Synthesis of Some 1-Imidoyl-2-(3-indolyl)-1,2-dihydroquinolines and -isoquinolines *via* Reissert-Type Condensations

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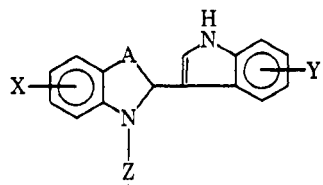
The reaction of *N*-imidoylcycloimmonium salts with indoles was used for the preparation of some 1-imidoyl-2-(3-indolyl)-1,2-dihydroquinolines (1) and -isoquinolines (2). Catalytic hydrogenation of these compounds gave the 1,2,3,4-tetrahydro derivatives. Various members of these series of compounds were alkylated at the indole nitrogen. The scope and some limitations of the reaction are presented.

We have been interested in 1-imidoyl-2-(3-indolyl)- and (2-indolyl)indolines for their biological effects[1] as well as a novel rearrangement[2] exhibited by some members of the series. In seeking to structurally extend this class of compounds, we developed a versatile reaction for the preparation of 1-imidoyl-2-(3-indolyl)-1,2-dihydroquinolines (1) and 2-imidoyl-1-(3-indolyl)-1,2-dihydroisoquinolines (2); their tetrahydro derivatives, 4 and 7; and their indolic N-alkylated derivatives, 3, 5, 6, and 8 (Scheme I).

von Dobeneck and Goltzsche,[3] and later Bergman,[4] applied nucleophilic attack of indole on *N*-acylcycloimmonium salts to form adducts 9[3,4] and 10.[3] We envisioned the possibility of extending the nucleophilic attack to N-imidoylated quinoline salts, either actual (12) or incipient (11),

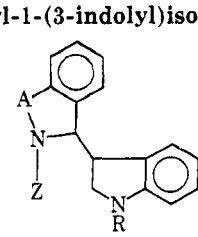
Table I
1-Imidoyl-2-(3-indolyl)quinolines



Compd	A	X	Y	Z	Yield,[a] %	Mp, °C	Formula	Analysis[b]
1a	CH=CH	H	H	$-CH=NCHMe_2$	15	187.5–189 dec	$C_{21}H_{21}N_3 \cdot HCl$	C, H, N
1b	CH=CH	H	5-OMe	$-CH=N(c\text{-}C_6H_{11})$	7	174–177	$C_{25}H_{27}N_3O \cdot HCl$	C, H, N
1c	CH=CH	5,6-Benzo	H	5,5-Dimethyl-1-pyrrolin-2-yl	14	222–223	$C_{27}H_{25}N_3 \cdot HCl$	C, H, N, Cl
1d	CH=CH	6-OMe	5-OMe	5,5-Dimethyl-1-pyrrolin-2-yl	37	200–203 dec	$C_{25}H_{27}N_3O_2 \cdot HCl$	C, H, N, Cl
1e	CH=CH	3,4-Benzo	H	1-Pyrrolinyl-2-yl	5	119.5–128.5 dec	$C_{25}H_{21}N_3 \cdot \frac{1}{2}C_6H_{14}O$	C, H, N
1f	CH=CH	H	H	1-Pyrrolinyl-2-yl	9	219.5–220.5	$C_{21}H_{19}N_3$	C, H, N
3a	CH=CH	H	N-Me	5-Methyl-1-pyrrolinyl-2-yl	10	175–177	$C_{23}H_{23}N_3$	C, H, N
4a	CH_2CH_2	6-OMe	5-OMe	5,5-Dimethyl-1-pyrrolin-2-yl	65	226.5–229.5	$C_{25}H_{29}N_3O_2 \cdot HCl$	C, H, N, Cl
4b	CH_2CH_2	H	H	1-Pyrrolinyl-2-yl	67	228–229	$C_{21}H_{21}N_3 \cdot HCl$	C, H, N, Cl
5a	CH_2CH_2	H	N-Me	$-CH=NCHMe_2$	52	108–111.5	$C_{22}H_{25}N_3$	C, H, N

[a] For the tetrahydro and *N*-alkyl analogs, the yield refers to conversion from the dihydro compounds. [b] The analytical data were acceptable if within 0.4% for C and 0.3% for other elements.

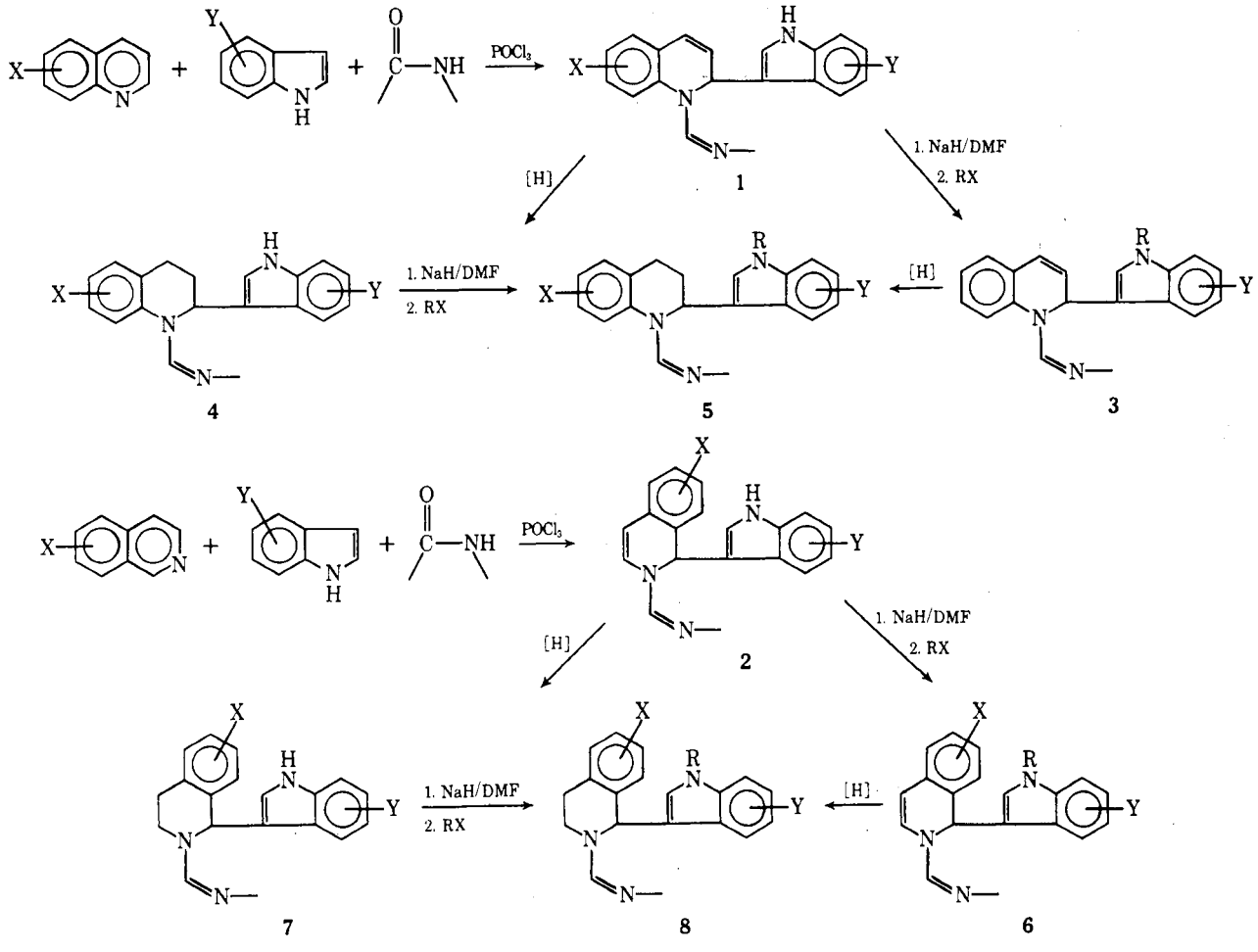
Table II
2-Imidoyl-1-(3-indolyl)isoquinolines

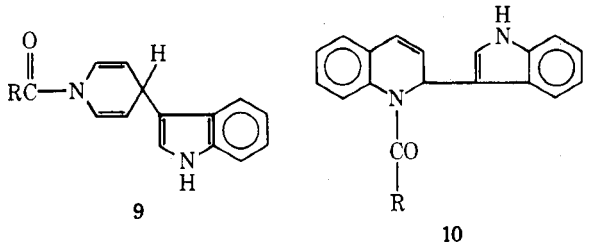


Compd	A	R	Z	Yield,[a] %	Mp, °C	Formula	Analysis[b]
2a	CH=CH	H	$-CH=NCHMe_2$	17	144–145.5	$C_{21}H_{21}N_3$	C, H, N
2b	CH=CH	H	5,5-Dimethylpyrrolin-2-yl	65	191.5–192	$C_{23}H_{23}N_3$	C, H, N
2c	CH=CH	H	1-Pyrrolin-2-yl	13	160–162.5	$C_{21}H_{19}N_3$	C, H, N
6a	CH=CH	Me	1-Pyrrolin-2-yl	65	186–189	$C_{22}H_{21}N_3$	C, H, N
7a	CH_2CH_2	H	5,5-Dimethylpyrrolin-2-yl	60	281–283.5 dec	$C_{23}H_{25}N_3 \cdot HCl$	C, H, N, Cl
8a	CH_2CH_2	Me	1-Pyrrolin-2-yl	69	167–168.5	$C_{22}H_{23}N_3$	C, H, N

[a] For the tetrahydro and *N*-alkyl analogs, the yield refers to conversion from the dihydro compounds. [b] The analytical data were acceptable if within 0.4% for C and 0.3% for other elements.

Scheme I





on the basis of the mechanistic sequence given in Scheme II.

Results

Table I lists some 1-imidolyl-2-(3-indolyl)quinolines prepared by this reaction. Table II lists some 2-imidoyl-1-(3-indolyl)isoquinolines. By varying the components we investigated the scope and limitations of the reaction. Table III summarizes variations of the reactions which did not produce desired products.

Spectra of the reaction products agreed with assignment of structures 1 and 2 analogous to spectral correlations for the imidoyl indolylindolines.[2] Although uv and ir spectra were consistent, NMR and mass spectra were more definitive.

NMR spectra of pyrrolinyl dihydroquinolines 16 and isoquinolines 17 exhibited the H-8 proton peaks at a chemical shift more downfield (~7.8–8.2 Hz, depending on substituents and solvent) than the other aromatic protons. This is attributable to the effect of magnetic anisotropy of the imino group upon H-8 in 16[2] and the indolyl π system on H-8 in 17. Mass spectra of these compounds gave a *m/e* 245

Scheme II

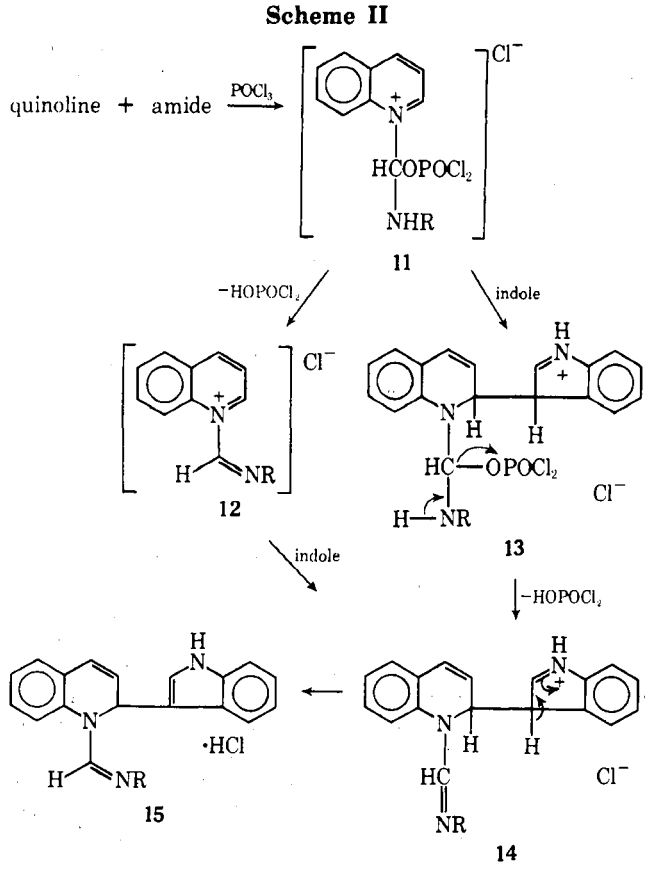
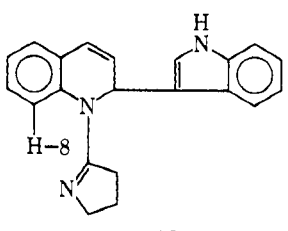


Table III
Reaction Component Variations[a]

Reaction	Base	Carboxamide	Nucleophile
1	Pyridine	$HC(=O)NHC(CH_3)_3$	Indole
2	Pyridine	$HC(=O)NHCH(CH_3)_2$	Skatole
3	Quinoline	5-Methyl-2-pyrrolidinone	2-Methylindole
4	Quinoline	$HC(=O)NHCH_2CH_3$	Skatole
5	Quinoline	Caprolactam	Indole
6	Quinoline	$HC(=O)NHCH_2N(CH_3)_2$	Indole
7	Quinoline	2-Pyrrolidinone	Pyrrole
8	Quinoline	2-Pyrrolidinone	KCN
9	Quinoline	$HC(=O)NHCH(CH_3)_2$	7-Azaindole
10	Quinoline	5-Methyl-2-pyrrolidinone	Imidazole[1,2-*a*]pyridine
11	Quinoline	$HC(=O)NHCH(CH_3)_2$	Dimethylaniline
12	Quinoline	$HC(=O)NHCH(CH_3)_2$	Diethyl malonate
13	Quinoline	Valerolactam	Indole
14	Isoquinoline	Valerolactam	Skatole
15	Isoquinoline	$HC(=O)NHCH_2CH_3$	Skatole
16	4-Phenylpyrimidine	$HC(=O)NHCH_2CH_3$	Indole
17	7-Azaindole	$HC(=O)NHCH(CH_3)_2$	7-Azaindole
18	1-Methylimidazole	$C_6H_5C(=O)Cl$	Indole
19	Quinaldine	2-Pyrrolidinone	Indole
20	Acridine	2-Pyrrolidinone	Indole
21	Lepidine	2-Pyrrolidinone	Indole

[a] These variations did not result in formation of an amidine product.



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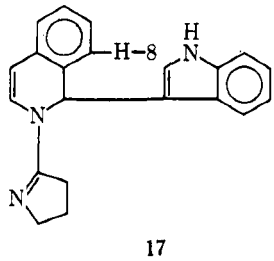
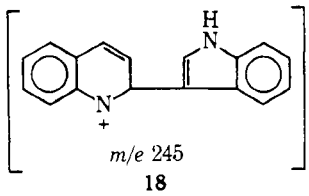


17

fragment in high abundances. This would correspond to fragment structure **18** or **19**. This assignment has been cor-



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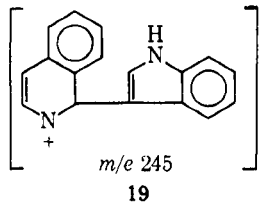


19

roborated by the predictable *m/e* change of the abundant fragment when substituents were attached to the heterocyclic ring systems.

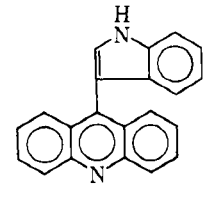
Discussion

The two main considerations which determined experimental success of the reaction were the stability of the intermediate and the activity of the nucleophile under reaction conditions. The N-imidoylated cycloimmonium salt intermediate, e.g., **11** (or **12**), seemed less stable than a corresponding *N*-acyl cycloimmonium salt. The shorter intermediate lifetime which resulted was demonstrated as follows: if the introduction of indole was delayed until after equilibration of the quinoline, carboxamide, and $POCl_3$, no amidine product was obtained. In other words, one factor responsible for success of the reaction was the ability of the base to stabilize the cycloimmonium salt intermediate. The added stabilization of the benzo ring, when quinoline or isoquinoline functioned as the base, also was critical to the success of the reaction since the reaction failed with pyridine as the base.

The second major factor to be taken into account was the potency of the nucleophile under reaction conditions. The extent of basic character that a nucleophile possessed inversely affected nucleophilic strength in this acidic reaction milieu owing to ready protonation. The negative results outlined in Table III would indicate that the requisite nucleophilicity fell within a rather narrow range.

In addition to the electronic considerations, steric hindrance is important in determining nucleophilic potency. Owing to the apparent close steric tolerances for reaction success,[5] we feel that **13** is more likely the reaction intermediate (see Scheme II).

The product **20** which resulted from reaction 20 in Table III demonstrates the similarity between the *N*-imidoylacridinium ion and the *N*-acylacridinium ion, because **20** has



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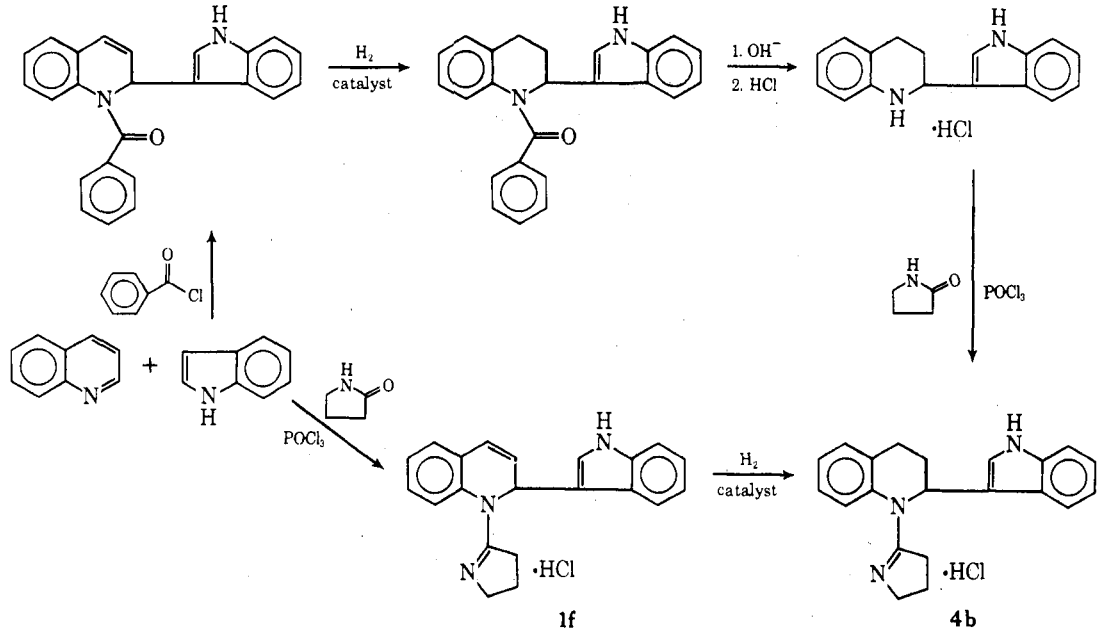
been reported[6] previously as arising from indole attack on the *N*-acylacridinium ion followed by oxidative elimination. The importance of the *N*-imidoylacridinium ion was confirmed by the fact that no reaction took place when acridine was treated with indole and $POCl_3$ without a carboxamide.

Reduction and Alkylation Products. Some synthetic modifications of the dihydro compounds were made. The 1-imidoyl-2-(3-indolyl)-1,2,3,4-tetrahydroquinolines **4** and 2-imidoyl-1-(3-indolyl)-1,2,3,4-tetrahydroisoquinolines **7** were conveniently prepared by catalytic hydrogenation of the corresponding dihydro analogs. Spectra of the tetrahydro compounds were consistent with assignment of structure. Again the salient spectral features were a downfield

Scheme III



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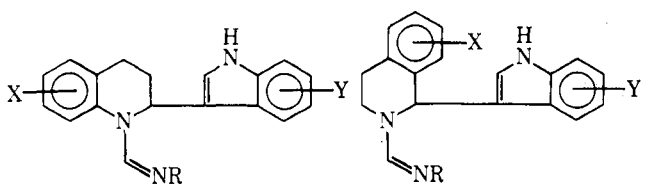

4 7

shift of the H-8 proton in NMR spectra of pyrrolinyl derivatives and the high abundance of fragment *m/e* 247 in mass spectra. This fragment corresponded to the tetrahydro analog of **18** or **19**, strengthening that structural assignment. A correlation scheme confirmed structural assignments for both series (Scheme III).

The most direct synthesis of *N*-alkylindole derivatives of imidoylquinolines and isoquinolines would involve the use of an *N*-alkylindole as the starting material. Unfortunately, this process was not general with *N*-alkylindoles and the desired product formed only in isolated instances. We found, as an alternative, that the indolic nitrogen could be selectively alkylated under mild conditions starting with an imidoylquinoline or isoquinoline from either the di- or tetrahydro series. The critical feature in this process was the irreversible formation of the anion under mild conditions, a prerequisite which the NaH–DMF system fulfilled quite well. Other base systems were not satisfactory. Potassium *tert*-butoxide in *tert*-butyl alcohol, for example, led to a mixture of alkylated and nonalkylated products owing to the reversibility of the butoxide–indole anion system.

Structure assignment of the *N*-alkylindole derivatives was straightforward. In the NMR spectra, the characteristic indolic N–H proton (> δ 8.5 Hz) disappeared and was replaced by an *N*-alkyl pattern displayed at about 3.5–4.0 Hz. The fragmentation pattern of the mass spectrum did not change from the N–H series. The major fragmentation was the loss of the imidoyl group which gave rise to a characteristic base peak for each series.

Experimental Section

NMR spectra were recorded on either a Varian A-60 or XL-100 spectrometer with tetramethylsilane as an internal standard. Ir spectra were taken on either a Beckman Model IR 8 or IR 18A. Mass spectral data were obtained from a CEC 21-104 mass spectrometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. Satisfactory analytical and spectra data were obtained on all of the compounds. A single experimental procedure is provided for a representative compound from each class.

The Dihydroquinoline and Dihydroisoquinoline Series. 3,4-Dihydro-4-(5,5-dimethyl-1-pyrrolin-2-yl)-3-indol-3-yl-benzo[*f*]quinoline Hydrochloride (1c). A solution of $POCl_3$ (4.60 g, 0.03 mol) in 10 ml of benzene was added dropwise to a stirred solution of 5,6-benzoquinoline (10.62 g, 0.06 mol), indole (3.51 g, 0.03 mol), 5,5-dimethyl-2-pyrrolidinone (3.39 g, 0.03 mol), and benzene (20 ml) over a period of 15 min. The reaction mixture was mildly exothermic and a tar precipitated. The reaction mixture was stirred for approximately 24 hr, at which time the benzene supernatant was decanted and discarded. The reaction tar was washed with H_2O and then stirred in Me_2CO. The tar went into solution, and a light yellow solid precipitated which was isolated by filtration. The solid was slurried in distilled H_2O and made basic with concentrated NH_4OH. This basic mixture was extracted with chloroform. The chloroform extracts were combined and concentrated to an off-white solid which was washed with hot hexane and recrystallized from isopropyl ether (mp 130–133.5°). Absolute ethanol was added to the solid, and the mixture was stirred until most of the solid was in solution. This mixture was filtered, and the stirred filtrate was treated with an excess of ethanolic HCl. The solution was triturated and chilled. Several crops of white solid were isolated to give 1.8 g of **1c** (14% yield), mp 222–223°. Anal. Calcd for $C_{27}H_{25}N_3 \cdot HCl$: C, 75.77; H, 6.12; N, 9.82; Cl, 8.29. Found: C, 75.59; H, 6.14; N, 9.63; Cl, 8.10.

1,2-Dihydro-1-(3-indolyl)-2-(5,5-dimethyl-1-pyrrolin-2-yl)isoquinoline (2b). The compound was prepared with a procedure similar to the one used for **1c** with the exception that the base was isolated. Recrystallization from benzene gave 3.5 g of white solid (65% yield), mp 191.5–192°. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.96; H, 6.68; N, 12.38.

Tetrahydroquinoline and Tetrahydroisoquinoline Series. 1-(5,5-Dimethyl-1-pyrrolin-2-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(5-methoxy-3-indolyl)quinoline Hydrochloride (4a). 1-(5,5-Dimethyl-1-pyrrolin-2-yl)-1,2-dihydro-6-methoxy-2-(5-methoxy-3-indolyl)quinoline hydrochloride (**1d**, 1.54 g, 0.0035 mol, prepared in the same manner as **1c**) was dissolved in 200 ml of absolute ethanol and 1 ml of ethanolic HCl with slight warming. This solution was poured into a Parr bottle containing 0.2 g of PtO_2 and hydrogenated on a Parr apparatus beginning at 50 psi. The theoretical amount of hydrogen was absorbed in 3 min; and after 15 min, no additional hydrogen uptake was observed. After the catalyst was removed by filtration, the solution was evaporated in vacuo to a pink foam. This foam was recrystallized in approximately 100 ml of acetone to give 1.0 g (65% yield) of a light pink solid, mp 226.5–229.5°. Anal. Calcd for $C_{25}H_{29}N_3O_2 \cdot HCl$: C,

68.24; H, 6.87; N, 9.85; Cl, 8.06. Found: 68.28; H, 6.77; N, 9.42; Cl, 8.02.

1,2,3,4-Tetrahydro-1-(3-indolyl)-2-(5,5-dimethyl-1-pyrrolin-2-yl)isoquinoline Hydrochloride (7a). The compound was prepared from **2b** with a procedure similar to the one used for **4a**. Recrystallization from isopropyl alcohol gave a 60% yield of a pink solid, mp 281.5–283.5°. Anal. Calcd for $C_{23}H_{25}N_3 \cdot HCl$: C, 72.71; H, 6.90; N, 11.06; Cl, 9.33. Found: C, 72.60; H, 6.80; N, 10.84; Cl, 9.48.

The 1-Alkylindole Derivatives. Method A. 1,2-Dihydro-1-(1-methyl-3-indolyl)-2-(1-pyrrolin-2-yl)isoquinoline (6a). A solution of 1,2-dihydro-1-(3-indolyl)-2-(1-pyrrolin-2-yl)isoquinoline (**2c**, 4.6 g, 0.015 mol) in 110 ml of DMF (dried over molecular sieves) was first treated under a nitrogen atmosphere, with sodium hydride (57% mineral oil dispersion, 0.70 g, 0.015 mol), then stirred for 3 hr, and finally treated with a solution of iodomethane (2.1 g, 0.015 mol) in 15 ml of DMF (dried over molecular sieves). After being stirred for an additional 24 hr, the reaction mixture was filtered. The clear yellow filtrate was poured into approximately 300 ml of stirred ice water, and the resulting precipitate was filtered, dried (vacuum oven at 65°), and recrystallized from EtOAc to give 3.2 g (65% yield) of an off-white solid, mp 186–189°. Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.83. Found: C, 80.89; H, 6.21; N, 12.71.

Method B. 1,2-Dihydro-2-(1-methyl-3-indolyl)-1-(5-methyl-1-pyrrolin-2-yl)quinoline (3a). The compound was prepared from 1-methylindole, 5-methyl-2-pyrrolidinone, and quinoline according to the procedure given for the synthesis of **1c**. Compound **3a**, purified as the free base, had mp 175–177°. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.75; H, 6.64; N, 12.48.

Acknowledgment. The authors wish to thank P. S. Schrecker and C. I. Kennedy for their contributions to structural analysis and R. E. Yeager for technical assistance. A special thanks is given to C. Combs by the authors for his invaluable aid and helpful suggestions in structural determination.

Registry No.—**1a**, 53159-51-6; **1b**, 53019-08-2; **1c**, 53019-07-1; **1d**, 53018-88-5; **1e**, 53019-04-8; **1f**, 53089-20-6; **2a**, 53018-80-7; **2b**, 53018-83-0; **2c**, 53018-81-8; **3a**, 53019-00-4; **4a**, 53159-52-7; **4b**, 53018-85-2; **5a**, 53881-35-9; **6a**, 53018-99-8; **7a**, 53089-14-8; **8a**, 53019-02-6; quinoline, 91-22-5; isoquinoline, 119-65-3; 5,6-benzoquinoline, 85-02-9; 6-methoxyquinoline, 5263-87-6; 3,4-benzoquinoline, 229-87-8; indole, 120-72-9; 5-methoxyindole, 1006-94-6; *N*-methylindole, 603-76-9; *N*-isopropylformamide, 16741-46-1; *N*-cyclohexylformamide, 766-93-8; 5,5-dimethyl-2-pyrrolidinone, 5165-28-6; 2-pyrrolidinone, 616-45-5; 5-methyl-2-pyrrolidinone, 108-27-0.

References and Notes

(1) Y. H. Wu, W. G. Lobeck, Jr., R. P. Ryan, and A. W. Gomoll, *J. Med. Chem.*, **15**, 529 (1972).
(2) R. P. Ryan, W. G. Lobeck, Jr., C. M. Combs, and Y. H. Wu, *Tetrahedron*, **12**, 2325 (1971).
(3) H. von Dobeneck and W. Goltzsche, *Chem. Ber.*, **95**, 1484 (1962).
(4) J. Bergman, *J. Heterocycl. Chem.*, **7**, 1071 (1970).
(5) This is a feature noted previously for imidoylation of the indolylindolines.[2] Increased ring size or a substituent in the 7 position of the indoline ring prevented imidoylation of the 2-(3-indolyl)indolines.
(6) A. K. Sheinkman, S. G. Potashnikova, and S. N. Baranov, *Khim. Geterotsikl. Soedin*, 1292 (1970); *Chem. Abstr.*, **74**, 125377n (1971); A. K. Sheinkman, A. N. Kost, S. G. Potashnikova, A. O. Ginzburg, and S. N. Baranov, *Khim. Geterotsikl. Soedin*, 648 (1971); *Chem. Abstr.*, **76**, 72342e (1972).
(7) Prepared by the procedures in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, pp 357, 652.

Rearrangement of 1,2-Dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines to 9-(3-Indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines[1]

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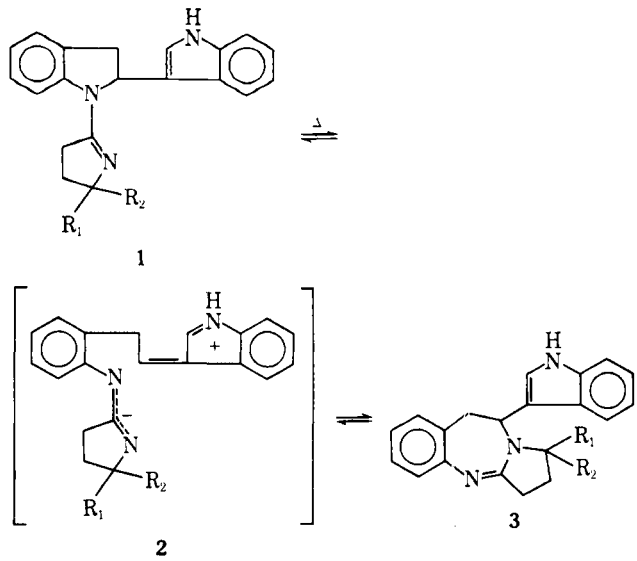
A series of 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines (**4**) undergoes a novel rearrangement to 9-(3-indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines (**10**). The structures of the rearranged products were assigned spectroscopically and further confirmed by a structure correlation scheme. A mechanism for the rearrangement is proposed and discussed in terms of kinetic and structural data.

In the course of work with 1-imidoyl-2-(2- and 3-indolyl)indolines,[2a] we reported[2b] the interconversion of 2-(3-indolyl)-1-[2-(1-pyrrolinyl)]indoles, **1**, to 2,3,5,6-tetrahydro-5-(3-indolyl)-1*H*-pyrrolo-[2,1-*b*][1,3]benzodiazepines **3**. The postulated mechanism for this interconversion (Scheme I) involves a reversible ring opening to give the intermediate **2**, which undergoes ring closure after geometric isomerization. Because of the novelty of this rearrangement and a desire to determine its scope, we extended our study to the reactions of 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines **4** and -isoquinolines **5** and the corresponding tetrahydro derivatives **6** and **7**, the preparations of which are described in the Experimental Section.

Scheme I



Results

Present in all of the compounds investigated was the structural fragment **8**; yet we found that only the 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines **4** underwent rearrangement. Moreover, the structures of the rearranged products were not the expected benzodiazocines **9** from analogy to the indolylindoline rearrangement, but were the stable pyrroloquinazolines, **10**.