Multinuclear Ferrocenes. II. Syntheses of Substituted Biferrocenyls[1-3]

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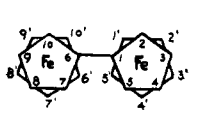
It has been found possible to effect coupling of substituted haloferrocenes by means of treatment with activated copper bronze to yield substituted biferrocenyls. In addition to coupling products, significant amounts of ferrocene derivatives are obtained which appear to result from formal replacement of halogen by hydrogen in the starting material.

Study of systems composed of directly bonded ferrocene nuclei has thus far encompassed only methods of preparation of the simplest member of this group, biferrocenyl (**1**).[4] It is apparent that progress in this field would be enhanced with the availability of reliable methods for obtaining biferrocenyl derivatives with known disposition of substituents. Since a large number of isomers are possible *via* direct substitution of biferrocenyl, the uncertainties surrounding preparation of a desired biferrocenyl derivative by means of a direct substitution process are obvious. In an effort to circumvent these difficulties, we have explored the feasibility of obtaining substituted biferrocenyls by means of direct coupling of substituted haloferrocenes. This strategy proved to be successful, and we wish to report representative examples of such syntheses.

Before doing so, however, it is necessary, because of the complexity of isomeric possibilities, to establish a nomenclature convention which will allow unambiguous designation of individual isomeric biferrocenyl derivatives. This purpose is accomplished in a simple way by merely defining a numbering system for the biferrocenyl nucleus in which unprimed numbers are assigned to the two directly bonded cyclopentadienyl rings with the lowest numbers (1 and 6) reserved for the ring-assembly atoms. Carbon atoms of each of the two nondirectly bonded rings are assigned primed numbers which correspond to the unprimed numbers assigned directly "above" when the molecule is oriented in the conformation shown in **1**. In this way, position isomers are readily and unequivocally designed. Thus, 2,6′-dimethylbiferrocenyl represents **2** and not **3** (1′,2-dimethylbiferrocenyl).



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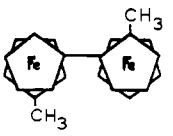

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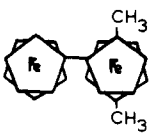

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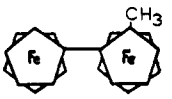
This numbering system also may be used eventually to designate absolute configuration of enantiomers by specifying the sequence (clockwise or counterclockwise) in which the numbers are assigned. If, for example, a clockwise sequence is used then absolute configurations of the two enantiomers, **4** and **5**, are incorporated into the systematic names, 2-methylbiferrocenyl and 10-methylbiferrocenyl, respectively.



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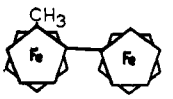

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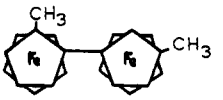
Use of the specified numbering sequence possesses another advantage, perhaps even more important. The convention eliminates the difficulty of distinguishing between isomers in which the location of one substituent relative to another would be otherwise ambiguous. Thus, **6** and **7** may be unequivocally designated as 3,10-dimethylbiferrocenyl and 4,10-dimethylbiferrocenyl, respectively.



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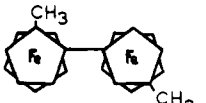

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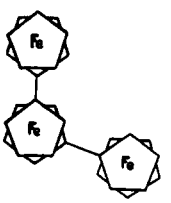
Finally, while systems composed of more than two directly bonded ferrocene nuclei have not been reported as yet, appearance of such molecules may be expected and the presently proposed nomenclature convention may be used as a basis for naming these molecules and their derivatives. For example, the three isomeric terferrocenyls, **8**, **9**, and **10**, may be conveniently named as substituted biferrocenyls, 1′-ferrocenylbiferrocenyl, 2-ferrocenylbiferrocenyl, and 3-ferrocenylbiferrocenyl, respectively.



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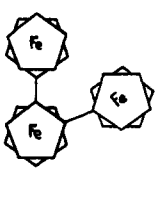

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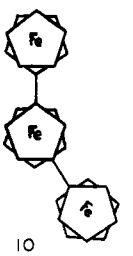

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The key compound used in the present investigation for the representative syntheses described later was 1-bromo-1′-acetylferrocene (**11**) which was obtained *via* acetylation of bromoferrocene (**12**). Compound **11** was prepared originally by Nesmeyanov, Sazonova, and Drozd[5] who, as did Hall and Richards[6] after them, assigned the heteroannular structure because of the absence of absorption near 9 and 10 μ in the infrared spectrum determined from this acetylation product. While the 9–10 rule has proved to be a reliable empirical

(1) Previous paper in this series: S. I. Goldberg, D. W. Mayo, and J. A. Alford, *J. Org. Chem.*, **28**, 1708 (1963).

(2) We are pleased to acknowledge generous support of this work by the National Science Foundation, Grant G24083. We also wish to express our sincere gratitude to that agency for an institutional grant which made possible the purchase of the n.m.r. spectrometer used in this work.

(3) Taken in part from the M.S. thesis of R. L. Matteson, University of South Carolina, 1963.

(4) See ref. 1 and work cited therein.

(5) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **137**, 102 (1961).

(6) D. W. Hall and J. H. Richards, *J. Org. Chem.*, **28**, 1549 (1963).

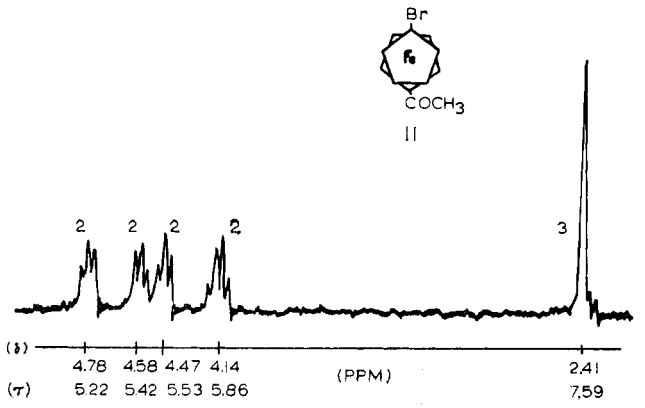

Figure 1.

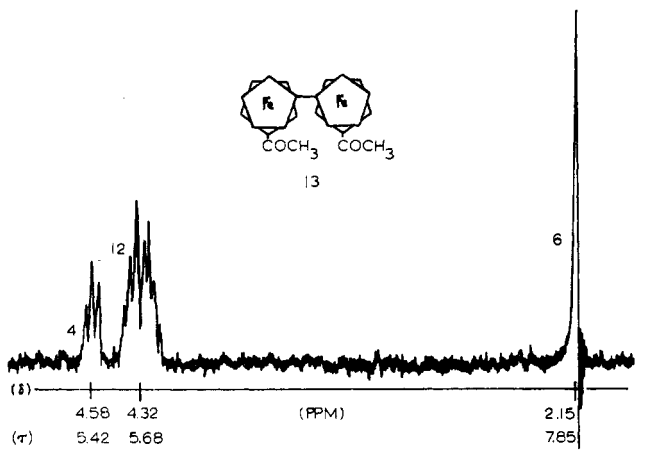

Figure 2.

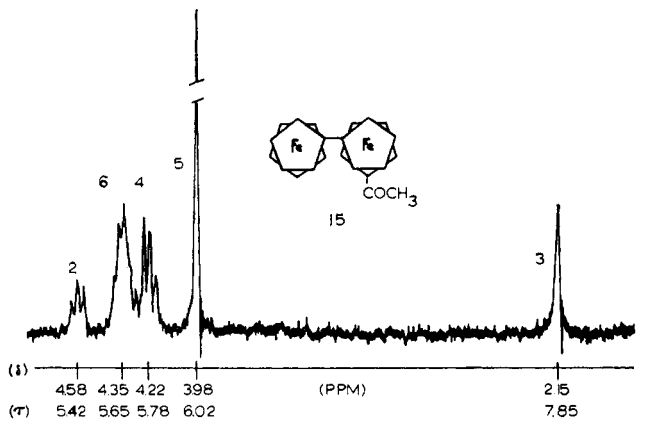

Figure 3.

generalization,[7] it was highly desirable for our purpose to obtain independent evidence for the heteroannular disposition of bromo and acetyl groups. Confirmation was readily obtained by examination of the n.m.r. spectrum (Fig. 1) determined from the acetylation product (**11**) of bromoferrocene. The absence of a signal near τ 6 provided the desired confirmation since this is the region in which a signal due to the equivalent protons of an unsubstituted cyclopentadienyl ring in a ferrocene compound appears. The signals present in the spectrum (Fig. 1) may be assigned by means of comparison with the individual n.m.r. spectra obtained from acetylferrocene and bromoferrocene. Thus, the two-proton triplet (J = 2 c.p.s.) at 5.22 τ is due to the two equivalent protons (2′ and 5′) which flank the acetyl group in **11** [two-proton triplet (J = 2 c.p.s.) at 5.25 τ from acetylferrocene]. The pair of two-proton triplets (J = 2 c.p.s.) at 5.42 and 5.53 τ are assigned to each pair of equivalent protons at 3′ and 4′, and 2 and 5, respectively, since the β-protons in acetylferrocene appear at lower field (5.53 τ) than do the α-protons of bromoferrocene (5.78 τ). The remaining two-proton triplet (J = 2 c.p.s.) at 5.86 τ arises from the equivalent protons at 3 and 4 (5.83 τ for β-protons in bromoferrocene). Finally, the three-proton singlet at 7.59 τ of the acetyl methyl group in **11** is found at 7.63 τ in acetylferrocene.

Treatment of **11** with activated copper bronze[8] gave rise to one product (31% yield) which was shown to be 1′,6′-diacetylbiferrocenyl (**13**) by means of its n.m.r. spectrum (Fig. 2). The four-proton triplet (J = 2 c.p.s.) at 5.42 τ is assigned to the four equivalent protons which flank the two equivalent acetyl groups [seen as the six-proton singlet at 7.85 τ]. The remaining metallocene protons give rise to the complex twelve-proton signal centered at 5.68 τ.

The reaction also produced acetylferrocene (**14**) in 39% yield. This result is not surprising in light of the fact that similar treatment of iodoferrocene leads to ferrocene as well as biferrocenyl.[4]

Formal replacement of halogen by hydrogen as well as coupling of haloferrocenes appears to be a consistent feature of this Ullmann-like process. Thus, treatment of a mixture of bromoferrocene (**12**) and 1-bromo-1′-acetylferrocene (**11**) gives rise to the three coupling products, 1′,6′-diacetylbiferrocenyl (**13**), 1′-acetylbiferrocenyl (**15**), and biferrocenyl (**1**), as well as the debromo compounds, ferrocene and acetylferrocene. Assignment of structure to **15** was readily made on the basis of the n.m.r. spectrum (Fig. 3) determined from the purified material. The two equivalent protons adjacent the acetyl group (seen as a three-proton singlet at 7.85 τ) give rise to the two-proton triplet (J = 2 c.p.s.) at 5.42 τ, and the four equivalent protons flanking the ring assembly atoms appear as a four-proton triplet (J = 2 c.p.s.) at 5.78 τ. The presence of one unsubstituted cyclopentadienyl ring is seen by the five-proton singlet at 6.02 τ, while the remaining protons appear as a broad complex signal centered at 5.65 τ.

Production of the coupling products and formation of the debromo compounds is suggestive of a free-radical process. While this explanation is attractive and does account for the observed results, no direct evidence has been obtained which supports generation and participation of ferrocenyl free radicals. Indeed, formation of the coupling products may occur by a different process and the debromo compounds may be accounted for in terms of electrophilic (proton) replacement of bromine. This latter mechanism represents a real possibility since the copper catalysts used are activated with acid[8] and it is likely that some acid is retained in spite of numerous acetone washings (see Fig. 4).

(7) K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957); M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958); A. N. Nesmeyanov, L. A. Kazitsyna, B. V. Lokshin, and V. D. Vilchesskaya, *Dokl. Akad. Nauk SSSR*, **125**, 1037 (1959).

(8) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans Green and Co., Inc., New York, N. Y., 1948, p. 188.

Our studies have not as yet proceeded to the point where we are able to distinguish among the mechanistic possibilities.

Experimental

Temperature measurements are uncorrected. Ultraviolet spectra were determined with a Carey, Model 14, recording spectrophotometer, infrared spectra with a Perkin-Elmer, Model 21, recording spectrophotometer, and n.m.r. spectra with a Varian, A-60, spectrometer at 60 Mc., employing a room temperature probe with chloroform solvent containing approximately 5% (v./v.) tetramethylsilane as interval standard. Combustion analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

All column chromatograms were performed on Merck, acid-washed alumina, using purified elution solvents. Columns were wrapped with aluminum foil to protect the developed chromatograms from light.

Ferroceneboronic Acid and 1,1′-Ferrocenediboronic Acid.[9]—Ferrocene (30.0 g., 0.160 mole), dissolved in a mixture of 330 ml. of pure dry tetrahydrofuran and 50 ml. of pure dry ether, was cooled to −40° with an external Dry Ice–acetone bath and kept under an atmosphere of purified nitrogen while *n*-butyllithium (286 ml. of 1.5 *N*) in hexane solution[10] was added at such a rate so as not to allow the temperature of the reaction mixture to rise above −30°. After all of the *n*-butyllithium had been added, the reaction mixture was stirred during 3 hr. at −30° and then allowed to warm to room temperature and remain, with stirring, overnight. The entire solution was then transferred carefully to an addition funnel through which it was added to a cold (−50°) solution of tri-*n*-butyl borate (72.5 g., 0.310 mole in 50 ml. of pure dry ether) at a rate which did not allow a rise in temperature. The reaction mixture was stirred during 3 hr. at −50° after the addition was completed, then allowed to warm to room temperature, and stirred continuously at room temperature overnight. Addition of 150 ml. of 10% aqueous sodium hydroxide solution was followed by another 3-hr. period during which the mixture was stirred at room temperature. The basic aqueous phase was separated, and the organic phase extracted with portions of 10% aqueous sodium hydroxide until the extracts appeared colorless. The combined basic extracts were then carefully acidified with 10% sulfuric acid at 0°, resulting in precipitation of the crude boronic acids which were collected, thoroughly washed with water, and air-dried. Separation of ferroceneboronic acid from the mixture was achieved by submitting the crude product to continuous extraction with ether in a Soxhlet apparatus and obtaining the monoacid by evaporation of the ether extract, 2.0 g. (11% yield). This material possessed an ill-defined melting point (135–150°) which is in agreement with previous observations.[9] The extraction residue was presumed to be crude ferrocenediboronic acid, 2.5 g. (11% yield), m.p. 177° dec., lit.[9] m.p. 180° dec.

Bromoferrocene (12).[9]—Ferroceneboronic acid (2.0 g., 0.009 mole) was heated in the presence of an aqueous solution of copper(II) bromide (1.00 g., 0.009 mole in 400 ml. of water) until the presence of a yellow oil could no longer be detected in the steam distillate. The distillate was phase separated, and the aqueous phase exhaustively extracted with ether. The combined organic material was dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 1.79 g. (74% yield) of bromoferrocene as an orange oil which crystallized upon cooling, m.p. 27–28°, lit.[9] m.p. 31–32°.

Acetylation of Bromoferrocene. 1-Bromo-1′-Acetylferrocene (11).[5]—Bromoferrocene (0.400 g., 0.0016 mole) was mixed with 2 ml. of polyphosphoric acid [2:1 (w./w.), 85% phosphoric acid–phosphorus(V) oxide] and 10 ml. of acetic anhydride and heated with agitation during 10 min. on a steam bath. After the reaction mixture was allowed to cool to room temperature, it was carefully poured into a cold aqueous saturated solution of sodium carbonate and allowed to stand until the odor of acetic acid could no longer be detected. Exhaustive ether extraction of the aqueous mixture was followed by combination drying and evaporation of the ether extracts, giving rise to a semisolid residue which was chromatographed on alumina. Elution with hexane provided some unchanged bromoferrocene, while elution with benzene gave rise to monoacetylated bromoferrocene, 0.280 g. (56% yield), m.p. 57–58° (lit.[5] m.p. 62–63°), which was shown to possess a heteroannular disposition of substituents by an n.m.r. spectrum (13% w./w.) determined from the material.

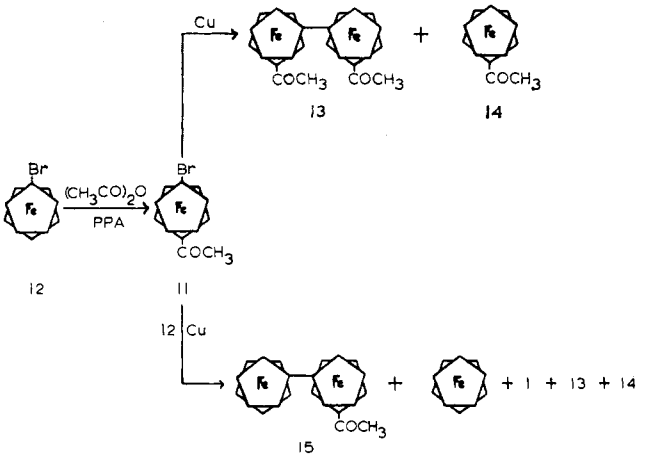

Figure 4.

Anal. Calcd. for $C_{12}H_{11}BrFeO$: C, 46.95; H, 3.61; Br, 26.03. Found: C, 47.16; H, 3.66; Br, 26.06.

Treatment of 1-Bromo-1′-Acetylferrocene (11) with Activated Copper Bronze. Preparation of 1′,6′-Diacetylbiferrocenyl (13).—1-Bromo-1′-acetylferrocene (255 mg., 0.831 mmole) was intimately mixed with 14 g. of activated copper bronze[8] and heated in an atmosphere of purified nitrogen at 75–85° during 18 hr. After the reaction mixture was allowed to cool to room temperature, it was repeatedly extracted with portions of chloroform until the chloroform extracts appeared colorless. The combined chloroform extracts were filtered and evaporated to a solid residue which was chromatographed on alumina. Elution with benzene yielded acetylferrocene (73 mg., 39% yield) which was identified by means of direct comparison with authentic material. Continued elution with 10:1 (v./v.) ether–methanol yielded 1′,6′-diacetylbiferrocenyl (57 mg., 31% yield), m.p. 187–188°; ultraviolet (ethanol), λ_{max} 227 mμ (log ε 4.4), 284 (4.2). For discussion of n.m.r. spectrum (Fig. 2, 5% w./w.), see text.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.47; H, 4.88. Found: C, 63.16; H, 4.78.

Treatment of a Mixture of 1-Bromo-1′-Acetylferrocene (11) and Bromoferrocene (12) with Acetylated Copper Bronze.—1-Bromo-1′-acetylferrocene (11, 2.027 g., 0.00662 mole) and bromoferrocene (12, 3.083 g., 0.0122 mole) were intimately mixed with 14 g. of activated copper bronze[8] and heated in an atmosphere of purified nitrogen at 90–92° during 28 hr. The reaction was exhaustively extracted with chloroform at room temperature, and the combined and filtered chloroform extracts yielded a solid residue upon evaporation. Chromatography of the residue on alumina yielded the following compounds in order of their elution.

Elution with hexane provided ferrocene (0.965 g., 42.4% yield)[11] which was identified by means of direct comparison with authentic material.

Continued elution with 4:1 (v./v.) hexane–benzene gave rise to biferrocenyl (1, 0.361 g., 29.6% yield)[12] whose identity was also established by direct comparison with authentic material.

Further elution with 3:2 (v./v.) hexane–benzene caused development of two reddish orange bands. Collection and evaporation of the faster moving band yielded acetylferrocene (14, 0.930 g., 61.6% yield[12]) which was again identified by comparison with authentic acetylferrocene.

Collection of the slower moving, reddish orange band yielded 1′-acetylbiferrocenyl (15, 0.444 g., 16.3% yield), b.p. 137–137.8°;

(9) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **126**, 1004 (1959).

(10) Foote Mineral Co., New Johnsonville, Tenn.

(11) Calculation based upon assumption that bromoferrocene served as the exclusive source of this product.

(12) Calculation based upon assumption that 1-bromo-1′-acetylferrocene served as the exclusive source of this product.

ultraviolet (ethanol), λ_{max} 217 mμ (log ε 4.66), λ_{sh} 260 mμ (log ε 4.10), 292 (4.00). For discussion of n.m.r. spectrum (Fig. 3, 3% w./w.), see text.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89. Found: C, 64.23; H, 4.90.

Final elution with 4:1 (v./v.) benzene–ether provided an eluent which, upon evaporation, yielded 1′,6′-diacetylbiferrocenyl (**13**, 0.172 g., 11.4% yield) which was found to be identical with the 1′,6′-diacetylferrocenyl obtained *via* coupling of 1-bromo-1′-acetylferrocene described previously.

Synthesis of 1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline and Perhydro-1*H*-pyrazino[1,2-*a*]quinoline

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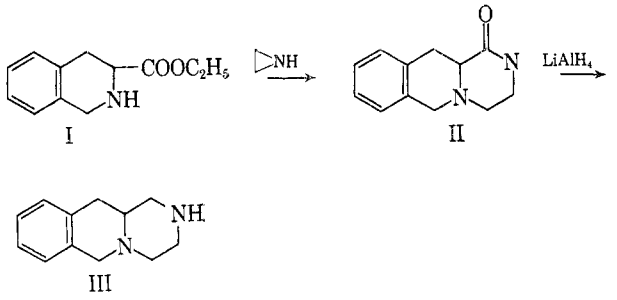
The reactions of ethyleneimine with ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate and ethyl decahydroquinoline-2-carboxylate are reported. Two diastereoisomeric forms of perhydro-1*H*-pyrazino[1,2-*a*]quinoline have been obtained.

In 1960 Freed and Day reported the reaction of ethyleneimine with ethyl 2-piperidinecarboxylate and with ethyl 2-pyrrolidinecarboxylate to form lactams which were reduced with lithium aluminum hydride to the corresponding fused ring piperazines containing a bridgehead nitrogen.[1] Thus a two-step route is available for the synthesis of 1,4-diazabicyclo[4.4.0]decanes and 1,4-diazabicyclo[4.3.0]nonanes. In the present paper we report the reactions of ethyleneimine with ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate and ethyl decahydroquinoline-2-carboxylate.

Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (I) reacted readily with ethyleneimine to form 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (II). The latter was then reduced with lithium aluminum hydride to give 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (III).

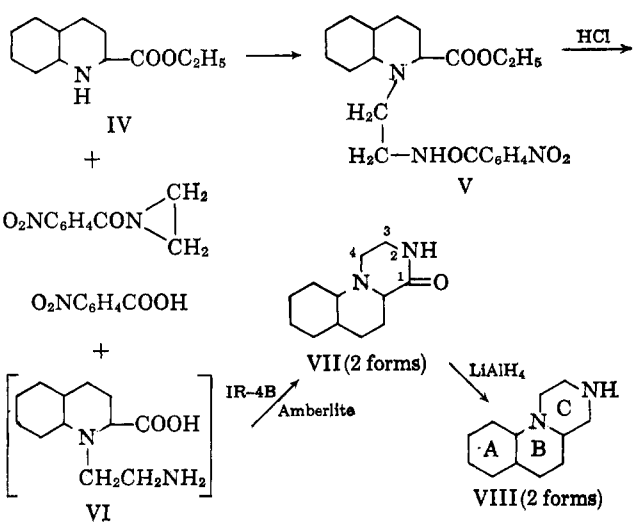


I II III

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline, when heated in benzene solution with one equivalent of ethyl iodide or benzyl chloride, respectively, gave quantitative yields of 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline hydroiodide or the corresponding hydrochloride. These products appear to result from elimination reactions involving tertiary amines or quaternary ammonium compounds, but they were not studied further.

Ethyl decahydroquinoline-2-carboxylate (IV) failed to form a lactam when treated with ethyleneimine and most of the starting ester was recovered. N-*p*-Nitrobenzoylethyleneimine has been used for the aminoalkylation of primary and secondary amines[2] and it was found in the present work that it condensed readily with ethyl decahydroquinoline-2-carboxylate. The resulting *p*-nitrobenzamidoethyl derivative (V) was difficult to purify, due, in part, to contamination with 2-*p*-nitrophenyloxazoline which results from a rearrangement of N-*p*-nitrobenzoylethyleneimine.[2] Hydrolysis of the *p*-nitrobenzamidoethyl derivative with hydrochloric acid gave a quantitative yield of *p*-nitrobenzoic acid, but efforts to isolate ethyl 1-(2-*p*-nitrobenzamidoethyl) decahydroquinoline-2-carboxylate (VI) by adjusting the pH of the filtrate from the *p*-nitrobenzoic acid were unsuccessful.

An attempt was made to neutralize the filtrate from the *p*-nitrobenzoic acid by passing it through a column of an ion-exchange resin (Amberlite IR-4B). It had been anticipated that compound VI could be isolated from the eluent from the column. Actually this intermediate cyclized spontaneously and separated as lustrous white plates on the resin and in the eluent. The yield of lactam VII was found to be a function of the pH of the eluent, the best yield being obtained at pH 6.0–6.2. The cyclization apparently was resin catalyzed, since a similar adjustment of the pH with sodium bicarbonate was ineffective in causing ring closure. Two compounds were obtained from the crude lactam, by fractional crystallization, melting at 150° and 200°, respectively. Each of the two compounds analyzed correctly for the desired lactam. Their infrared spectra were practically identical.



(1) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2105, 2108 (1960).

(2) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).