

Configurational Study of Some 9-Substituted 3-Oxabicyclo[3.3.1]nonanes by Nuclear Magnetic Resonance

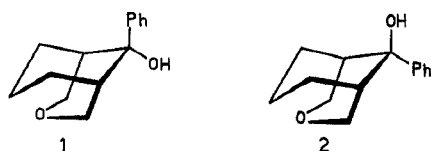
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Received May 27, 1969

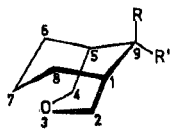
Several 9-substituted 3-oxabicyclo[3.3.1]nonanes were synthesized and their configurations and conformations were assigned by nmr spectroscopy.

When 1-phenylcyclohexene was subjected to the Prins reaction, two diastereoisomeric products were obtained.¹ It was possible to assign to them structures 1 and 2 by chemical means, which, however, did not establish their configurations.²



An nmr study of the two compounds and of a series of analogs appeared as the most promising approach to the determination of the configuration and possibly of the conformations of the two rings in the molecule. To this purpose, the compounds reported in Table I were prepared.

TABLE I



Compd	R	R'	Compd	R	R'
1	Ph	OH	2	OH	Ph
3	Ph	H	4	H	Ph
5	C ₆ H ₁₁	OH	6	OH	C ₆ H ₁₁
7	C ₆ H ₁₁	H	8	H	C ₆ H ₁₁
9	H	OH	10	OH	H
11	H	H			

Compounds 3 and 4 were obtained from 1 and 2, respectively, by hydrogenolysis, compounds 5, 6, 7, and 8, from 1, 2, 3, and 4, respectively, by catalytic hydrogenation of the phenyl to cyclohexyl group in the presence of rhodium on alumina.

Compounds 9 and 10 were prepared by reduction of 3-oxabicyclo[3.3.1]nonan-9-one and separated by column chromatography.

We thus have two correlated series of compounds, *i.e.*, the series 1, 3, 5, and 7, and the series 2, 4, 6, and 8, besides the two products 9 and 10 and the parent compound 11³.

(1) G. Lippi and B. Macchia, *Chim. Ind. (Milan)*, **50**, 697 (1968).

(2) The configuration of the substituents at C-9 of 3-oxabicyclo[3.3.1]nonane is indicated following the convention adopted for the description and the representation of the steroids [*J. Amer. Chem. Soc.*, **82**, 5577 (1960)]. Using the the C-O-C bridge as a reference group, the substituent which is oriented on the same side as the oxygen with respect to the general plane of the cyclohexane ring is denoted by β , and the substituent with opposite configuration, *i.e.*, located on the opposite side with respect to the reference group, is called α . The hydrogen atoms are indicated with the number of the carbon atom to which they are bonded and with the designation "a" or "e" according to whether they are axial or equatorial with respect to the ring to which they belong.

TABLE II
CHEMICAL SHIFTS AND COUPLING CONSTANTS
RELATIVE TO THE 2 AND 4 PROTONS^a

Compd	τ'	τ''	$J_{2,2'}$	$J_{2e,9\alpha}$	$J_{2a,8a}$
1	5.60 (a)	6.20 (e)	10.9	...	b
2	6.21	6.34	10.9
3	5.87 (e)	6.12 (a)	11.2	...	b
4	6.14 (a)	6.32 (e)	11.4	1.0 ^c	...
5	5.81 (a)	6.34 (e)	10.9	...	b
6	6.09	6.21	11.6
7	6.02 (e)	6.36 (a)	10.9	...	b
8	6.12	6.36	11.2
9	5.93 (a)	6.39 (e)	10.9	0.8	...
10	6.03 (e)	6.31 (a)	11.2	...	b
11	6.11 (e)	6.26 (a)	10.9

^a Chemical shifts (τ' and τ'' , τ' being less than τ'') were measured directly from spectra determined at a sweep width of 500 cps with a scanning time of 500 sec and are expressed in parts per million; J values are in cycles per second and were measured using a sweep width of 250 cps and the same scanning time. The letters "a" and "e" in parentheses indicate axial and equatorial protons. ^b The lines of the axial 2,4 protons after double resonance on the 1 and 5 protons are appreciably broader with respect to the equatorial ones. No quantitative measurements have been made, but the order of magnitude of the coupling is <0.5 cps. ^c The coupling is between the benzylic proton and the high-field 2 and 4 protons.

Stereochemical assignments of these compounds could not be made by chemical means, using the technique followed by House, *et al.*,³ for analogous compounds having an NCH₃ group in place of the oxygen atom.

The only compound for which a configuration had been proposed is 10.⁴ However, such an assignment, though plausible, cannot be confirmed by the absence of an OH-O bond in the infrared spectrum of 10, as admitted by the authors themselves,⁴ since the ir spectra of 9, 5, and 6 also show no evidence for an OH-O bond, but only the free OH bands at 3623 cm⁻¹ for 9 and 10, and at 3619 cm⁻¹ for 5 and 6. On the contrary, in the spectra of 1 and 2 there is a shift of the OH stretching band toward longer wavelengths attributable to OH- π bonding.⁵ Therefore infrared spectroscopy does not give useful data for solving the problem.

Results

Table II reports the chemical shifts and, when present, the coupling constants relative to the hydrogens at

(3) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); H. O. House and W. M. Bryant, III, *ibid.*, **30**, 3634 (1965).

(4) A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.*, **79**, 6025 (1957).

(5) M. Tichý in "Advances in Organic Chemistry. Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 4; B. Macchia, F. Macchia, and L. Monti, unpublished data, 1968.

positions 2 and 4. The assignments of the peaks to the axial or equatorial protons is justified later. Actually, all spectra show some couplings between the relevant protons and those at position 1 and 5. Such couplings have not been directly measured but were systematically eliminated by double resonance.

Discussion

The presence of the phenyl substituent in the α or β position would be expected to influence differently the chemical shifts of the methylene protons of the cyclohexane ring, as well as of those in position 2 and 4. In particular, since the molecules in question are presumably rigid, it is possible to estimate with a fair approximation, using Johnson and Bovey tables,⁶ the differences between the chemical shifts of the various protons for the more probable conformation. Let us first consider the cyclohexyl ring protons. When the phenyl group is in the β position, the ring protons should be on the average deshielded, and also the substituent effects should be very similar for the various protons. On the contrary, the effects of an α -phenyl group will be notably different because of the different positions of the protons with respect to the benzene ring (compare, for example, protons 1 and 5 with respect to 6, 7, and 8). The expected cyclohexyl proton spectrum of the α -phenyl compounds should therefore be more diffuse than that of the β -phenyl ones, with the center of gravity strongly shifted toward low field. If this is true, this would enable us to assign configuration to **3** and **4** and would also give information about **1** and **2**, which are the respective starting products. Actually, it is not certain that the hydrogenolysis of the hydroxyl group takes place with retention of configuration; this is the usual course of the Raney nickel hydrogenolysis of benzylic hydroxyl groups,⁷ but apparent exceptions caused by equilibration of the products under the reaction conditions have been reported.⁸

From an examination of the spectra it is evident that the spectra of compounds **3** and **4** agree with the expectation for the α - and β -phenyl derivatives, respectively. In fact, the cyclohexyl envelope is much broader in **3** than in **11** and with the center of gravity practically unchanged, whereas in **4** there is a clear shift toward low field.

The nmr spectra of compounds **1** and **2** are complicated by the effect of the dipole moment of the hydroxyl group, which can affect the chemical shifts.⁹ Moreover, even if the presence of a OH- π bond indicates a preferential conformation of the hydroxyl group, the weight of such a conformation is obviously not known. It may be assumed that the effect of the hydroxyl group will be the same as in cyclohexanols.¹⁰ Particularly if the hydroxyl group is α , the two axial protons 6 and 8 should experience its deshielding action (ca. 0.5 ppm¹⁰), whereas the other protons should be less affected. If,

instead, the hydroxyl group is β , the effect of the lone-pair electric dipole of oxygen should be much smaller. The effect on protons 1 and 5 is, of course, identical in both cases.

The spectra of compounds **1** and **2** are in good agreement with these expectations about the effects of the hydroxyl and the phenyl groups. The signals for protons 1 and 5 are at the same position ($J \cong 7.7$) in both spectra, but in the spectrum of **2** they are overlapped by those of two other protons, *i.e.*, axial 6 and 8, for which a deshielding of about 0.5 ppm by the α -hydroxyl group can be expected.¹⁰ The center of gravity of the spectrum of compound **1** is very little shifted. The fact that expectations have been confirmed suggests that the reduction of hydroxyl group¹ has taken place with retention of configuration.

The spectrum of the cyclohexyl protons in **10** has the center of gravity shifted toward low field with respect to the unsubstituted compound **11**, whereas the center of gravity of the spectrum of protons 2 and 4 is almost unchanged. On the contrary, compound **9** has the center of gravity of the cyclohexyl protons almost unchanged, whereas that of protons 2 and 4 is shifted toward low field. Furthermore, two of these protons, namely those at higher field, are coupled with the hydrogen in **9**. All this is in full agreement with the assignment given for **10** by Blomquist.⁴

Attention should now be paid to the spectra of the four protons, chemically equivalent in pairs, in positions 2 and 4. The corresponding peaks are isolated from the other ones and therefore their chemical shifts and couplings constants with other protons can be measured easily and accurately. Moreover, in these molecules small long-range couplings are possible,¹¹ which are particularly sensitive to configuration and conformation. A tentative interpretation is possible if we suppose that the contributions of each substituent to the chemical shifts of these protons are additive. First of all, it is necessary to assign, in each spectrum, the lines of the AB doublets (sometimes split by "long-range" couplings) freed through double resonance from the effect of the coupling with protons 1 and 5.

Compounds **11**, **1**, **3**, **5**, **7**, and **9** carry the 9-phenyl or 9-cyclohexyl substituents in the α position and the hydroxyl one in the β position. It must be pointed out that, if we assume a chair-chair conformation, which is rather likely on the basis of the results obtained with similar compounds,¹² a long-range coupling is expected between the α hydrogen at C-9 and the equatorial protons at C-2 and C-4. Moreover, each axial proton at C-2 and at C-4 should be coupled with an axial proton of the cyclohexyl ring. Now, if we exclude **11** and **9**, all mentioned compounds have the α position substituted, and therefore equatorial 2 and 4 protons should not show any long-range coupling. One can expect a coupling of the axial protons 2 and 4, respectively, with the axial protons 8 and 6; this provided a method for the assignments reported in Table II. A clear coupling of 0.8 cps is observed in **9**,

(6) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(7) S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 1354 (1963); S. Mitsui and Y. Kudo, *ibid.*, 381 (1965), and references cited therein.

(8) J. A. Zderic, M. E. C. Rivera, and D. C. Limón, *J. Amer. Chem. Soc.*, **82**, 6373 (1960); E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3363 (1962).

(9) P. Bucci, *J. Amer. Chem. Soc.*, **90**, 252 (1968).

(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 183.

(11) Reference 10, p 115.

(12) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); I. Laszlo, *Rec. Trav. Chim. Pays-Bas*, **84**, 251 (1965); N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind. (London)*, 1903 (1963); H. O. House and W. M. Bryant, III, *J. Org. Chem.*, **31**, 3482 (1966); J. E. Douglass and T. B. Ratliff, *ibid.*, **33**, 355 (1968).

which may be attributed to $J_{2e,9\alpha}$ and $J_{4e,9\alpha}$, since its value is greater than $J_{2a,8a}$, which in general could not be measured but only observed as a line broadening. The assignments of the protons of **11** is not possible on the basis of the single spectrum, since the two chemical shifts are very similar (their difference is only 8.7 cps). In cyclohexane the axial proton chemical shifts are at higher fields, but this consideration is useless here because of the presence of the oxygen atom and the substitution of two CH axial bonds with the second cycle. Our assignment will therefore be uniquely based on the best agreement obtained with the additivity of the substituents effects.

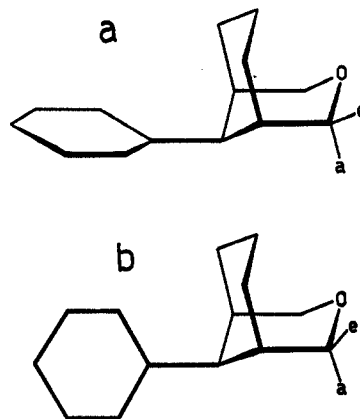
The α -phenyl group may either assume, with respect to the rest of the molecule, the position shown in Figure 1a (the most probable one, under those steric conditions), or rotate freely. In the former case, we may expect⁶ changes in chemical shift of -0.11 and -0.16 ppm for the equatorial and axial protons near to the oxygen, respectively. In the latter case, a good estimate of the changes is obtained by averaging the above values with those obtainable when the plane of the benzene ring is orthogonal to the previous position (Figure 1b). They are, respectively, -0.08 and -0.14 , with a mean value of -0.095 and -0.15 . If we adopt for **11** the assignment reported in Table II, one obtains, respectively, shifts equal to -0.24 and -0.14 ppm. The poor agreement may be caused by various factors (substitution of the C-H dipole with the C-Ph group, differences in solvent interaction, etc.). The significant fact is, however, that both protons are deshielded by not very different amounts. On the basis of the assignment of the spectrum of **11** we may obtain the contributions of cyclohexyl in the α position and of the hydroxyl group in β position reported in Table III.

TABLE III

Group	Position	H_{2a} and H_{4a}	H_{2e} and H_{4e}
Phenyl	α	-0.14	-0.24
Cyclohexyl	α	$+0.10$	-0.09
Hydroxyl	β	-0.33	$+0.27$

By means of these contributions we can calculate the expected shifts for compounds **1** and **5**. They are -0.47 and $+0.03$ (compound **1**) and -0.23 and $+0.18$ (compound **5**), respectively, for axial and equatorial protons. The experimental values are -0.66 and $+0.09$ (**1**) and -0.45 and $+0.23$ (**5**). The agreement in order of magnitude and sign is good, especially if we consider that we have neglected the probably notable interactions between two geminal substituents (for example, the OH- π bond in **1**, which is easily observed in the ir spectra).

The chemical-shift changes induced by the hydroxyl group (toward low field for the axial protons, smaller and toward high field for the equatorial protons) can easily be rationalized; in fact, the electric field generated by the "lone pairs," directed along the C-H_a direction, causes a charge shift from the axial hydrogen to the carbon atom and, to a lesser extent, from the carbon to the equatorial hydrogen. All assumptions made so far fully agree with the configurations assigned to compounds **1**, **3**, **5**, **7**, and **9**, and also with the supposed chair-chair conformation.

Figure 1.—Conformations of the 9 α -benzene ring.

We shall now consider the series **11**, **2**, **4**, **6**, **8**, and **10**. Most interesting is the spectrum of **4**. In fact, it is possible to observe here a clear coupling between the benzylic 9 α proton and two of the protons in **2** and **4**. By triple resonance (*i.e.*, by simultaneously irradiating protons 1 and 5 and proton 9) it has been possible to assign unambiguously such coupling. On the basis of the presence of a long-range coupling, which causes a broadening of the corresponding peaks, we have assigned the spectrum of **10**. The changes in chemical shift (-0.08 and $+0.05$ for equatorial and axial protons, respectively) are here not significant and indicate the small effect of the hydroxyl group in the α configuration.

An analysis of the data, carried out on the same basis as that applied to the previous series of compounds, gave contradictory results. In fact, it is not possible, within reasonable limits of error, to establish any additivity of substituent effect or to explain the chemical shifts observed when β phenyl or β cyclohexyl are present. A possible explanation for this fact is the nonvalidity of the assumption of the chair-chair conformation when a bulky substituent is on the side of the tetrahydropyran ring. It may, in fact, be assumed that, owing to the smaller steric requirements of the oxygen atom with respect to a methylene group,¹³ the boat conformation of the tetrahydropyran ring is preferred because of its smaller interaction with the substituent. Such a hypothesis, or at least the presence of a rapid equilibrium between the two forms, can explain the broadness of the peaks relative to one of the two hydrogen types in position 2 and 4 in the cyclohexyl derivatives. Such broadness indicates a much greater coupling with the protons in positions 1 and 5 than that observed in all other examined spectra. In fact, the band at lower field is *ca.* 5 cps broad, against the usual 2.5–3.5 cps. This fact is not observed in the spectra of the corresponding compounds with the phenyl group in the β position. In this case, assuming a chair-chair conformation and a suitable assignment, changes of -0.12 and $+0.21$ are obtained for the chemical shift of the axial and equatorial protons, respectively, caused by the phenyl substituent in **4**. Such values, which are found almost unchanged in the spectrum of **2**, are not consistent with the calculated ones, assuming as before the free rotation of the phenyl group, *i.e.*, -0.02 and -0.05 ppm.

(13) E. L. Eliel and S. M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).

The experimental values, which are actually not very large, might be due to changes in the solvation of the oxygen atom because of steric hindrance.

From the previous considerations, the assignment of the configurations to the relevant compounds is largely demonstrated. The configuration of **10** agrees with that already assigned.⁴ It is also almost certain, in accordance with the results for analogous compounds found in the literature,¹² that the chair-chair conformation is the most stable, with the exception of the β -cyclohexyl derivatives, for which there is some evidence of a different situation.

Experimental Section¹⁴

9-Phenyl-3-oxabicyclo[3.3.1]nonan-9 β -ol (1) and **9-phenyl-3-oxabicyclo[3.3.1]nonan-9 α -ol (2)** were obtained¹ by the sulfuric acid catalyzed reaction of 1-phenylcyclohexene with formaldehyde in acetic acid solution: **1**, mp 141–142°, ir^{15} 3608 cm^{-1} ; **2**, mp 147–148°, ir^{15} 3608 cm^{-1} .

9 α -Phenyl-3-oxabicyclo[3.3.1]nonane (3) and **9 β -phenyl-3-oxabicyclo[3.3.1]nonane (4)** were prepared¹ by hydrogenolysis with Raney nickel of alcohols **1** and **2**, respectively: **3**, mp 54–55°; **4**, mp 46–48°.

9-Cyclohexyl-3-oxabicyclo[3.3.1]nonan-9 β -ol (5).—A suspension of 0.300 g (1.37 mmol) of **1** and 0.300 g of 5% rhodium on alumina in 15 ml of water was shaken under hydrogen at room temperature and atmospheric pressure. When the absorption stopped, the mixture was extracted with ether. Evaporation of the dried ether extract gave 0.302 g of **5**, mp 172–174° (from petroleum ether), ir^{15} 3616 cm^{-1} .

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.95; H, 10.78. Found: C, 74.92; H, 10.69.

9-Cyclohexyl-3-oxabicyclo[3.3.1]nonan-9 α -ol (6).—A suspension of 0.150 g (0.68 mmol) of **2** and 0.150 g of 5% rhodium on alumina was hydrogenated under the conditions used above. The residue (0.147 g) was dissolved in petroleum ether and chromatographed through a 1.0 \times 15 cm column of neutral alumina (grade II). Elution with 8.5:1.5 petroleum ether-benzene yielded 0.110 g of **6**, mp 114° [from petroleum ether (bp 30–50°)], ir^{15} 3619 cm^{-1} .

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.95; H, 10.78. Found: C, 74.85; H, 10.89.

(14) Melting points were determined on a Kofler hot stage, unless stated otherwise, and are uncorrected. Infrared spectra for comparisons between compounds were taken with a Perkin-Elmer Model 137 Infracord and those for determination of hydroxyl stretching bands with a Perkin-Elmer Model 237 grating spectrophotometer. Nuclear magnetic resonance spectra were determined on ca. 7% solutions in chloroform with a Varian DA-60 IL spectrometer using tetramethylsilane as an internal standard. Petroleum ether refers to the fraction boiling at 40–70°. Magnesium sulfate was used as the drying agent.

(15) Infrared spectra were determined in dried carbon tetrachloride, using the indene band at 3110 cm^{-1} as a calibration standard. A quartz cell of 2-cm optical length was employed, and the concentration of the solutions was ca. 3×10^{-3} M.

9 α -Cyclohexyl-3-oxabicyclo[3.3.1]nonane (7).—Reduction of 0.300 g of **3** as described above gave 0.297 g of **7**, which was crystallized from ethanol, mp 88–90°.

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}$: C, 80.71; H, 11.61. Found: C, 80.60; H, 11.46.

9 β -Cyclohexyl-3-oxabicyclo[3.3.1]nonane (8).—Hydrogenation of 0.071 g of **4** as above yielded a crude residue which was dissolved in petroleum ether (bp 30–50°) and chromatographed through a 1.0 \times 15 cm column of neutral alumina (grade II). Elution with petroleum ether (bp 30–50°) gave 0.046 g of pure **8** as an oil, n_D^{20} 1.49489.

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}$: C, 80.71; H, 11.61. Found: C, 80.90; H, 11.73.

3-Oxabicyclo[3.3.1]nonan-9 α -ol (10).—This compound was prepared according to the procedure of Blomquist and Wolinsky,⁴ mp 205–207° (sealed capillary), ir^{15} 3624 cm^{-1} (lit.⁴ mp ca. 205°).

3-Oxabicyclo[3.3.1]nonan-9-one.—A solution of 1.50 g of **10** in 40 ml of acetone was treated dropwise with 2.75 ml of Jones reagent,¹⁶ left for 3 min at room temperature, diluted with water, and extracted with ether. The ether extract was washed with 10% aqueous sodium carbonate, dried, and evaporated to give 1.40 g of the product, which after sublimation melted at 155–157° (lit.⁴ mp 154–157°).

3-Oxabicyclo[3.3.1]nonan-9 β -ol (9).—To a mixture of 2.30 g (0.10 g-atom) of sodium and 50 ml of boiling toluene was added rapidly a solution of 1.40 g (0.01 mol) of 3-oxabicyclo[3.3.1]nonan-9-one in 23 ml of absolute ethanol. The mixture was refluxed for 1 hr, cooled, and diluted with ether. Evaporation of the resulting washed and dried solution gave a crude mixture of alcohols **9** and **10**, which was chromatographed through a 1.5 \times 35 cm column of neutral alumina (grade II). Elution with 6:4 petroleum ether-benzene gave 0.41 g of **10**, and further elutions with increasing amounts of benzene yielded 0.11 g of a mixture of **9** and **10** and finally 0.37 g of pure **9**. After crystallization from petroleum ether (bp 30–50°), **9** melted at 209–210° (sealed capillary), ir^{15} 3624 cm^{-1} .

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.93. Found: C, 67.40; H, 9.75.

3-Oxabicyclo[3.3.1]nonane (11).—A sample kindly provided by Dr. E. L. Wittbecker,¹⁷ after sublimation, melted at 135–138° (sealed capillary) (lit.¹⁷ mp 135–138°).

Registry No.—**1**, 23328-19-0; **2**, 23328-20-3; **3**, 23328-21-4; **4**, 23328-22-5; **5**, 23328-23-6; **6**, 23328-24-7; **7**, 23328-25-8; **8**, 23328-26-9; **9**, 23328-27-0; **10**, 23328-28-1; **11**, 280-71-7.

Acknowledgments.—This work was supported by a contribution from the Consiglio Nazionale delle Ricerche. The authors would like to thank Professor G. Berti for many useful discussions and Dr. M. Panocchia for help in the experimental work.

(16) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(17) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1960).