A Study of Some 1-Alkyl-2,3-dihydroimidazo[1,2-*a*]benzimidazoles

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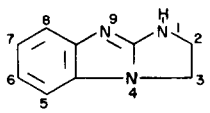
Dedicated to Professor Allan R. Day

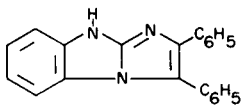
A series of 1-alkyl-7-nitro (and 7-amino)-2,3-dihydroimidazo[1,2-*a*]benzimidazoles has been prepared. Similarly, a series of 1-alkyl-2,3-dihydroimidazo[1,2-*a*]benzimidazoles has been prepared. The prototropic tautomerism of this system has been studied. The site of electrophilic attack (alkylation) has been examined. 1-Alkylation takes place under strongly basic conditions and 9-alkylation occurs under neutral conditions.

This report is primarily concerned with the preparation of selected 1-alkyl-2,3-dihydroimidazo[1,2-*a*]benzimidazoles and with their physical and chemical properties. This represents an extension of our interest in nitrogen bridgehead compounds (1). The 1*H*-2,3-dihydroimidazo-[1,2-*a*]benzimidazole system (I) is relatively new and little is known about its physical, chemical and physiological properties.



I

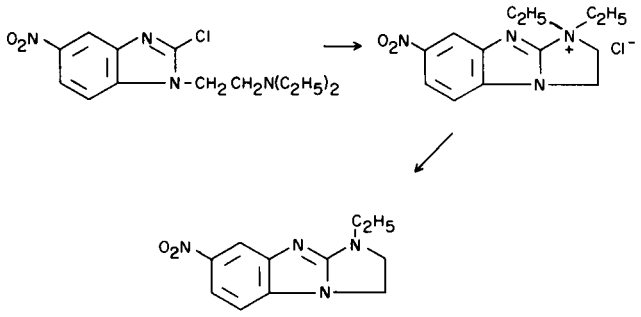
The ring system first appeared in the literature in 1959 (2). The reaction of *o*-phenylenediamine with 2-chloro-4,5-diphenyloxazole gave a product reported to be 2,3-diphenyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (II).



II

Hunger *et al.* reported the formation of a small amount of 1*H*-1-ethyl-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (III) when 1-diethylaminoethyl-2-chloro-5-nitrobenzimidazole was heated with diethylamine (3).

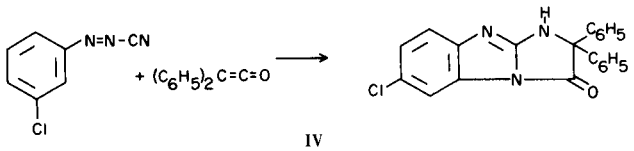
SCHEME 1



III

Bird obtained a ring system (4), *via* a thermal rearrangement of the adduct obtained from diphenylketene and *m*-chlorobenzenediazocyanide, which he reported to be 1*H*-6 chloro-3-oxo-2,2-diphenyl-2,3-dihydroimidazo[1,2-*a*]benzimidazole (IV) (Scheme 2).

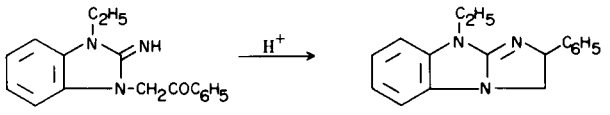
SCHEME 2



IV

Simonov and Kochergin published the first directed synthesis of the 9*H* system (5). They alkylated 1-ethyl-2-aminobenzimidazole with phenacyl bromide to obtain a benzimidazolonimine which when heated with dilute mineral acids underwent cyclodehydration to form 9-ethyl-2-phenyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (V) (Scheme 3).

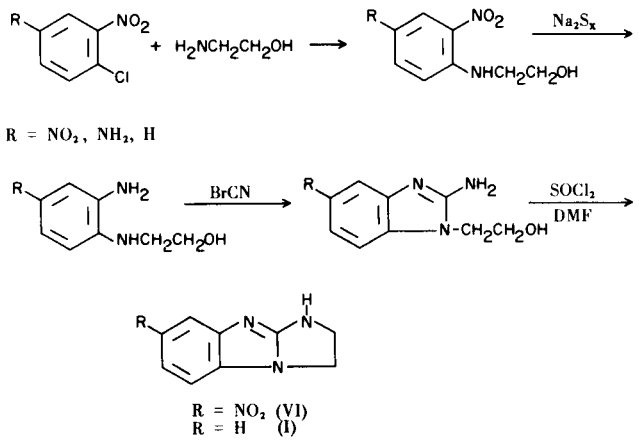
SCHEME 3



V

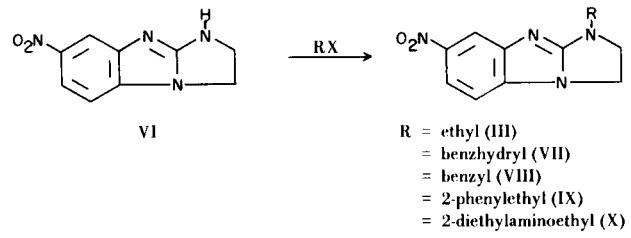
The objectives of the present study were: (1) to find a suitable method for the synthesis of the 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole ring system; (2) to study the prototropic tautomerism of this system; and (3) to prepare both 1-alkyl and 9-alkyl derivatives. The method finally adopted for making this ring system was the four-step synthesis developed by Freedman (6) (Scheme 4).

SCHEME 4



Alkylation of 7-nitro-1*H*-2,3-dihydroimidazo[1,2-*a*]-benzimidazole (VI) with the appropriate alkyl halide in the presence of sodium amide in liquid ammonia produced the 1-ethyl- (III), 1-benzhydryl- (VII), 1-benzyl- (VIII), 1-phenylethyl- (IX) and 1-(2-diethylaminoethyl)-7-nitro-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazoles (X) in good yields (Scheme 5).

SCHEME 5

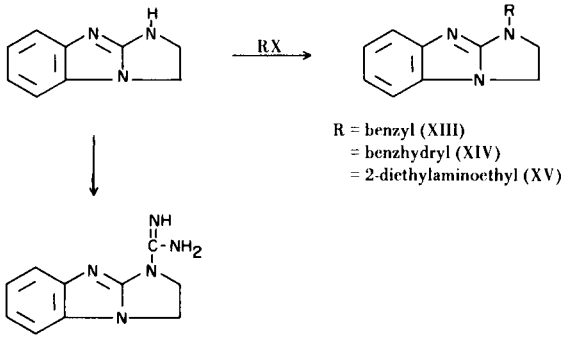


Hunger *et al.* (3) has previously reported the 1-ethyl derivative. Our melting point for the hydrochloride (245-248°) agreed with the value reported but the free base melted at 170.5-171.5° whereas the reported value was 161-163°. A mixed melting point determination with a sample kindly supplied by Dr. Hunger (7), showed no depression (170.5-171.5°). It would appear that direct ethylation produced the 1-derivative under the conditions noted. The preparation of the 1-(2-diethylaminoethyl) derivative (X) required a modification of the sodamide-liquid ammonia procedure (8).

Catalytic hydrogenation of IX over Raney Nickel gave the corresponding amino compound 1-(2-phenylethyl)-7-amino-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XI). The benzhydryl derivative (XII) could not be prepared by this method because of losing the benzhydryl group through hydrogenolysis. It was successfully prepared by the method of Furst *et al.* which involved the use of Raney Nickel and hydrazine (9).

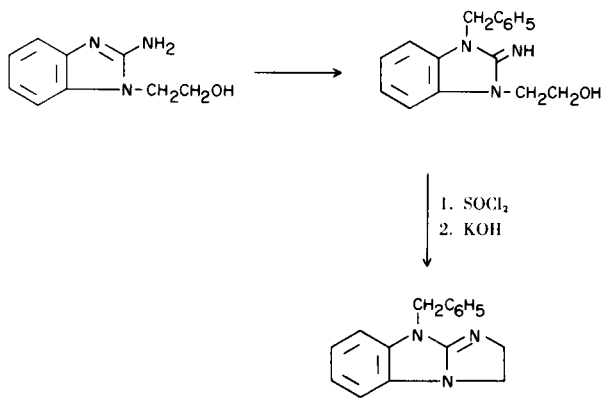
The 1-benzyl (XIII), 1-benzhydryl (XIV) and 1-(2-diethylaminoethyl) (XV) derivatives of 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (I) were prepared by the sodamide-liquid ammonia method. The 1-guanyl (amidino) derivative (XVI) was prepared from the parent compound (I) by treatment with 3,5-dimethyl-1-guanylpyrazole nitrate (DGPN). This is a *trans* acylation reaction (10) (Scheme 6).

SCHEME 6



It has been assumed thus far that alkylation occurred in the one position. This was assumed since comparison of the ethylated product (III) with an authentic sample of 1-ethyl-7-nitro-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole proved them to be identical. Further evidence was obtained by comparing spectra of authentic samples of the 1- and 9-benzyl derivatives. The 9-benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XVII) was prepared by the method of Siminov (5, 11) (Scheme 7). The 9-benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XVIII) was a clear viscous liquid (b.p. 192-194°/0.15 mm.). The infrared spectrum in chloroform showed a band at 1660 cm^{-1}. This was associated with the C=N bond. This band was found at 1630 cm^{-1} in the infrared spectrum of the 1-benzyl compound and at 1640 cm^{-1} for the parent 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimida-

SCHEME 7

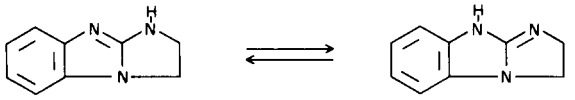


XVII

zole. This increase in double bond character for the 9-benzyl structure, resulting in a higher absorption frequency, is in the direction expected on the basis of infrared spectra of other benzimidazoles and benzimidazolonimines (12).

A comparison of the nmr spectra of the 1-benzyl and 9-benzyl derivatives (in deuteriochloroform) showed some marked differences in shifts of the methylenic benzyl protons and of the benzene protons of the benzimidazole moiety. In the 1-benzyl derivative, the methylenic protons absorb at δ 4.65. These protons are adjacent to the electron withdrawing -C=N- group. In the 9-benzyl derivative, the methylenic protons are adjacent to two electron withdrawing groups resulting in an absorption at δ 4.93, slightly more downfield. The four benzene protons of the heterocyclic ring system in the 9-benzyl compound absorb as a symmetrical multiplet at δ 6.75. However, in the 1-benzyl derivative the three protons at positions 5, 6, and 7 absorb as an unsymmetrical multiplet at δ 7.1 while the proton at position 8, being adjacent to the electron withdrawing group -C=N-, absorbs downfield of δ 7.4. This shift has been noted for other 1-substituted benzimidazoles (13). Two substituted benzimidazoles show two characteristic bands in the ultraviolet. One at 240-250 mμ has been assigned to the amidine group of the aromatic imidazole ring and the other at 280-300 mμ has been assigned to benzenoid absorption. It is significant that 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole, 1-benzyl-2,3-dihydroimidazo[1,2-*a*]benzimidazole, and 9-benzyl-2,3-dihydroimidazole all absorb in the ultraviolet (methanol) at 278-287 mμ. However, only the first two absorb at 242-247 mμ, the region ascribed to the aromatic imidazole system. Thus, u.v. spectra may be used to distinguish between the 1- and 9-substituted derivatives.

1*H*-2,3-Dihydroimidazo[1,2-*a*]benzimidazole and 9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole represent a potentially tautomeric system in which the 1-*H* isomer would be expected to predominate. Information concerning the



1-*H* isomer (A) 9-*H* isomer (B)

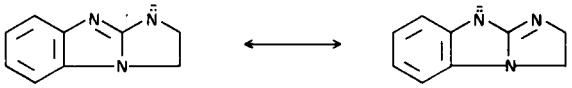
tautomeric composition was obtained as follows: (1) chemically relating the structures of reaction products to the structures of starting materials; (2) determination of pK_a values; and (3) comparison of ultraviolet spectra.

When 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole was alkylated, with benzyl chloride, under strongly basic, neutral (protic and aprotic), and acidic conditions, the following products were observed:

1-alkylation under basic conditions 9-alkylation under neutral conditions

Alkylation did not take place under acidic conditions.

The interpretation of these data is based on the mechanisms proposed by Grimison *et al.* for *N*-substitution in simple imidazoles and benzimidazoles (14). 1-Alkylation in liquid ammonia was established by examing the ultraviolet spectrum in methanol and observing a band at 240-250 mμ indicating the imidazole ring. The anion is attacked by the alkylating agent under strong basic conditions. Greater resonance stabilization results from



A B

the alkylations of extreme structure A.

9-Alkylation of the neutral molecule can be rationalized by considering the structures of the intermediates formed by electrophilic attack at the 1- and 9- positions.

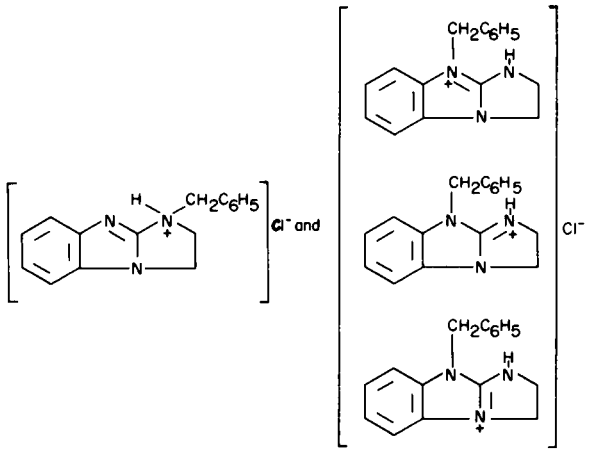


TABLE I

Potentiometric Titration of 9-Benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole in 44.25% Ethanol at 25°

ml. of 0.0557 *N* KOH in 44.25% C_2H_5OH	observed *p*H	*p*H corr.	BH^+	B	$\log \frac{BH^+}{B}$	pK_a
0	3.91					
0.890	7.29	---	.00470	0		
1.339	7.75	7.57	.00423	.00047	+0.95	8.52
1.788	8.09	7.91	.00376	.00094	+0.60	8.51
2.237	8.33	8.15	.00329	.00141	+0.37	8.52
2.689	8.49	8.31	.00282	.00188	+0.18	8.49
3.135	8.66	8.48	.00235	.00235	0.00	8.48
3.584	8.85	8.67	.00188	.00282	-0.18	8.49
4.033	9.01	8.83	.00141	.00329	-0.37	8.46
4.482	9.25	9.07	.00094	.00376	-0.60	8.47
4.931	9.58	9.40	.00047	.00423	-0.95	8.45
5.380	9.95		0	.00470		

$pK_a = 8.48 \pm 0.03$.

TABLE II

Potentiometric Titration of 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole in 44.25% Ethanol at 25°

ml. of 0.0557 *N* KOH in 44.25% C_2H_5OH	observed *p*H	*p*H corr.	BH^+	B	$\log \frac{BH^+}{B}$	pK_a
0	3.85		.00470			
0.890	5.20		.00470			
1.339	5.45	5.27	.00423	.00047	+0.95	6.22
1.788	5.80	5.62	.00376	.00094	+0.60	6.22
2.237	6.04	5.86	.00329	.00141	+0.37	6.23
2.689	6.22	6.04	.00282	.00188	+0.18	6.22
3.135	6.38	6.20	.00235	.00235	0.00	6.20
3.584	6.55	6.37	.00188	.00282	-0.18	6.19
4.033	6.72	6.57	.00141	.00329	-0.37	6.17
4.482	6.96	6.78	.00094	.00376	-0.60	6.18
4.931	7.31	7.13	.00047	.00423	-0.95	6.18
5.380	8.38			.00470		

$pK_a = 6.20 \pm 0.03$.

Addition at position nine forms a cation which is more stabilized by resonance.

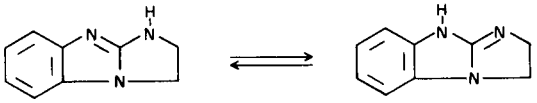
The failure of the protonated amine to undergo alkylation might be expected since the protonated species would be expected to be a poor nucleophile.

Comparison of the ultraviolet spectra and pK_a measurements indicated that 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole exists predominantly in the amino form as was expected. Comparison of the ultraviolet spectrum of 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole with the spectra of both the 1- and 9-alkyl derivatives indicated the predominance of the amino tautomer. Both the 1-benzyl and the parent compound exhibit absorption maxima at 240-250 mμ whereas the 9-benzyl derivative does not. The electronic spectrum of a compound arises from its π electron system and is relatively unaffected by substitution of an alkyl group for hydrogen. Thus comparison of the ultraviolet spectrum of a potentially tautomeric compound with the spectra of both alkylated forms often indicates which tautomer predominates at equilibrium (15).

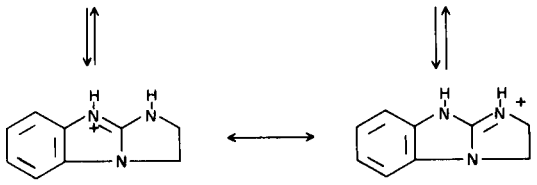
Steck, Ewing and Nachod compared the ultraviolet spectra of benzimidazole and 2-aminobenzimidazole in

ethanol and noticed the absence of fine structure in 2-aminobenzimidazole as compared with the parent compound (16). The absence of fine structure is also noted in 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole.

These data along with pK_a measurements indicate the great predominance of tautomer A over tautomer B. The determination of pK_a values is probably the most generally useful method for the investigation of tautomerism (15). When protonated the amino and imino forms of a tautomeric amine yield the same resonance cation. The tautomeric equilibrium constant can be calculated from K_a (amino) and K_a (imino) which are the acid dissociation constants of the cation, as the cation of the conjugate acid of the amino and imino forms, respectively.

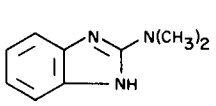


amino form (A) imino form (B)

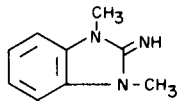


$$K_{taut.} = \frac{K_a \text{ amino}}{K_a \text{ imino}}$$

Application of the above relation is limited by the difficulty of determining the dissociation constants of both tautomers. Scheinker *et al.* (12), in a study of the tautomerism of 2-aminobenzimidazoles, determined the pK_a values for structures A and B as models of the amine and imine forms of 2-aminobenzimidazole, potentiometrically in 50% ethanol. They obtained values of 8.92 for B and 6.71 for A. They concluded that 2-aminobenzimidazole existed predominantly as the amino form but possessed a greater tendency to exist in the imine form as compared with most other heterocyclic amines.

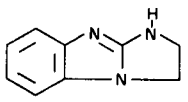


A amine



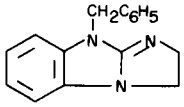
B imine

In the current work the pK_a's of 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (I) and 9*H*-9-benzyl-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XVII) were determined in the same manner. The results of two runs are listed below.



I

$pK_a = 6.20 \pm 0.03$
$pK_a = 6.23 \pm 0.04$



XVII

$pK_a = 8.48 \pm 0.03$
$pK_a = 8.49 \pm 0.04$

Assuming previous conclusions (12) to be correct, it must be concluded that 1*H*-2,3-dihydroimidazo[1,2-*a*]-benzimidazole exhibits a greater tendency to exist in the amine form. Attempts were made to measure the pK_a of 1-benzyl-2,3-dihydroimidazo[1,2-*a*]benzimidazole. Unfortunately, turbidity of the solution occurred at 40% neutralization and no reliable pK_a value could be obtained.

A problem arises in interpreting observed *p*H values for a partially aqueous solvent system from a *p*H meter which has been standarized against aqueous buffers. Bates (17) deals with this problem and suggests two corrections which he combines into one (5).

$\delta = \bar{E}_j - \log m\lambda_H$

δ = combined correction factor expressed in *p*H units

$\bar{E}_j$ = residual liquid junction error

$\log m\lambda_H$ = logarithm of the medium effect for hydrogen ion activity

Bates has tabulated values for δ for various ethanol-water combinations at 25° but does not include a value for 44.25% ethanol which we used. However Donaldson (18) plotted δ against various % ethanol-water mixtures and graphically obtained a value of $\delta = 0.18$ *p*H units for 44.25% ethanol.

In the calculation of the dissociation constants no activity corrections were necessary since the solutions used were sufficiently dilute. Although the pK_a values for I and XVII are not presented as highly accurate ones we feel that they are reliable relative ones since they were determined under similar conditions. The pK_a's showed a similar spread (2.27 pK_a units) for the amine and imine forms as reported by Scheinker *et al.* (12). These values are only valid for 44.25% ethanol.

The tautomeric equilibrium constant was calculated to be 1.87×10^2.

$$K_{taut.} = \frac{K_a \text{ I}}{K_a \text{ XVII}} = \frac{\text{antilog } 6.21}{\text{antilog } 8.48} = 1.87 \times 10^2$$

EXPERIMENTAL

All melting points were determined with the Thomas-Hoover capillary melting point apparatus and are uncorrected.

Infrared spectra were obtained with a Perkin-Elmer Model 521 Recording Spectrophotometer. Ultraviolet spectra were determined on a Cary 14 Recording Spectrophotometer. Nuclear magnetic resonance spectra were determined at 60 MC/sec. on a Varian Associates Nuclear Magnetic Resonance Spectrometer (Model HA-60) for 10% solutions in deuteriochloroform with tetramethylsilane as an internal standard.

pK_a Measurements were made with a Beckman Research *p*H Meter.

A. Syntheses of 1-Alkyl-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]-benzimidazoles. 1-(2-Hydroxyethyl)-2-amino-5-nitrobenzimidazole.

To a suspension of 79.2 g. (0.4 mole) of 2-amino-4-nitro-*N*-(2-hydroxyethyl)aniline (19) in 400 ml. of water was added 42.4 g. (0.4 mole) of cyanogen bromide. The mixture was stirred and warmed on a steam bath until a mild exothermic reaction occurred and then heated for an additional 30 minutes. The solution was neutralized with saturated sodium bicarbonate solution and heated for a few minutes on a steam bath. The solid was then removed and washed with 50% aqueous ethanol. The crude product was recrystallized by suspending 40 g. in 1000 ml. of 50% alcohol and slowly adding 310 ml. of dimethylformamide to the refluxing mixture. The resulting solution was treated with decolorizing carbon, filtered and the filtrate diluted with 590 ml. of water or until reddish-brown needles appeared. The mixture was allowed to stand until no more crystals appeared, yield 77.5%, m.p. 253-255° (6).

Anal. Calcd. for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.20. Found: C, 48.81; H, 4.60; N, 25.23.

1*H*-7-Nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (VI).

A solution of 6.9 g. (0.058 mole) of thionyl chloride in 20 ml. of dry dimethylformamide was added dropwise with stirring to a solution of 11.8 g. (0.053 mole) of 1-(2-hydroxyethyl)-2-amino-5-nitrobenzimidazole in 200 ml. of dry dimethylformamide at 0°. The mixture was stirred for 30 minutes and then slowly allowed to reach room temperature. After standing overnight the dark solution was refluxed for 8 hours, the last two hours in the presence of decolorizing carbon. After filtering, the solvent was removed *in vacuo*. Water was added to the residue and the mixture was neutralized with a saturated sodium bicarbonate solution. The solid was removed, washed with water and recrystallized from ethanol, yield 75%, yellow powder, m.p. 262-263° (6). Thin layer chromatography on silica gel produced only one spot, by elution with 9:1 chloroform-methanol. Hydrochloride, m.p. 280°.

Anal. Calcd. for $C_9H_8N_3O_2$: C, 52.94; H, 3.97; N, 27.43. Found: C, 52.95; H, 4.02; N, 27.53.

1-Ethyl-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (III).

A sodamide solution (0.018 mole) in liquid ammonia (20) was cooled in dry ice-2-propanol and 3.6 g. (0.017 mole) of 1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole was added with stirring. After stirring for 30 minutes, a solution of 5.5 g. (0.051 mole) of ethyl bromide in 25 ml. of dry ether was added dropwise with stirring. The dark blue mixture was stirred for 2 hours and the ammonia then allowed to evaporate. Water was added to the solid residue and the mixture was filtered. The crude product was recrystallized from ethanol, yield 77%, yellow needles, m.p. 171-172° (lit. m.p. 161-163° (3)). A mixed melting point determination with an authentic sample (7) showed no depression.

Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.88; H, 5.21; N, 24.12. Found: C, 57.01; H, 5.34; N, 24.31.

1-Benzhydryl-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (VII).

7-Nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (5 g., 0.0245 mole) was added in small portions to a stirred suspension of 1.03 g. (0.026 mole) of sodamide in 200 ml. of liquid ammonia. From here on, the procedure was the same as that used for preparing the ethyl derivative except that benzhydryl bromide was used. After removing the ammonia, the residue was washed with ether, dried and recrystallized from dimethylformamide-water. Yield 71%, yellow needles, m.p. 217-218°. Thin layer chromatography on silica gel produced only one spot by elution with 9:1 chloroform-methanol, and gave a higher R_f value than the starting material.

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.33; H, 4.89; N, 15.12. Found: C, 71.47; H, 4.91; N, 15.25.

1-Benzyl-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (VIII).

This compound was prepared by the procedure used for the 1-ethyl derivative, using benzyl chloride as the alkylating agent. After evaporating off the ammonia, the residue was stirred with water, the mixture filtered and the solid washed well with ether. The product was recrystallized from DMF-water, yield 72%, yellow platelets, m.p. 174.5-176°. Thin layer chromatography on silica gel gave only one spot on elution with 9:1 chloroform-methanol, with a higher R_f value than the starting material.

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.79; N, 19.03. Found: C, 65.11; H, 4.78; N, 19.17.

1-(2-Phenylethyl)-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (IX).

This product was prepared by the procedure used for the 1-ethyl derivative, except that the 2-phenylethyl bromide was added all at once. After removing the ammonia, water was added to the residue and the mixture was filtered. The gummy residue was triturated with hexane to produce a crystalline solid. Recrystallization from benzene gave bright yellow needles, yield 41%, m.p. 159-160°.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.21; H, 5.23; N, 18.17. Found: C, 66.02; H, 5.33; N, 18.30.

1-(2-Diethylaminoethyl)-1*H*-7-nitro-2,3-dihydroimidazo[1,2-*a*]-benzimidazole (X).

A different method was necessary in this case. 7-Nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole (5 g., 0.0245 mole) was added gradually with stirring to a suspension of sodamide (1 g., 0.027 mole) in 150 ml. of liquid ammonia. The mixture was stirred for 1 hour after completion of the addition. The ammonia was removed in a stream of dry nitrogen and the residue was stirred with 150 ml. of toluene for 30 minutes. To this suspension, still under dry nitrogen, was added 3.2 g. (0.024 mole) of 2-diethylaminoethyl chloride in 50 ml. of dry toluene dropwise and with stirring. After the addition, the contents were stirred at 25° for 1 hour, at 60° for 1.5 hour, and at 90° for 3 hours. The mixture was allowed to stand overnight. Water was added and the mixture filtered. The toluene was removed *in vacuo* leaving a red oil which solidified on standing. The product was recrystallized from benzene-hexane with the aid of decolorizing carbon, yield 47%, yellow crystals, m.p. 120-121°. Thin layer chromatography on silica gel, as carried out previously, showed only one spot.

Anal. Calcd. for $C_{15}H_{21}N_5O_2$: C, 59.38; H, 6.97; N, 23.08. Found: C, 59.49; H, 7.12; N, 23.21.

B. Preparation of 1-Alkyl-1*H*-7-amino-2,3-dihydroimidazo[1,2-*a*]-benzimidazoles. 1-Benzhydryl-7-amino-2,3-dihydroimidazo[1,2-*a*]-benzimidazole (XII).

A modification of Furst and Moore's reduction procedure was employed (9). 1-Benzhydryl-7-nitro-2,3-dihydroimidazo[1,2-*a*]-benzimidazole (1.25 g., 0.0033 mole) was treated with concentrated hydrochloric acid to yield 1.13 g. of the hydrochloride. After drying, the salt was dissolved in 150 ml. of a 1:1 solution of DMF-95% ethanol, a small amount of freshly prepared Raney nickel was added and the suspension gently heated on the steam bath. Hydrazine hydrate (0.53 g., 0.0168 mole) was slowly added. Considerable frothing occurred. The suspension was heated for an additional hour with stirring. An additional small amount of Raney nickel was added to destroy any excess hydrazine. The suspension was filtered and the filtrate evaporated to dryness. The residue was chromatographed on alumina by elution with 99:1 chloroform-methanol to give 0.5 g. of solid which was recrystallized from chloroform-ligroin, yield 34%, light tan needles, m.p. 228-230°.

Anal. Calcd. for $C_{22}H_{20}N_4$: C, 77.61; H, 5.92; N, 16.45. Found: C, 77.42; H, 6.05; N, 16.32.

1-(2-Phenylethyl)-1*H*-7-amino-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XI).

One gram of 1-(2-phenylethyl)-7-nitro-2,3-dihydroimidazo-[1,2-*a*]benzimidazole was dissolved in 100 ml. of ethanol and hydrogenated over Raney nickel at 55 lbs. pressure. After removing the catalyst, the solution was evaporated to dryness. The residue was chromatographed on alumina with 99:1 chloroform-methanol to give a light tan solid which was recrystallized from chloroform-ligroin, yield 80%, light tan needles, m.p. 123-125°.

Anal. Calcd. for $C_{17}H_{18}N_4$: C, 73.35; H, 6.51; N, 20.13. Found: C, 73.17; H, 6.48; N, 20.25.

C. Preparation of 1-Alkyl-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazoles. 1-(2-Hydroxyethyl)-2-aminobenzimidazole.

To a suspension of 35 g. (0.23 mole) of 2-amino-*N*-(2-hydroxyethyl)aniline (19) in 175 ml. of water was added 24.4 g. (6.23 mole) of cyanogen bromide in small portions with stirring. After the moderately exothermic reaction was over, the solution was gently heated (60-70°) for 20 minutes, cooled and neutralized with saturated sodium bicarbonate solution. The solution was concentrated on the steam bath and allowed to stand overnight. The solid product was removed and recrystallized from water with the aid of decolorizing carbon, yield 76%, tan platelets, m.p. 163-165° (6).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.01; H, 6.21; N, 23.70. Found: C, 60.87; H, 6.36; N, 23.60.

1*H*-2,3-Dihydroimidazo[1,2-*a*]benzimidazole (I).

To a cooled solution of 18 g. (0.1 mole) of 1-(2-hydroxyethyl)-2-aminobenzimidazole in 500 ml. of dry dimethylformamide, was added a solution of 8 ml. (0.1 mole) of thionyl chloride in dimethylformamide, dropwise with stirring, at such a rate that the temperature did not exceed 2°. After the addition, stirring was continued for 1 hour at 0° and then the solution was slowly warmed to room temperature. The solution was slowly heated to boiling (1 hour) and then refluxed for 3 hours. The solvent was removed *in vacuo*, the solid dissolved in water and the solution filtered. The filtrate was neutralized with saturated sodium bicarbonate solution and the precipitated product removed. The crude product was recrystallized from 1,4-dioxane, yield 68%, colorless platelets, m.p. 204-206° (6).

1-Benzyl-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XIII).

The method used for preparing 1-benzhydryl-2,3-dihydroimidazo[1,2-*a*]benzimidazole was employed here using benzyl chloride as the alkylating agent. The crude product was recrystallized from benzene-hexane, yield 80%, m.p. 115-116°.

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.07; H, 6.06; N, 16.88. Found: C, 77.14; H, 6.06; N, 16.96.

1-Benzhydryl-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XIV).

This compound was prepared from 1*H*-2,3-dihydroimidazo-[1,2-*a*]benzimidazole and benzhydryl bromide by the procedure used for making 1-benzhydryl-7-nitro-2,3-dihydroimidazo[1,2-*a*]-benzimidazole. After evaporating the ammonia, the residue was washed with ether, then with water. The crude product was recrystallized from benzene-ligroin, yield 67%, m.p. 206.5-207.5°.

Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.22; H, 5.88; N, 12.91. Found: C, 81.12; H, 5.69; N, 13.03.

1-(2-Diethylaminoethyl)-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole Dihydrochloride (XV).

This product was prepared from 1*H*-2,3-dihydroimidazo[1,2-*a*]-benzimidazole and diethylaminoethyl chloride by the procedure used for making 1-(2-diethylaminoethyl)-7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole. After removing the toluene, the residual oil in this case could not be crystallized. The oil was converted to a dihydrochloride in ethanol solution with dry hydrogen chloride and the salt was recrystallized from 2-propanol, yield 85%, m.p. 255-257°.

Anal. Calcd. for $C_{15}H_{24}Cl_2N_4$: C, 54.37; H, 7.30; N, 16.91; Cl, 21.40. Found: C, 54.29; H, 7.24; N, 16.85; Cl, 21.38.

1-Guanyl-1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole Nitrate (XVI).

A solution of 1 g. (0.0063 mole) of 2,3-dihydroimidazo[1,2-*a*]-benzimidazole and 0.625 g. (0.0031 mole) of 1-guanyl-3,5-dimethylpyrazole (10) in 15 ml. of ethanol was refluxed for 4 hours. The resulting solid was removed and recrystallized from water, yield 31%, m.p. 270-272° (dec.).

Anal. Calcd. for $C_{10}H_{12}N_6O_3$: C, 45.44; H, 4.57; N, 31.80. Found: C, 45.36; H, 4.66; N, 31.89.

D. Preparation of 9-Alkyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazoles. 3-Benzyl-1-(2-hydroxyethyl)-2-iminobenzimidazole (XVII).

Using Simonov's method (5) a mixture of 4.5 g. (0.025 mole) of 2-amino-1-(2-hydroxyethyl)benzimidazole and 36 g. (0.21 mole) of benzyl bromide in 150 ml. of methylethylketone was refluxed for 6 hours. The precipitate, which formed on standing, was removed and washed with acetone. The crude hydrobromide was dissolved in 50 ml. of boiling water and the solution was added to a boiling saturated sodium bicarbonate solution. After refluxing for 3 hours, the solution was extracted with three 50 ml. portions of chloroform. After drying (magnesium sulfate) the chloroform was removed leaving a colorless, fluffy solid (m.p. 108-112°) which was converted to its hydrochloride in ethanol solution with dry hydrogen chloride. The hydrochloride was recrystallized from ethanol, yield 68%, m.p. 263-264°.

Anal. Calcd. for $C_{16}H_{18}ClN_3O$: C, 63.25; H, 5.97; N, 13.83. Found: C, 63.42; H, 6.15; N, 13.79.

9-Benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole (XVIII).

3-Benzyl-1-(2-hydroxyethyl)-2-iminobenzimidazole hydrochloride (1 g., 0.003 mole) was refluxed with 1.18 g. (0.01 mole) of thionyl chloride in 15 ml. of dry chloroform. After 3 hours, the

salt had completely dissolved. The solvent was distilled leaving a reddish brown solid. A solution of potassium hydroxide (0.56 g.) in 15 ml. of methanol was added and after refluxing for 15 minutes the solid was completely dissolved. The solution was refluxed for 4 hours, cooled and the precipitated potassium chloride removed. The methanol was evaporated and the residue taken up in ether and dried (magnesium sulfate). A solution of picric acid in ethanol was then added to precipitate the product as its picrate. It was recrystallized from 95% alcohol, m.p. 204-206°.

Anal. Calcd. for $C_{22}H_{18}N_6O_7$: C, 55.22; H, 3.79; N, 17.56. Found: C, 55.39; H, 3.61; N, 17.75.

The picrate was chromatographed on alumina by elution with chloroform to yield the free amine as a yellow oil, yield 22%, b.p. 192-194° (0.15 mm.).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.07; H, 6.06; N, 16.85. Found: C, 76.93; H, 6.07; N, 16.94.

E. Reaction of 1*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazole with Benzyl Chloride under Neutral (Protic and Aprotic) Conditions.

Neutral Protic Conditions.

1*H*-2,3-Dihydroimidazo[1,2-*a*]benzimidazole (2 g., 0.0126 mole) and 3.19 g. (0.0254 mole) of benzyl chloride were dissolved in 20 ml. of 95% ethyl alcohol and the solution was refluxed for 4 hours. After standing overnight, the precipitate was removed, washed with ether and dried, yield 80% of 9-benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazolium chloride, m.p. 262-264°. The benzimidazolium chloride was dissolved in water, the solution neutralized with sodium carbonate and extracted with ether. After drying (sodium sulfate), the ether was removed and the residual oil distilled, b.p. 192-194° (0.15 mm.), yield 80% based on the hydrochloride. The boiling point and infrared spectrum were identical with those of the authentic sample from the previous experiment.

Neutral Aprotic Conditions.

1*H*-2,3-Dihydroimidazo[1,2-*a*]benzimidazole (2 g., 0.0126 mole) and 3.19 g. (0.0254 mole) of benzyl chloride were dissolved in 20 ml. of dimethylformamide and the solution was refluxed for 4 hours. After standing overnight, the precipitated 9-benzyl-9*H*-2,3-dihydroimidazo[1,2-*a*]benzimidazolium chloride was removed and washed with ether, yield 85%, m.p. 262-264°. The infrared spectrum of the salt was identical with that of the salt obtained under neutral protic conditions.

pK_a Measurements.

Samples of the two amines were dissolved in absolute ethanol. Twenty-five ml. of the ethanol solution containing 2.5×10^{-4} equivalents of amine, were pipetted into a titration cell surrounded by a glass jacket through which water from a constant temperature bath kept at 25° ± 0.1° was circulated. An equal volume of ion free water was added to the cell followed by 2.67 ml. of 0.1125 *N* hydrochloric acid and 2.67 ml. of absolute alcohol, producing 53.35 ml. of solution containing 2.5×10^{-4} equivalents of protonated amine and 0.5×10^{-4} equivalents of excess hydrochloric acid. The cell was covered with Parafilm and purged with nitrogen. Openings were set in the film for insertion of glass and saturated calomel electrodes and a 5 ml. microburet calibrated in 0.01 ml. units. The buret was protected with a soda-lime absorption tube and the solution in the titration cell was kept stirred with a magnetic stirrer.

Standardized potassium hydroxide, made up in 44.25% ethanol was added in small amounts and the *p*H was read from a Beckman Research *p*H Meter after each addition. The meter was calibrated in 0.1 *p*H units allowing estimation to 0.01 *p*H units. It was standardized with aqueous buffers supplied by Beckman Instruments, Inc. Values of corrected *p*H, obtained between 30% and 70% neutralization were used in the calculation of pK_a.

$$pK_a = pH_{corr.} + \log \frac{B^+H}{B}$$

where pK_a = acid dissociation constant of the protonated amine in 44.25% ethanol at 25°.

$pH_{corr.}$ = observed *p*H reading minus 0.18 *p*H units.

B^+H = stoichiometric concentration.

B = stoichiometric concentration of free amine.

The data are tabulated in Tables I and II.

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