	8.39

tetrahydroquinoline. Furthermore, attempted acylation of 8-[[4-(diethylamino)-1-methylbutyl]amino]-1,2,3,4-tetrahydro-6-methoxy-quinoline gave a complex mixture from which 10% of I (R=CH_3) was isolated.

Elderfield and coworkers (8) also observed the formation of I (R=CH_3) *via* a process involving a carbon-carbon bond rupture. Thus they found that when either a mixture of 5-(diethylamino)-2-pentanone and 8-amino-6-methoxyquinoline or the preformed Schiff base was reduced over Raney nickel at 100-160° and 400-800 p.s.i.g., 50% of I (R=CH_3) was formed. The other cleavage product, *N,N*-diethylpropylamine was also shown to be present. This facile cleavage was shown to occur also when 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline was heated at 150-200° with 2-octanone or 1-phenyl-2-propanone leading to formation of I (R=CH_3) and elimination of hexane and toluene respectively (9). These observations were also extended to a series of other carbonyl compounds in a later study (10).

We have found that reduction of a variety of amides of 8-amino-6-methoxyquinoline over platinum oxide in glacial acetic acid at room temperature leads directly to the desired 2-substituted-5,6-dihydro-8-methoxy-4*H*-imidazo-[4,5,1-*ij*]quinolines (I). The reaction apparently proceeds by initial reduction to the amide of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline, followed by the rapid condensation of the amide carbonyl and the ring amine, with loss of water to yield I. The acid reaction medium apparently facilitates the condensation since reduction of 8-acetamido-6-methoxyquinoline over Raney nickel at high pressure in dioxane affords 8-acetamido-1,2,3,4-tetrahydro-6-methoxyquinoline (II). The facile conversion of II to I (R=CH_3) can be demonstrated by observing the change in ultraviolet spectrum of a sample of II. The conversion was shown in this manner to proceed at essentially the same rate at room temperature at *p*H 1 or 7, to the extent of about 20% after 20 hours. Thus the dehydrating ability of the acetic acid medium is also presumed to be beneficial to the rapid, one-step procedure described. In this manner analogs of I wherein R=$CH_2N(C_2H_5)_2$, $CH_2C_6H_5$, $CHOHC_6H_5$, $CH_2CH_2CO_2H$, C_6H_5, $(CH_2)_{10}CH_3$ were prepared (Table II). The amide precursors are described in Table I. The bis compound III was prepared similarly. 7-Amino-5,6-dihydro-8-methoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline was prepared analogously in a single step from 8-acetamido-6-methoxy-5-nitroquinoline. The synthesis using 8-acetamido-5,6-dimethoxyquinoline was less facile, and both 8-acetamido-1,2,3,4-tetrahydro-5,6-dimethoxyquinoline and 5,6-dihydro-7,8-dimethoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline were isolated. 5,6-Dihydro-8-methoxy-2,4-dimethyl-4*H*-imidazo[4,5,1-*ij*]quinoline also was prepared satisfactorily from the corresponding 8-acetamido-6-methoxyquinaldine. Surprisingly *N*-(6-methoxy-8-quinolyl)formamide could not be induced to take up hydrogen in several trials, and with carefully purified material. Compound I (R=H) was prepared readily however by heating together 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and formic acid. Attempts to prepare I (R=CF_3) either by reduction of 6-methoxy-8-(2,2,2-trifluoroacetamido)quinoline or from 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and trifluoroacetic acid failed. Attempts to apply the reductive cyclization to *N*-(6-methoxy-8-quinolyl)-2-thiophene-carboxamide, *N*-(6-methoxy-8-quinolyl)nicotinamide and *N*-(6-methoxy-8-quinolyl)-2-furamide led only to gross mixtures from which none of the desired imidazo[4,5,1-*ij*]-quinolines could be isolated. Competition from the readily reducible heterocyclic systems might have been expected to preclude successful application of the technique in these instances.

An attempt was made to extend the generality of the procedure to preparation of derivatives such as I (R=OC_2H_5 and NHR). Reduction of ethyl 6-methoxy-8-quinolinecarbamate afforded primarily the product of the reduction of the quinoline ring, ethyl 1,2,3,4-tetrahydro-6-methoxy-8-quinolinecarbamate, along with a small amount of 5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (IV) resulting from intramolecular amide formation. Apparently if any further change is to take place with this reasonably stable intermediate, loss of ethanol predominates over loss of water leading to the cyclic urea rather than the imidazoquinoline (I). Similarly, reduction of 3-(6-methoxy-8-quinolyl)-1,1-dimethylurea led to isolation only of IV attesting again to the preference for transamidation with the more favorable loss of dimethylamine as opposed to water. Utilizing a poor leaving group such as aniline led to formation only of the saturated intermediate. Thus a good yield of 1-phenyl-3-(1,2,3,4-tetrahydro-6-methoxy-8-quinolyl)urea was obtained by reduction of 1-phenyl-3-(6-methoxy-8-quinolyl)urea. Under more vigorous conditions transamidation could be achieved. Heating the reduced urea under reflux with 4*N* hydrochloric acid gave 76% of the cyclic area IV.

The cyclic urea IV was readily prepared in quantity by treatment of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline in acetic acid with phosgene. Compound IV was converted into 2-chloro-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline (I, R=Cl) with phosphorous oxychloride. Compound I (R=Cl) upon treatment with aliphatic amines provided the corresponding amines I [R=NC_5H_{10}, $N(CH_3)_2$]. The primary amine I (R=NH_2) was obtained from 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and cyanogen bromide.

Several variations of structure I were obtained directly from 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline. Treatment with glycolic acid for example provided I

(R=CH_2OH). Warming with pyruvic acid gave a material presumed to be 6,7-dihydro-9-methoxy-2-methyl-3*H*,5*H*-pyrido[1,2,3-*de*]quinoxalin-3-one (V).

Miscellaneous related systems prepared were: 2, 3-dihydro-9-methoxy-2-oxo-1*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium chloride (VI), obtained by heating 8-(2-chloroacetamido)-6-methoxyquinoline to its melting point; 9-methoxy-2-phenyl-3*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium bromide (VII), obtained by heating 8-amino-6-methoxyquinoline with 2-bromoacetophenone in ethanol.

Treatment of I (R=NH_2) with 2-bromoacetophenone gave a compound presumed to be the uncyclized VIII, although a simple quaternary salt involving the quinoline ring nitrogen cannot be excluded.

Examination of these materials in a variety of pharmacological and chemotherapeutic assays revealed no interesting biological activity.

EXPERIMENTAL

5,6-Dihydro-8-methoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline (11).

Method A.

A mixture of 10 g. (0.04 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline dihydrochloride, 25 ml. of acetic acid, 2.5 ml. of acetic anhydride and 15 g. of sodium acetate was heated under reflux for 2 hours. Water (150 ml.) was added and the mixture was cooled, made basic with ammonium hydroxide and extracted with chloroform. The extracts were dried, the solvent removed *in vacuo* and the oily residue which solidified on standing was recrystallized twice from a mixture of benzene and petroleum ether to give 3.0 g. of the product (37.5%) as beige needles, m.p. 121.5-124.5°.

Method B.

8-Acetamido-6-methoxyquinoline (21.6 g., 0.1 mole) in 200 ml. of glacial acetic acid was hydrogenated over 1 g. of platinum oxide at 25° and an initial pressure of 50.5 p.s.i.g. The catalyst was removed by filtration and the filtrate was poured into water and made basic with ammonium hydroxide. The oil was extracted with chloroform, dried and concentrated to dryness *in vacuo*. The residue recrystallized twice from a mixture of benzene and petroleum ether afforded 10.9 g. (54%) of the product, m.p. 120-123°, identical with the material obtained in Method A.

8-Acetamido-6-methoxyquinoline (12).

8-Amino-6-methoxyquinoline hydrochloride (100 g., 0.465 mole) was added to 100 ml. of water and a saturated aqueous solution of 200 g. of sodium acetate. To the oily mixture was added 200 ml. of acetic anhydride. The temperature rose to 45° and a brown solid formed rapidly. After about 1 hour the product was removed by filtration and crystallized from 95% alcohol to give 84.7 g. (82.7%), m.p. 127.5-128.5°.

8-Acetamido-1,2,3,4-tetrahydro-6-methoxyquinoline.

A solution of 21.6 g. (0.1 mole) of 8-acetamido-6-methoxyquinoline in 150 ml. of dioxane was reduced over 5 g. Raney nickel at 98° and 1200 p.s.i.g. The cooled mixture was filtered, a small amount of water was added and the solvent was removed *in vacuo*. The residual solid was recrystallized twice from a mixture of benzene and petroleum ether to give 8.1 g. (36.8%) of product, m.p. 117.5-119.5°. The melting point of a mixture of this material and the 5,6-dihydro-8-methoxy-2-methyl-4*H*-imidazo-[4,5,1-*ij*]quinoline was depressed. In addition the ultraviolet and infrared spectra of the two were distinctly different.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.64; H, 7.31; N, 12.74.

8-Amino-1,2,3,4-tetrahydro-6-methoxyquinoline.

A solution of 44 g. (0.25 mole) of 8-amino-6-methoxyquinoline in 100 ml. of dioxane was hydrogenated over 4 g. of copper-chromium oxide at 155° and an initial pressure of 1500 p.s.i.g. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was dissolved in ether and dry hydrogen chloride was bubbled into the solution. The solid was recrystallized from water to give 36.3 g. (57.5%) of the product as the dihydrochloride, m.p. 215-219°.

5,6-Dihydro-8-methoxy-α-phenyl-4*H*-imidazo[4,5,1-*ij*]quinoline-2-methanol.

A solution of 10.8 g. (0.031 mole) of 8-(2-acetoxy-2-phenylacetamido)-6-methoxyquinoline in 250 ml. of glacial acetic acid was hydrogenated over 1 g. of 20% platinum on carbon at 24° and 52 p.s.i.g. The mixture was filtered and the solvent removed *in vacuo*. The residue was taken up in water, made basic with aqueous sodium hydroxide and extracted with chloroform. The extracts were dried, and the solvent removed *in vacuo*. The oily residue was dissolved in ethanol and 25 ml. of concentrated hydrochloric acid and heated under reflux overnight. The solvent was removed and the residue dissolved in water and made basic with sodium hydroxide. The solid which formed was recrystallized from dimethylformamide to give 4.0 g. (44%) of product, m.p. 230.5-236°.

5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline.

A mixture of 12.2 g. (0.0685 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and 50 g. of formic acid was heated on a steam bath for 2 hours, poured onto ice and made basic with ammonium hydroxide. The reddish oil which formed was extracted with chloroform. The extract was dried over magnesium sulfate and solvent removed *in vacuo*. The residue was recrystallized twice from a mixture of benzene and petroleum ether (b.p. 30-60°) to give 6.2 g. of the product.

5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline-2-methanol (17).

A solution of 13.2 g. (0.074 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and 5.52 g. (0.073 mole) of glycolic acid in 80 ml. of 4*N* hydrochloric acid was heated under reflux for 40 minutes, cooled and made basic with ammonium hydroxide. The solid was removed and recrystallized twice from 2-propanol to give 3.3 g. (21%) of the product as a dull red solid, m.p. 190-192°.

N,*N*′-Bis(6-methoxy-8-quinolyl)succinamide.

To a solution of 104.4 g. (0.6 mole) of 8-amino-6-methoxyquinoline in 450 ml. of benzene at 10-15° was added dropwise 46.5 g. (0.3 mole) of succinoyl chloride. The mix was allowed to warm to room temperature and filtered to give 153.5 g. of yellow solid, m.p. 242-245°. This material was triturated with dilute ammonium hydroxide and filtered to give 82.1 g. of solid, m.p. 248-250°. Recrystallization from dimethylacetamide gave 52.7 g. (41%) of the product as a pale lavender solid, m.p. 262-263°.

Anal. Calcd. for $C_{24}H_{22}N_4O_4$: C, 66.95; H, 5.15; N, 13.02. Found: C, 66.73; H, 5.27; N, 12.95.

2,2′-Ethylenebis[5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]-quinoline (III).

N,N′-Bis(6-methoxy-8-quinolyl)succinamide (21.5 g., 0.05 mole) in 250 ml. of glacial acetic acid was hydrogenated over platinum oxide at 23° and 51.5 p.s.i.g. The reduction proceeded with some difficulty. Four additional 1 g. portions of platinum oxide and 400 ml. of acetic acid were added until the reaction was complete after three days. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was recrystallized twice from dimethylacetamide to give 8.7 g. (43.5%) of pale yellow needles, m.p. 239-240°.

Anal. Calcd. for $C_{24}H_{26}N_4O_2$: C, 71.61; H, 6.51; N, 13.92. Found: C, 71.40; H, 6.54; N, 13.84.

8-Acetamido-6-methoxy-5-nitroquinoline (14).

To a solution of 15 g. (0.0695 mole) of 8-acetamido-6-methoxyquinoline in 60 ml. of concentrated sulfuric acid cooled to 0° was added dropwise 30 ml. of nitric acid. The temperature was maintained below 10° during the addition. The mixture was stirred for one hour and poured into iced water. The crude product was removed by filtration and recrystallized from acetonitrile to give 12.5 g. (69%) of the product, m.p. 197-199°.

5,6-Dihydro-7,8-dimethoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline.

8-Acetamido-5,6-dimethoxyquinoline (24.9 g., 0.088 mole) in 500 ml. glacial acetic acid was hydrogenated over 2 g. of 20% platinum on carbon at 25° and 51 p.s.i.g. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was dissolved in water and made basic with ammonium hydroxide to give 15.2 g. of pink solid, m.p. 120-123°. Two recrystallizations from carbon tetrachloride gave 5.5 g. of 8-acetamido-1,2,3,4-tetrahydro-5,6-dimethoxyquinoline, m.p. 141-142°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.37; H, 7.25; N, 11.19. Found: C, 62.12; H, 7.43; N, 11.17.

The filtrates from the two crystallizations were combined and the solvent removed *in vacuo*. The residue was recrystallized from a mixture of ethylene chloride and petroleum ether to give a small amount of high-melting solid. Addition of more petroleum ether to the filtrate and cooling gave 2.7 g. (13%) of the desired 5,6-dihydro-7,8-dimethoxy-2-methyl-4*H*-imidazo[4,5,1-*ij*]quinoline, m.p. 161-163°.

N-(6-Methoxy-8-quinolyl)-2-thiophenecarboxamide.

To a solution of 17.4 g. (0.1 mole) of 8-amino-6-methoxy quinoline and 12.8 g. (0.1 mole) of 2-thiophenecarboxylic acid in 150 ml. of ethyl acetate was added in portions 20.6 g. (0.1 mole) of dicyclohexylcarbodiimide. The reaction was slightly exothermic and the temperature rose to 32°. The mix was allowed to stir at room temperature overnight. The dicyclohexylurea (11.2 g.) was removed by filtration, and the filtrate was concentrated to dryness. The residue was recrystallized three times from 95% ethanol to give 6.5 g. (23%) of product as off-white needles, m.p. 146-148°.

3-(6-Methoxy-8-quinolyl)-1,1-dimethylurea.

To a pyridine solution of 69.6 g. (0.4 mole) of 8-amino-6-methoxyquinoline was added 43 g. (0.4 mole) of dimethylcarbamoyl chloride. The mixture was heated on the steam bath for 4 hours, poured into iced water and filtered. The solid was extracted with warm ethanol and filtered to give 15 g. of insoluble material. The filtrate was warmed, water added to the cloud point and chilled to give 48.6 g. of the desired product, m.p. 124.5-131°. One further crystallization from dilute ethanol gave 37.4 g. (38.2%), m.p. 128.5-131.5°.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.17; N, 17.13. Found: C, 63.65; H, 6.29; N, 17.23.

The first crop of 15 g. was recrystallized from *N,N*-dimethylformamide to give 11 g. of 1,3-bis(6-methoxy-8-quinolyl)urea, m.p. 252-254°.

Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.97. Found: C, 67.00; H, 5.03; N, 15.21.

5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one.

A solution of 12.3 g. (0.05 mole) of 3-(6-methoxy-8-quinolyl)-1,1-dimethylurea in 150 ml. of glacial acetic acid was hydrogenated over 1 g. of 20% platinum on carbon at a starting pressure of 51.5 p.s.i.g. and 21.5°. After a pressure drop of 8 p.s.i.g. the mix was removed from the bomb, filtered and the solvent removed *in vacuo*. The residue was dissolved in water, made basic with ammonium hydroxide and the solid that formed was removed by filtration. Recrystallization from benzene gave 3.1 g. of product, m.p. 234.5-237° (29.5%) identical with the material described below.

5,6-Dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (IV).

To a solution of 178.2 g. (1.0 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxy-quinoline in 150 ml. of glacial acetic acid was added a solution of 98.9 g. (1.0 mole) of phosgene in 200 ml. of chlorobenzene. The mixture was stirred at room temperature for several hours and then heated under reflux for 6 hours. The solid which formed upon cooling was removed by filtration and recrystallized from ethanol and then from dimethylformamide to give 100 g. (49%) of the product, m.p. 233-234°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.51; H, 6.04; N, 13.55.

2-Chloro-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline.

A mixture of 10 g. (0.05 mole) of 5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]-quinolin-2(1*H*)-one and 40 ml. of phosphorous oxychloride was heated under reflux for 1.5 hours and the solution was then poured onto ice and neutralized with ammonium hydroxide. The crude solid which resulted was recrystallized from ethanol to give 7.5 g. (68%) of the product, m.p. 132-134°.

Anal. Calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.97; N, 12.58. Found: C, 59.08; H, 4.81; N, 12.60.

1-(6-methoxy-8-quinolyl)-3-phenylurea.

To a solution of 26.2 g. (0.15 mole) of 8-amino-6-methoxyquinoline in 200 ml. of benzene was added dropwise 17.9 g. (0.15 mole) of phenyl isocyanate. The temperature rose to 50° and a solid formed. The mixture was stirred for an additional hour and filtered. The solid was recrystallized from 95% ethanol to give 39.3 g. (89%) of product, m.p. 205-206°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.83; H, 5.07; N, 14.33.

Reduction of 1-(6-methoxy-8-quinolyl)-3-phenylurea.

1-(6-Methoxy-8-quinolyl)-3-phenylurea (26.1 g., 0.089 mole) in 200 ml. of glacial acetic acid was hydrogenated over 2 g. of 20% platinum on carbon at 25° and 51.5 p.s.i.g. After removal of the catalyst the solvent was removed *in vacuo*. The residue was triturated with water to give 25.9 g. of solid, m.p. 178-180°. Recrystallization from a mixture of dimethylformamide and water gave 20.4 g. (77%) of 3-phenyl-1-(1,2,3,4-tetrahydro-6-methoxy-8-quinolyl)urea as an off-white solid, m.p. 198-199°.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.79; H, 6.50; N, 14.38.

Five g. of the reduced urea heated under reflux with 150 ml. of 4*N* hydrochloric acid gave on filtration 2.6 g. (76%) of 5,6-

dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1 *H*)-one, m.p. 233-236°.

Reduction of Ethyl 6-Methoxy-8-quinolinecarbamate (16).

A solution of 24.6 g. (0.1 mole) of carbamate in 250 ml. of glacial acetic acid was hydrogenated over 2 g. of 20% platinum on carbon at 22° and 51 p.s.i.g. After the uptake was complete the mixture was removed from the bomb, filtered and concentrated to dryness *in vacuo*. The residue was dissolved in water, made basic with ammonium hydroxide, and extracted with chloroform. The extracts were dried and concentrated to give a red oil. Trituration with ether afforded 1.8 g. of solid, m.p. 230-234°. Recrystallization from a mixture of chloroform and petroleum ether gave 1.0 g. of 5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, m.p. 234-235°.

The ether filtrate was concentrated to dryness, the residue was taken up in 2-propanolic hydrogen chloride and triturated with ether to give 20.7 g. of solid, m.p. 178-184°. Two recrystallizations from 2-propanol gave 13.5 g. (47%) of tan crystals, m.p. 188-190° of the hydrochloride of ethyl 1,2,3,4-tetrahydro-6-methoxy-8-quinolinecarbamate.

Anal. Calcd. for $C_{13}H_{19}ClN_2O_3$: C, 54.44; H, 6.68; N, 9.77. Found: C, 54.49; H, 6.77; N, 9.87.

5,6-Dihydro-8-methoxy-2-piperidino-4*H*-imidazo[4,5,1-*ij*]quinoline.

2-Chloro-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline (5 g., 0.022 mole) was heated under reflux in excess piperidine for 4 hours. The mix was cooled and the solid piperidine hydrochloride removed by filtration. The filtrate was concentrated to dryness and recrystallized from *n*-heptane to give 3.5 g. (57%) of the product, m.p. 71-73°.

Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.55; H, 7.72; N, 15.57.

2-(Dimethylamino)-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]-quinoline, 0.9 Hydrochloride.

A solution of 10 g. (0.045 mole) of 2-chloro-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline in 100 ml. of 40% dimethylamine was heated in a bomb for 6 hours at 150°. The solution was concentrated to dryness and the residue was recrystallized four times from a mixture of 2-propanol and petroleum ether (40-60°) to give 2.6 g. (22%) of the product, m.p. 189-191°.

Anal. Calcd. for $C_{13}H_{17}N_3O \cdot 0.9HCl$: C, 59.12; H, 6.83; N, 15.91. Found: C, 59.13; H, 6.48; N, 15.46.

6,7-Dihydro-9-methoxy-2-methyl-3*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-3-one (V) (17).

A mixture of 7 g. (0.0392 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline and 5.75 g. (0.064 mole) of pyruvic acid was warmed briefly on the steam bath. The mixture was cooled, triturated with ammonium hydroxide, stirred for 1 hour and filtered. Recrystallization from *n*-heptane afforded the product as yellow crystals (2.0 g., 22%), m.p. 146-147°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.98; H, 6.22; N, 12.34.

2-Amino-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline.

To a slurry of 82.2 g. (0.462 mole) of 8-amino-1,2,3,4-tetrahydro-6-methoxyquinoline in 300 ml. of water stirred under nitrogen was added 49.15 g. (0.462 mole) of cyanogen bromide in small portions. Heat was evolved during the addition and a precipitate formed. After completion of the addition the mixture was stirred 4 hours at room temperature, allowed to stand overnight under nitrogen and filtered. The solid was slurried in 10% sodium hydroxide, washed with water and dried. Recrystallization from ethanol gave 53 g. (39%) of the product, m.p. 266-268°.

Anal. Calcd. for $C_{11}H_{14}N_3BrO \cdot 1/2H_2O$: C, 45.06; H, 5.16; N, 14.29; H_2O, 3.08. Found: C, 45.08; H, 4.99; N, 14.45; H_2O, 3.33;

A portion of the hydrobromide was dissolved in hot water, made basic with sodium hydroxide, filtered and recrystallized from alcohol to give the base, m.p. 229-230°.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.44; N, 20.60. Found: C, 64.63; H, 6.32; N, 20.64.

2,3-Dihydro-9-methoxy-2-oxo-1*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium Chloride (VI).

Five g. (0.02 mole) of 8-(2-chloroacetamido)-6-methoxyquinoline was heated in an oil bath to 150°. The solid melted and gradually solidified until the entire mass was a yellow solid. This material was removed from the flask, powdered and extracted with boiling methanol. The insoluble material was removed by filtration and dried *in vacuo* to give 2.9 g. (58%) of product, m.p. > 300°. The material exhibited a strong carbonyl absorption at 1708 cm^{-1}, NH at 3440 cm^{-1}, and C=N at 1635 cm^{-1}. The ultraviolet spectrum in methanol showed λ 382 $E^{1\%}_{1cm}$, =94; λ 340, $E^{1\%}_{1cm}$ = 169; λ 274 $E^{1\%}_{1cm}$ = 765; λ 251 $E^{1\%}_{1cm}$, 578; λ 229 $E^{1\%}_{1cm}$, = 928; λ 217 $E^{1\%}_{1cm}$, = 1135.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.18; Cl^-, 14.14. Found: C, 57.76; H, 4.34; N, 11.37; Cl^-, 13.98.

9-Methoxy-2-phenyl-3*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium Bromide, 0.25 Hydrate (VII).

A solution of 17.4 g. (0.1 mole) of 8-amino-6-methoxyquinoline and 20 g. (0.1 mole) of 2-bromoacetophenone in ethanol was heated under reflux for 4 hours. A red solid gradually formed. The mixture was allowed to stand at room temperature overnight and filtered to give 16.0 g. of red crystals, m.p. 222-226° dec. Crystallization once from water and twice from methanol gave 5.8 g. (16%) of product, m.p. 233-236°.

Anal. Calcd. for $C_{18}H_{15}BrN_2O \cdot 0.25H_2O$: C, 60.09; H, 4.34; N, 7.79; H_2O, 1.25. Found: C, 59.86; H, 4.67; N, 7.57; H_2O, 0.91.

2-(5,6-Dihydro-2-imino-7-methoxy-4*H*-imidazo[4,5,1-*ij*]quinolin-1-(2*H*)-yl)acetophenone (VIII).

A suspension of 10 g. (0.049 mole) of 2-amino-5,6-dihydro-8-methoxy-4*H*-imidazo[4,5,1-*ij*]quinoline, and 9.8 g. (0.049 mole) of 2-bromoacetophenone in ethanol was warmed. A heavy white precipitate formed rapidly. Several hundred ml. of ethanol was added and the mixture was heated under reflux for 2 hours with vigorous stirring. The mixture was filtered hot to afford 16.6 g. (85%) of the product, m.p. 287-289° dec., (prior shrinkage from 280°). The infrared spectrum of this material exhibits peaks at 1694 (C=O), 1667 (C=N), and 3400 (NH) cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}BrN_3O_2$: C, 56.72; H, 5.01; N, 10.44. Found: C, 56.91; H, 4.97; N, 10.27.

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