14210-73-2; III (R = $C_{15}H_{31}$), 14320-27-5; III (R = $C_{15}H_{31}$) hydrochloride, 14210-74-3; IV (R = $C_{15}H_{31}$), 14210-75-4; VI (R = Ph), 14210-76-5; VI (R = Ph) hydrochloride, 14210-77-6; VI (R = p-$O_2NC_6H_4$), 14210-78-7; VI (R = $C_{15}H_{31}$), 14320-31-1; VI (R = CH_3), 14213-49-1; VI (R = CH_3) picrate, 14213-50-4; VIII (R = Ph), 5223-10-9; VIII (R = Ph) hydrochloride, 14210-83-4; VIII (R = p-$O_2NC_6H_4$) hydrochloride, 14320-28-6; VIII (R = $C_{15}H_{31}$), 14210-84-5; VIII (R = $C_{15}H_{31}$) hydrochloride, 14210-85-6; VIII (R = CH_3), 14210-86-7.

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Bromination of the 3,6-Endoxo-Δ^4-Tetrahydrophthalic Anhydride System. Stereochemistry and Mechanism of the Reaction

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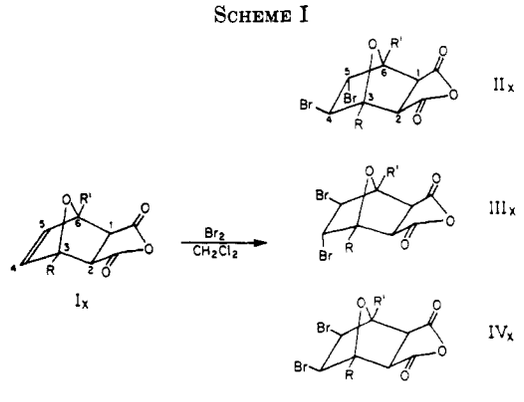
The bromination reactions of two different methyl derivatives of the 3,6-endoxo-Δ^4-tetrahydrophthalic anhydride have been studied. On the basis of the stereochemical course of the reaction, the effects of methyl substitution upon it are discussed. The validity of a mechanism proposed for this reaction in an earlier work is questioned.

Some years ago, Berson and Swidler studied the bromination reaction of *exo-cis*-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (Ia)[2] in various solvents. In that elegant work, the stereochemistry of bromine addition to the bicyclic olefin Ia was clearly established and the authors put forward the hypothesis of the existence of a special free-radical mechanism to rationalize the unusually high proportion of *cis*-bromination product IVa formed in the reaction. In their scheme, a concurrent ionic mechanism was responsible for the formation of at least part of the *trans*-bromination products IIa–IIIa, which constitute a racemate.

We decided to study further this reaction with a dual purpose—first, to determine the influence that methyl substitution might have on the stereochemical course of this bromination reaction and, second, to continue the study of long-range couplings in the nmr spectra of bicyclic molecules which are of general interest to us.

The bromination of 3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (Ia) and of the 3-methyl (Ib) and 3,6-dimethyl (Ic) derivatives was carried out in methylene chloride (see Scheme I). All products obtained were analyzed by nmr and elemental analysis and the results are summarized in Table I. The reported values for the bromination of Ia are the ones obtained in this work and they are substantially the same as the ones reported by Berson.[1] Table II contains all the information relative to the nmr spectra for every one of the dibromo compounds obtained.

SCHEME I



x : a (R = R' = H)
x : b (R = CH_3, R' = H)
x : c (R = R' = CH_3)

TABLE I

BROMINATION OF OXOBICYCLIC OLEFINS

Olefin	Total yield, %	Product distribion, %		Stereochemical course
Ia	86	IIa ≡ IIIa	65.1	*trans*
		IVa	34.9	*cis*
Ib	83	IIb	22.4	*trans*
		IIIb	60.3	
		IVb	17.3	*cis*
Ic	80	IIc ≡ IIIc	100	*trans*
		IVc	0	*cis*

Discussion of the Results

The values for product distribution collected in Table I clearly indicate that methyl substitution at the bridgehead of the oxobicyclic system Ia has a marked effect on the stereochemistry of bromine addition. When a methyl group is located on the bridgehead carbon atom (Ib), the proportion of *cis*-bromination product is lowered by a factor of 0.5 with respect to the unmethylated substrate Ia and no *cis* bromination occurs when the two bridgehead carbon atoms are methyl substituted (Ic). Also, from the two *trans*-bromination products of possible formation in the case of Ib, the one with the bromine at the *endo* position on the carbon atom α to the bridgehead carrying the methyl substituent (IIIb) predominates by a factor of 2.4 over the other isomer (IIb). These facts seem to indicate that regardless of the mechansim, some important steric

(1) To whom correspondence should be addressed: Universidad Central de Venezuela, Escuela de Quimica, Caracas, Venezuela.

(2) J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **76**, 4060 (1953).

TABLE II

NMR SPECTRAL DATA ON THE DIBROMO ADDITION PRODUCTS

Compd	Solvent	Protons	Chemical shift,[a] ppm	Multiplicity	Coupling constant,[b] cps
IIb	CD_3COCD_3–$CDCl_3$[c]	C-1,2	3.96	m (AB)	$J_{1,2} = 7.6$
		C-4,5	4.50	m (AB)	$J_{4,5} = 4.0$
		C-6	5.15	d	$J_{5,6} = 5.0$
		3-CH_3	1.70	s	
IIIb	CD_3COCD_3–$CDCl_3$[c]	C-1,2	4.02	m (AB)	$J_{1,2} = 7.4$
		C-4,5	4.40	m (AB)	$J_{4,5} = 4.0$
		C-6	5.06	d	$J_{4,6} = 0.7$
		3-CH_3	1.72	s	
IVb	CD_3COCD_3	C-1,2	3.91	m (AB)	$J_{1,2} = 7.4$
		C-4,5	5.13	m (AB)	$J_{4,5} = 7.2$
		C-6	5.06	s	
		3-CH_3	1.80	s	
IIc–IIIc	$CDCl_3$	C-1,2	3.71	m (AB)	$J_{1,2} = 7.6$
		C-4,5	4.20	m (AB)	$J_{4,5} = 4$
		3-CH_3	1.73	s	
		6-CH_3	1.67	s	

[a] Tetramethylsilane was used as external standard. [b] All spectra were analyzed on a first-order basis. [c] 20% $CDCl_3$ by volume.

effect, introduced by the presence of methyl substitution, is operating in this bromine addition.

If product distribution in this reaction is, as Berson suggests, an indication of the relative reaction rates leading to each one of the compounds formed, then some interesting conclusions can be drawn from the data reported.

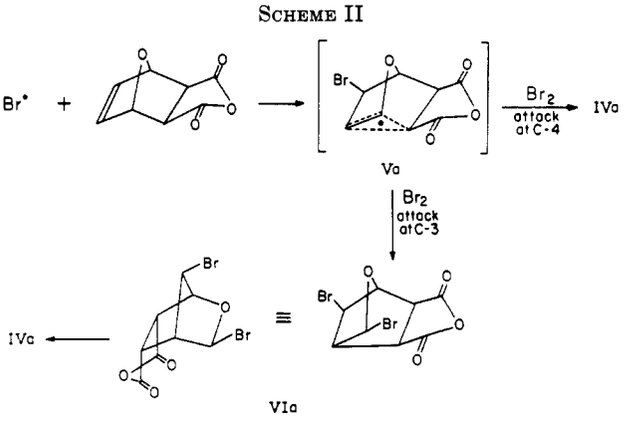
The fact that all products in which bromine is at the *exo* position on the α-carbon to the substituted bridgehead are formed at lower rates, whether they come from a *cis* addition (IVb and IVc) or from a *trans* addition (IIb), seems to indicate that the Br–CH_3 interaction in this situation is important or, at least, that the *exo*-bromine introduces much more strain in the molecule than the *endo*-bromine when methyl substitution at the bridgehead is present. A Fisher–Taylor–Hirschfelder molecular model of IIb shows that overcrowding is greater when an *exo*-bromine is close to the methyl group.

Since the ratio of *cis*-bromination products decreases as methyl substitution increases and, if *cis* bromination occurs *via* a free-radical mechanism, one has to conclude that the above-discussed steric effect makes more energetic the transition state leading to *cis*-bromination products; the increase in energy content of the transition state being greater as methyl substitution increases. A consequence is also that the interatomic spatial relations in the transition state for the *cis*-bromination reaction should be close to those on the final products, since it is in the latter where the Br–CH_3 interaction shows up more clearly. At this point it is convenient to note that no interconversion of products occurs under the reaction conditions and, therefore, the relative yields are a valid estimate of the relative rates of formation for the different products.

If the *trans*-bromination products arise from the simultaneous operation of an ionic and a free-radical mechanism in the manner suggested by Berson,[1] the above considerations apply to their formation, since also for them the proportion of the compound having the *endo*-bromine and the methyl group from the same side of the molecule (IIIb) is greater than the other isomer (IIb).

Mechanism.—As it has already been pointed out above, a mechanism for this bromination reaction has been proposed in an earlier work.[1] To account for the unusually high proportion of *cis*-bromination product in the case of the unmethylated substrate Ia, the operation of a free-radical mechanism, with the inclusion of the nonclassical intermediate Va, was postulated (see Scheme II). It was in the presence of Va where

SCHEME II



the driving force for the *cis*-addition process had to be found. The *trans*-addition process followed both an ionic and a regular free-radical paths.

In our opinion the mechanism proposed by Berson is the one applicable here, with the only exception that there seems to be no direct way to implicate or rule out nonclassical intermediates such as Va. Steric factors alone may account for the exceptionally high proportion of *cis* addition to Ia. Whatever the nature of these factors, they are very readily overcome by bridgehead methyl substitution (Ib and Ic).

Nmr Spectra.—Since the identification of the different compounds studied here is based mainly on their nmr spectra, it seems appropriate to comment briefly on the assignments made. The nmr spectra of IIa–IIIa and IVa have been discussed elsewhere[3] and no doubt is left with respect to the validity of the assignments.

Compound IVb has a very simple and characteristic spectrum (see Table II). It is composed of two AB-type structures easily assignable to hydrogens 4 and 5, one set, and to hydrogens 1 and 2 the remaining one, at higher field. Since no more couplings are to be

(3) D. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. France*, 2627 (1963).

expected in this molecule,[4,5] the 6-hydrogen gives rise to a sharp singlet. The 3-CH_3 group shows up as a singlet at $\delta = 1.80$ ppm.

Compound IIIb presents also an easily analyzable spectrum and distinction between IIb and IIIb can be made in a straightforward manner by the absence in the latter of the $J_{5,6}$ coupling. From the nmr point of view it is interesting to note the magnitude (0.7 cps) and clearness with which the long-range coupling $J_{4,6}$ appears.

The case of IIb was the one which was most difficult to study. This compound was always obtained mixed with IIIb (see Experimental Section) and none of the various attempts to separate the two isomers was successful. Nevertheless, by trying different solvent mixtures and with the previous knowledge of the nmr spectrum of IIIb, the spectrum of IIb was analyzed and the assignments were made in an unequivocal way, since none of the other compounds of theoretically possible formation would have shown an nmr spectrum of similar characteristics. All the necessary parameters are given in Table II. Finally, IIc–IIIc also presents two AB-type structures ($J_{4,5}$ and $J_{1,2}$) and two singlets corresponding to the two methyl groups.

Experimental Section[6]

Diels–Alder Adducts Ia, Ib, and Ic.—These were prepared in the usual manner[7] from the corresponding furans and maleic anhydride. The nature of the *exo* adducts obtained was checked by nmr spectroscopy.

***exo-cis*-Endoxo-4,5-*trans*-dibromotetrahydrophthalic Anhydride (IIa–IIIa) and *exo-cis*-3,6-Endoxo-4,5-*cis*-dibromotetrahydrophthalic Anhydride (IVa).**—The method outlined by Berson for the bromination of Ia was followed.[1] The total yield of the bromination reaction was 86%. Product distribution was 34.8 (IVa) and 65.1% (IIa–IIIa).

***exo-cis*-3,6-Endoxo-3-methyl-4,5-*exo-cis*-dibromotetrahydrophthalic Anhydride (IVb).**—To a solution of Ib (10 g, 0.055 mole) in CH_2Cl_2 (250 ml), bromine (3 ml, 0.055 mole) was added in 0.5-ml portions, under diffuse sunlight, with permanent stirring. The white precipitate formed was filtered and washed with a small amount of cold ether to yield 2.74 g (17.3%) of IVb, mp 266–268° dec.

Anal. Calcd for $C_9H_8O_4Br_2$: C, 31.45; H, 2.21; Br, 47.47. Found: C, 31.79; H, 2.37; Br, 47.01.

***exo-cis*-3,6-Endoxo-3-methyl-4-*endo*-5-*exo*-dibromotetrahydrophthalic Anhydride (IIIb).**—The mother liquor of the preceding preparation was kept under refrigeration for 24 hr. The precipitate formed (IIIb) was filtered off and washed with ether (5.30 g, 34%), mp 165–167°.

Anal. Calcd for $C_9H_8O_4Br_2$: C, 31.45; H, 2.21; Br, 47.47. Found: C, 31.50; H, 2.37; Br, 47.11.

***exo-cis*-3,6-Endoxo-3-methyl-4-*exo*-5-*endo*-dibromotetrahydrophthalic Anhydride (IIb).**—The liquid portion left from the preparation of IIIb was evaporated to dryness under reduced pressure to afford 7.6 g (48.7%) of a white solid, mp 125–126°. The nmr spectrum of this product showed it to be a mixture of IIIb (54%) and IIb (46%). The composition of the mixture was determined by comparing the integral values of the 6-H signal for both compounds in their nmr spectrum. Elemental analysis of the mixture confirmed the above statement. None of the various attempts made to separate the two isomers was successful.

***exo-cis*-3,6-Endoxo-3,6-dimethyl-4,5-*trans*-dibromotetrahydrophthalic Anhydride (IIc–IIIc).**—To a solution of Ic (10.7 g, 0.055 mole) in CH_2Cl_2 (200 ml) bromine (3 ml, 0.055 mole) was added in small portions with cooling and permanent stirring. When the addition was completed, the solution was concentrated to 20 ml and ether (100 ml) added. Upon concentration of the solution under reduced pressure, a solid crystallized out. Recrystallization in ether afforded 15.6 g (80%) of IIc–IIIc, mp 127–128°.

Anal. Calcd for $C_{10}H_{10}O_4Br_2$: C, 33.92; H, 3.05; Br, 45.15. Found: C, 33.50; H, 3.17; Br, 44.87.

Registry No.—IIb, 13618-68-3; IIc–IIIc, 13618-69-4; IIIb, 13618-70-7; IVb, 13618-71-8.

Acknowledgments.—We wish to thank Professor J. A. Berson for his valuable criticism and to acknowledge the stimulating comments of one of the referees.

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(6) All melting points are uncorrected. Microanalyses were performed by F. Pascher, Mikroanalytisches Laboratorium, Bonn, Germany. Nmr spectra were run on a Varian A-60 spectrometer.

(7) O. Diels and K. Alder, *Ber.*, **490**, 243 (1931).

Quinazolines and 1,4-Benzodiazepines. XXXVII.[1] Synthesis and Rearrangements of a Substituted 5-Phenyl-1H-1,4-benzodiazepine

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The three-step synthesis of N-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepine-3-carboxamide (IV) from 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (I) is described. The 1H compound was subsequently oxidized to N-methyl-6-nitro-4-phenyl-2-quinazoline carboxamide (XV) and rearranged in acid to 5-nitro-3-phenylindole (XIX) and N-methyl-5-nitro-3-phenyl-2-indoleglyoxalamide (XVIII). A by-product isolated from the synthesis of the 1H compound was shown to be 3,10b-dihydro-1-methyl-9-nitro-10b-phenylimidazo[1,2-*c*]-quinazolin-2(1H)-one (XXVI). Evidence is given for the structures assigned and possible mechanisms for the formation of these compounds are presented.

As a continuation of our studies on the synthesis and transformations of the 1,4-benzodiazepine ring system, we have prepared the open amides IIa and IIb from 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (I) by means of a transamidation reaction. Compound IIa, on treatment with dimethylformamide acetal, gave the dimethylaminomethylenimino derivative (III) which, on heating in solution, gave the 1H-1,4-benzodiazepine (IV) (Scheme I).

The structure of IIb was confirmed by the series of reactions outlined in Scheme I. On treatment with acetic anhydride and potassium acetate, IIb gave the N-acetyl derivative V. Mild acid hydrolysis of either IIb or V gave the corresponding benzophenones VII and VI in almost quantitative yield. The hydrolysis of IIb also gave an excellent yield of glycylpiperidide

(1) Paper XXXVI: R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Heterocyclic Chem.*, **4**, 355 (1967).