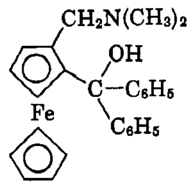
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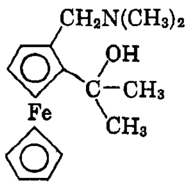
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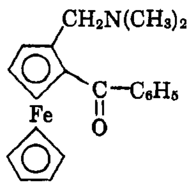
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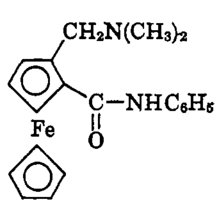
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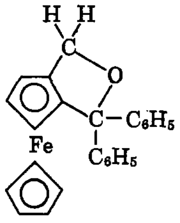
V

Results and Discussion

The n.m.r. results are summarized in Table I, chemical shifts being reported in cycles per second downfield from the internal TMS standard. In Table I protons 1 and 2 refer to the methylene group protons and ν_1 and ν_2, respectively, are their calculated[11] chemical shifts. The quantity $J_{1,2}$ is the measured coupling constant; $\delta_{1,2}$ is the difference in the 1,2-proton chemical shifts. For each compound and in every solvent protons 1 and 2 were magnetically nonequivalent, while the N-methyl protons appeared equivalent. In addition, for compound II the C-methyl protons were nonequivalent.

TABLE I[a]

N.M.R. DATA FOR 36° AND 60 MC.

Compd.	Solvent	ν_1	ν_2	$\delta_{1,2}$	$J_{1,2}$
I	$CDCl_3$	159.2	218.0	58.8	13.4
	CCl_4	156.0	224.5	68.5	13.2
	CH_3CN	158.0	222.1	64.1	13.5
	CH_3COCH_3	161.9	228.5	66.6	13.5
	C_6H_6	147.6	222.6	75.0	13.2
	$(CH_3)_2CHCOOCH_3$	160.1	228.0	67.9	13.1
	C_6H_5CN	158.0	224.3	66.3	13.5
	RNH_2[b]	158.4	222.0	63.6	13.5
II[c]	$CDCl_3$	156.8	242.3	85.5	12.6
	CCl_4	151.3	241.0	89.7	12.3
	C_6H_6	145.9	244.2	98.3	12.7
III	$CDCl_3$	207.0	258.4	51.4	13.4
	CCl_4	203.2	262.3	59.1	13.1
	C_6H_6	214.4	284.6	57.2	13.4
IV	$CDCl_3$	177.1	247.9	70.8	12.8
	CH_3COCH_3	171.1	260.0	88.9	12.6
	CH_3CN	181.6	253.1	71.5	12.5
	C_6H_6	150.5	231.9	81.4	12.9
	C_6H_5CN	161.5	245.9	74.4	12.5
	$C_6H_5CH_3$	152.9	233.7	80.8	12.8
V	$CDCl_3$	265.8	286.0	20.2	11.0
	CH_3COCH_3	261.0	287.8	26.8	10.9
	C_6H_6	262.8	277.9	15.1	10.3

[a] See the text for the meaning of the symbols. The data are all in cycles per second, TMS being used as an internal reference. Coupling constants and chemical shifts are expressed to the nearest 0.1 c.p.s. Each coupling constant value is the arithmetical mean of all data taken. Single measurements for each constant varied from the reported value by as much as a few tenths of a cycle per second. [b] $(CH_3)_2CHCH_2C(CH_3)_2NH_2$. [c] Relative chemical shifts for the nonequivalent C-methyl group protons are 21.0, 17.5, and 16.0 ± 0.5 c.p.s. in $CDCl_3$, CCl_4, and C_6H_6, respectively.

The chemical shift differences observed for the methylene group protons are large and constitute a relatively novel instance of magnetic nonequivalence in a system of low symmetry. From previous results[7,8] on benzene analogs of I–V, magnetic nonequivalence of the methylene group protons was expected. Nevertheless, the compounds reported are a significant addition to the number of 1,2-disubstituted ferrocenes previously reported[12,13] which are capable of exhibiting nonequivalent methylene- or *gem*-dimethyl-group protons. Since not all reported asymmetric 1,2-disubstituted ferrocenes show magnetically nonequivalent protons, the present results could be important in establishing the origin of this type of nonequivalence. A firm basis for assigning the conformational preferences of compounds I–V is not yet available. Consequently, a reliable decision as to the probable cause of the observed nonequivalence cannot be made.

Experimental Section

The compounds were prepared and characterized as part of another investigation.[14] Compounds I–IV are 2 derivatives of N,N-dimethylaminomethylferrocene. Compound V is the ferrocene analog of 1,1-diphenylphthalan. Spectra were obtained on a Varian A-60 n.m.r. spectrometer equipped with a Varian V-6057 variable temperature accessory, TMS being used as an internal standard. Solvents were reagent grade or better. Concentrations were 0.2 *M* and the probe temperature was 36 ± 1°. A minimum of two spectra were run for each solution.

Acknowledgment.—This investigation was supported by the U. S. Public Health Service, Grant GM-07653, Division of General Medical Sciences. The authors wish to thank their associates for helpful comments.

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Small Charged Rings. VIII. Isolation and Stereochemistry of Acyl Aziridinium Salt Intermediates[1,2]

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The early postulate of aziridinium salt intermediates to explain certain rearrangements and conversions of

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[1] For preceding article in this series, see N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **30**, 821 (1965).

[2] This investigation was supported by a research grant (USPHS-RG5829, afterward designated GM-05829) from the National Institutes of Health, U. S. Public Health Service, to whom we are pleased to acknowledge our thanks.

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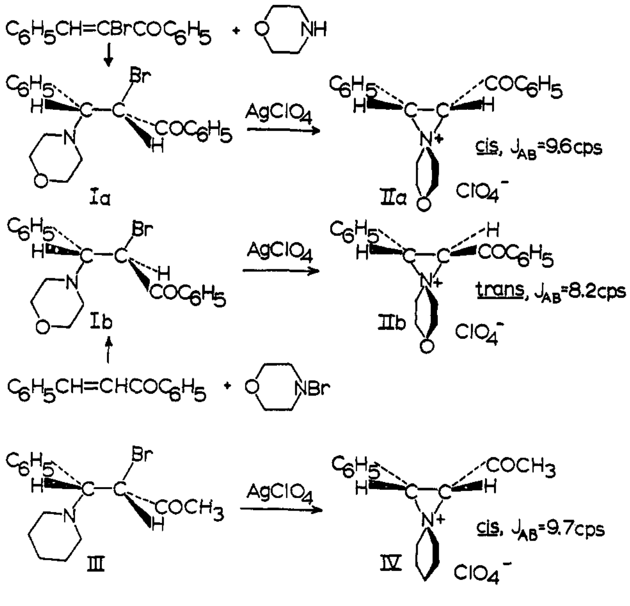
α-bromo-β-(tertiary amino) ketones[4,5] and the subsequent rationalization of the stereochemical course of these reactions on the basis of probable configurations of the intermediates[6-9] make the isolation and structure determination of representative aziridinium salts of critical importance.[10] Specifically, it was desirable to obtain the aziridinium intermediate IIa, which had been suggested to explain the reactions of *dl-threo*-α-bromo-β-morpholinobenzylacetophenone ("form A") (Ia),[4,15-20] and the isomeric aziridinium salt IIb, which bears a similar relation to *dl-erythro*-α-bromo-β-morpholinobenzylacetophenone ("form B") (Ib).[8,20]



dl-threo-α-Bromo-β-morpholinobenzylacetophenone (Ia) was prepared by the addition of morpholine to α-bromobenzalacetophenone.[4,16-19] The desired aziridinium intermediate was isolated as the perchlorate (IIa) by treatment of Ia in methylene chloride at low temperature with silver perchlorate in acetone,[1,21] with some analogy to the isolation of aziridinium picrylsulfonates by treatment of β-haloethylamines with sodium picrylsulfonate.[22,23] The infrared spectrum was consistent with the formulation in that it indicated, in part, the absence of $^+N{-}H$ and C=C and the presence of aryl C=O near a positive nitrogen. The separate n.m.r. spectra of the perchlorate salt were invariant in trifluoroacetic acid, nitromethane, and acetonitrile to at least 30 min. after addition of the solvent to the sample. The AB doublet signals for the methine hydrogens were exhibited best in acetonitrile solvent, at τ 4.86 (C_6H_5CH) and 4.77 (C_6H_5COCH), with a coupling constant of 9.6 ± 0.2 c.p.s.

The isomer of Ia, *dl-erythro*-α-bromo-β-morpholinobenzylacetophenone (Ib), was prepared by the method of Southwick and Walsh,[20] the addition of N-bromomorpholine to chalcone. Treatment of this compound in methylene chloride with silver perchlorate in benzene afforded the aziridinium perchlorate IIb, isomeric with the compound described above. Attempts at recrystallization under the mildest conditions lowered the melting point and broadened the melting range. The infrared spectrum supported the formulation as an aziridinium salt by the same criteria described for its isomer (IIa). Compound IIb remained intact within the time it took to run the n.m.r. spectra in trifluoroacetic acid and acetonitrile, in which the AB doublet signals for the methine hydrogens were found at τ 4.75 and 4.42, and 4.90 and 4.61, respectively, with a coupling constant of 8.2 ± 0.2 c.p.s. In dimethyl sulfoxide, a chemical change took place with this isomer as with IIa, as evidenced by the change in the n.m.r. spectra within 2 min. after contact of solute with solvent. Both solid aziridinium perchlorates were stable over a 2-year period when stored at 5° in a vacuum desiccator.

It is possible to assign the structures, *dl-cis*-1-benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]octane (IIa) and *dl-trans*-1-benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]-octane perchlorate (IIb), to the isomeric aziridinium salts on the basis of the comparison of the coupling constants for the methine hydrogens in the n.m.r. spectra, $J = 9.6$ *vs.* 8.2 c.p.s., respectively. The accumulated examples indicate that the coupling constants for *cis* vicinal hydrogens are greater than those for *trans* hydrogens in closely related cyclopropanes,[24-26] ethylene oxides,[27-29] and ethylenimines,[30,31] and the values here reported for the aziridinium perchlorates IIa and IIb show reasonable agreement with the general correlation of Wiberg and Nist[24] for the *cis* and *trans* coupling constants from available data, whereas the reverse assignment would not be consistent.

The infrared carbonyl stretching frequency is higher for the *cis* isomer IIa, 1707 cm.$^{-1}$, than for the *trans* isomer IIb, 1690 cm.$^{-1}$, a relation which is parallel to that observed for isomeric pairs of aroylarylaziri-

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dines assigned the *cis–trans* relationship by Cromwell and his co-workers.[11,32] The ultraviolet spectra for IIa [$\lambda_{max}^{CH_3CN}$ 256 mμ (ε 14,000), 297 (sh); λ_{min} 225 mμ (ε 3300)] and IIb [$\lambda_{max}^{CH_3CN}$ 258 mμ (ε 12,000), ~300 (sh); λ_{min} 228 mμ (ε 4100)] appear to indicate lower energy electronic excitations than those for benzylacetophenone [$\lambda_{max}^{CH_3OH}$ 243 mμ (ε 13,300), 280 (100),[33,34]] and comparability in wave lengths, although not in extinction coefficients, of the maxima to those of the pair: *cis*-2-benzoyl-1-cyclohexyl-3-phenylaziridine, $\lambda_{max}^{CH_3OH}$ 247 mμ (ε 12,000), and *trans*-2-benzoyl-1-cyclohexyl-3-phenylaziridine, $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 14,600).[33]

Our isolation of the aziridinium salts IIa and IIb and the determination of their *cis–trans* configurations by independent means support the postulate of the involvement of these aziridinium intermediates in the myriad reactions of the α-bromo-β-morpholinobenzylacetophenones Ia and Ib and are in full accord with earlier stereochemical assignments of intermediates and products.[6–9] We were also able to isolate an aziridinium intermediate from another "form A" [6–9] α-bromo-β-(tertiary amino) ketone. The product of the addition of piperidine to α-bromobenzalacetone,[5,35] *dl-threo*-α-bromo-β-piperidinobenzylacetone (III), was convertible to *dl-cis*-1-acetyl-2-phenyl-3-azoniaspiro[2.5]octane perchlorate (IV) by silver perchlorate in acetone at −40°. The AB doublet signals for the methine hydrogens in the n.m.r. spectra in trifluoroacetic acid and acetonitrile were found at τ 5.26 (C_6H_5CH) and 5.62 (CH_3COCH), and 5.20 and 5.50, respectively, with a coupling constant, $J = 9.7 \pm 0.3$ c.p.s., in the same range as for the *cis* isomer (IIa) of the pair described above. The corresponding aziridinium fluoborate (IV, BF_4^-) was obtained by treating III with silver fluoborate in acetone. The *dl-cis*-1-acetyl-2-phenyl-3-azoniaspiro-[2.5]octane salts were stable for at least 2 years when kept refrigerated under vacuum.

Experimental Section[37]

dl-cis-**1-Benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]octane Perchlorate (IIa).**—To a solution of 6.0 g. (16 mmoles) of *dl-threo*-α-bromo-β-morpholinobenzylacetophenone (form A) (Ia)[4,6,16–19,37] in 240 ml. of methylene chloride maintained at −40° was added 3.32 g. (16 mmoles) of silver perchlorate in 100 ml. of anhydrous acetone. The silver bromide was removed by filtration, and the filtrate was treated with absolute ether to yield an off-white precipitate. Recrystallization from methylene chloride gave 5.0 g. (79%) of colorless elongated prisms: m.p. 150°; ν_{max}^{Nujol} 1707 (s), 1596 (m), 1505 (w), 1283 (m), 1234 (m), 1221 (m), 1100 (s, broad), 966 (m), 950 (m), 874 (m), 790 (m),743 (m), 712 (m), 697 (m), 617 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.62; H, 5.19; N, 3.79.

dl-trans-**1-Benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]octane Perchlorate (IIb).**—*dl-erythro*-α-Bromo-β-morpholinobenzylacetophenone (form B) (Ib) was prepared by the method of Southwick and Walsh[20]: m.p. 137–139°, $\nu_{max}^{CHCl_3}$ 860 and 885 cm.$^{-1}$, a doublet distinguishing it from the *threo*, form A; n.m.r. signals ($CDCl_3$) at τ 1.8–2.7 (phenyl), 4.42 (α-CH), 4.96 (β-CH), an AB system with $J = 11$ c.p.s., 6.75 (CH_2OCH_2), and 7.55 (CH_2NCH_2). To a solution of 1.0 g. (2.67 mmoles) of this form B in 20 ml. of anhydrous methylene chloride chilled in Dry Ice was added a solution of 0.553 g. (2.67 mmoles) of anhydrous silver perchlorate in benzene. Silver bromide formed instantly, mixed with colorless aziridinium perchlorate. Within 5 min., the addition and reaction were complete, and the suspension was filtered immediately. The solid was washed rapidly with two portions of 10 ml. of benzene and rinsed with anhydrous ether. The aziridinium perchlorate was separated from silver bromide by dissolving in 50 ml. of anhydrous methylene chloride and filtering. The filtrate was concentrated under vacuum without heating. The colorless needles which formed were collected by rapid filtration, m.p. 146–148°, yield 0.5 g. (50%). A second crop with lower melting point but essentially identical infrared spectrum was obtained by adding ether to the filtrate: 0.4 g. (38%); ν_{max}^{Nujol} 1690 (s), 1602 (m), 1500 (w), 1281 (m), 1234 (m), 1100 (s, broad), 955 (m), 862 (m), 768 (m), 739 (m), 705 (m), 620 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.75; H, 5.20; N, 3.61.

dl-cis-**1-Acetyl-2-phenyl-3-azoniaspiro[2.5]octane Perchlorate (IV).**—To a solution of 2.0 g. (6.4 mmoles) of *dl-threo*-α-bromo-β-piperidinobenzylacetone (form A) (III)[5,35] in 200 ml. of anhydrous acetone maintained at −40° was added 1.34 g. (6.4 mmoles) of silver perchlorate in 100 ml. of anhydrous acetone. After filtration of the silver bromide, the filtrate was evaporated to dryness under vacuum and the remaining colorless residue was washed well with absolute ether. Recrystallization from anhydrous acetone yielded 1.05 g. (61%) of colorless crystals, m.p. 135–135.5°, ν_{max}^{Nujol} 1730 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{15}H_{20}ClNO_5$: C, 54.64; H, 6.10; N, 4.25. Found: C, 54.69; H, 6.25; N, 4.06.

The fluoroborate (IV, BF_4^-) was made in anhydrous acetone from III and silver fluoborate. Crystallization was induced by addition of ether to the filtered and concentrated acetone solution, yielding 84% of colorless crystals, m.p. 129–130°, ν_{max}^{Nujol} 1728 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{15}H_{20}BF_4NO$: C, 56.80; H, 6.36; N, 4.42. Found: C, 56.55; H, 6.60; N, 4.60.

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(37) We are grateful to Professor P. L. Southwick, Carnegie Institute of Technology, for identifying our synthesized material independently as form A on the basis of infrared spectrum (a single band present at *ca.* 875 cm.$^{-1}$ ($CHCl_3$) distinguishes form A from form B), crystal habit, and melting point (in order of decreasing usefulness).

The Acylation of Benzamidoximes

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The classical approach to the 1,2,4-oxadiazole ring is through the reaction of amidoximes with acid chlorides and anhydrides.[1,2] The intermediate in this reaction is generally accepted to be the O-acylamidoxime, although this assignment has been based solely on infrared and chemical properties.[1–3] In order to elucidate further the nature of the intermediate acylamidoxime, the reaction of benzamidoxime and benzoyl chloride has been studied.

The synthesis of O-benzoylbenzamidoxime 1 has now been accomplished in an unequivocal manner by the reaction of O-benzoylbenzhydroxamoyl chloride[4]

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