Reaction of Reissert Anion with Allyl Chloride—To 10.4 g (0.04 mole) of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline in 100 ml of dimethylformamide and 8.0 g of allyl chloride was added 2.00 g of 50% sodium hydride in oil, and the mixture was stirred for 1 hr. The reaction mixture was poured over ice and allowed to stand overnight. The solution was extracted with chloroform, and the chloroform extracts were washed with water. The dried (sodium sulfate) chloroform extracts were taken to dryness *in vacuo*, and the residue was recrystallized from 95% ethanol to give 6.7 g (55%) of 1-allyl-2-benzoyl-1-cyano-1,2-dihydroisoquinoline (XI), mp 98–100°; IR (KBr): 1680 cm^{-1}; NMR (CCl_4): δ 7.5 (9H), 6.4 (1H), 5.6 (1H), 5.4 (1H), 5.2 (2H), and 3.1 (2H) ppm.

Anal.—Calc. for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.33. Found: C, 80.08; H, 5.43; N, 9.37.

Hydrolysis of X—A solution containing 3.00 g (0.01 mole) of X, 35 ml of water, 5 ml of ethanol, and 12 g of potassium hydroxide was refluxed for 48 hr. The basic reaction mixture was poured into 200 ml of water, and the aqueous solution was extracted with chloroform. The chloroform extracts were extracted with 5% HCl, the acid extracts were made basic with sodium carbonate, and the basic solution was extracted with chloroform. The dried (sodium sulfate) extracts were distilled at 88°/0.1 mm to give 1.24 g (73%) of 1-isoquinolylpropene (XII). The compound was converted to the picrate for analysis, mp 180–182°; IR (NaCl): 3080 and 1650 cm^{-1}; NMR (CCl_4): δ 8.0 (8H) and 1.9 (3H) ppm.

Anal.—Calc. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54; N, 14.06. Found: C, 53.51; H, 3.63; N, 13.92.

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COMMUNICATIONS

Unusual Reversible Attack by Sodium Bisulfite on Physostigmine

Keyphrases □ Sodium bisulfite—effect on physostigmine molecule in solution □ Physostigmine—effect of sodium bisulfite on molecule in solution □ Antioxidants—sodium bisulfite, effect on physostigmine molecule in solution □ Ophthalmic cholinergics—physostigmine, effect of sodium bisulfite on molecule in solution

To the Editor:

Sodium bisulfite is used as an antioxidant in ophthalmic preparations containing physostigmine. Although physostigmine was shown to be stable in the presence of sodium bisulfite (1), the previous study was mainly concerned with the catalytic effect of the antioxidant on the hydrolysis rate of the carbamate linkage of the drug.

We recently observed interesting reactions between physostigmine and bisulfite. When sodium bisulfite solutions ranging in concentration from 0.01 to 0.4 *M* were mixed with 1×10^{-4} *M* physostigmine at pH 5.5 directly into the spectrophotometric[1] cell, the absorbance at 330 nm rapidly increased. At this wavelength and concentration, physostigmine has no absorbance; sodium bisulfite was present in both the sample and the blank. A semilog plot of $(A_\infty - A_t)$ against time resulted in a first-order plot (Fig. 1). The observed first-order rate constants depended on the bisulfite concentration (Fig. 2). Furthermore, at a given physostigmine concentration and in the presence of varying bisulfite concentrations, the equilibrium absorbance at 330 nm changed as a function of the bisulfite concentration (Fig. 3), indicating that an equilibrium condition existed between the species involved.

The ^{13}C-NMR spectra of aqueous solutions of physostigmine and physostigmine containing excess sodium bisulfite (molar ratio 2:1) indicate that the reaction between the two species involved an attack by bisulfite on carbon-10a of physostigmine. As seen from the NMR spectra (Fig. 4), the signal from carbon-10a (δ 98.92 ppm) disappeared when bisulfite was added. Instead, two new signals were observed, δ 88.74 and 92.32 ppm, suggesting the formation of two new species.

Since carbon-10a is partly responsible for the optical activity of physostigmine, one would anticipate changes in the optical rotation of physostigmine upon the addition

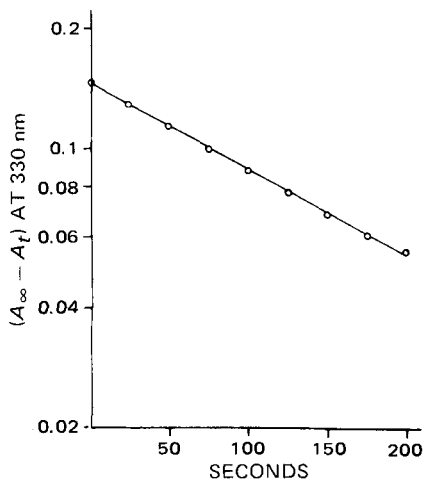


Figure 1—*Semilog plot of* $(A_\infty - A_t)$ *at 330 nm against time at pH 5.5 and 25°. Sodium bisulfite = 4.87* $\times 10^{-2}$ *M; physostigmine = 2.5* $\times 10^{-3}$ M.

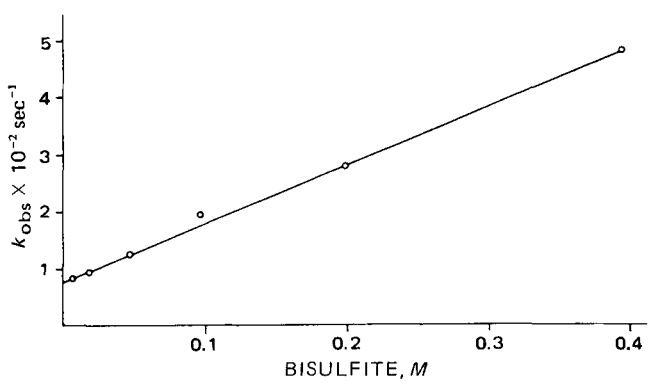


Figure 2—*Dependency of the observed first-order rate constant at pH 5.5 on bisulfite concentration.*

[1] Cary 15 recording spectrophotometer.

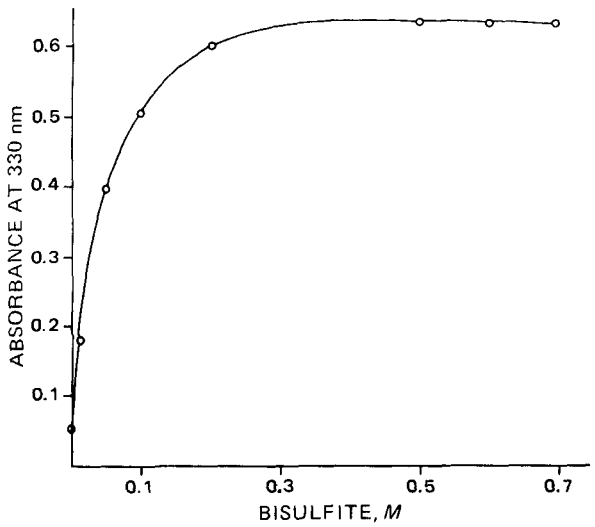


Figure 3—*Dependency of the physostigmine–bisulfite equilibrium absorbance at 330 nm on bisulfite concentration in the presence of a constant physostigmine concentration.*

of sodium bisulfite. Such changes did occur (Fig. 5). In the presence of excess bisulfite, the optical rotation was completely reversed. However, upon dilution of the physostigmine–bisulfite mixture at pH 5.5 with buffer (pH 9.5) and extraction of physostigmine with hexane, the optical rotation of the hexane solution corresponded to that of an equimolar solution of physostigmine. This result indicates that the reverse reaction resulted in the formation of physostigmine in its original configuration.

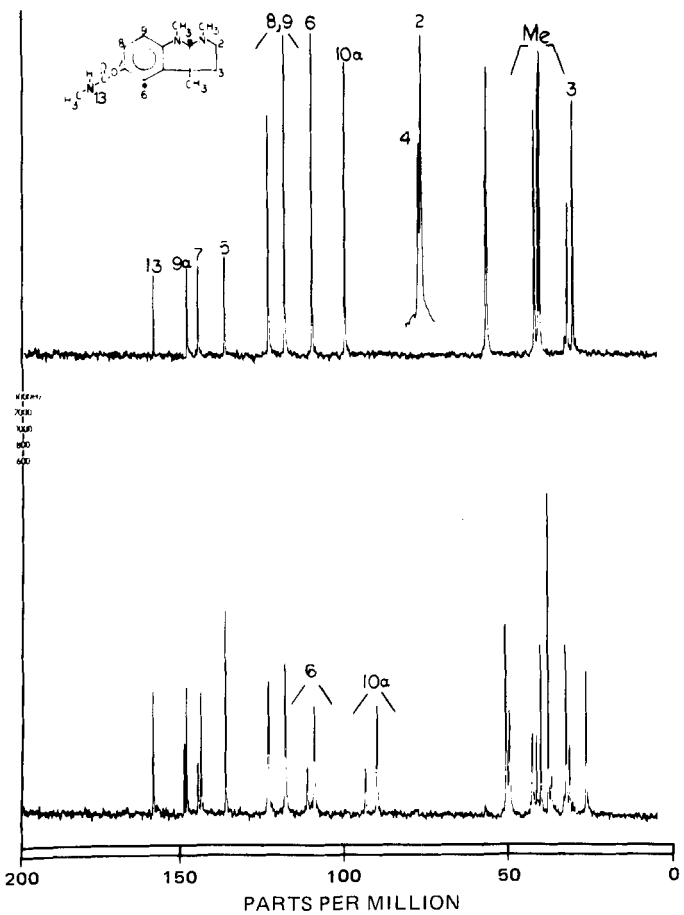


Figure 4—^{13}C-*NMR spectra of physostigmine and physostigmine–bisulfite solutions.*

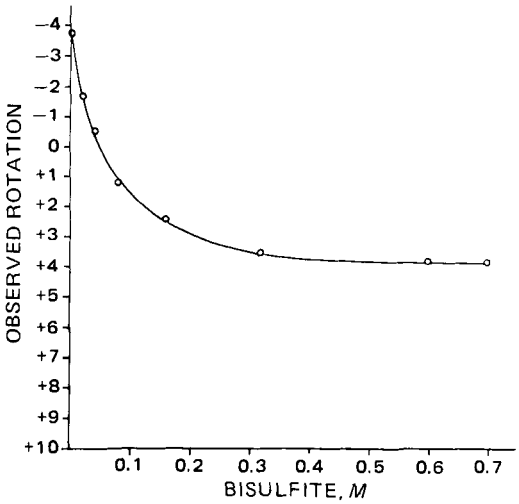
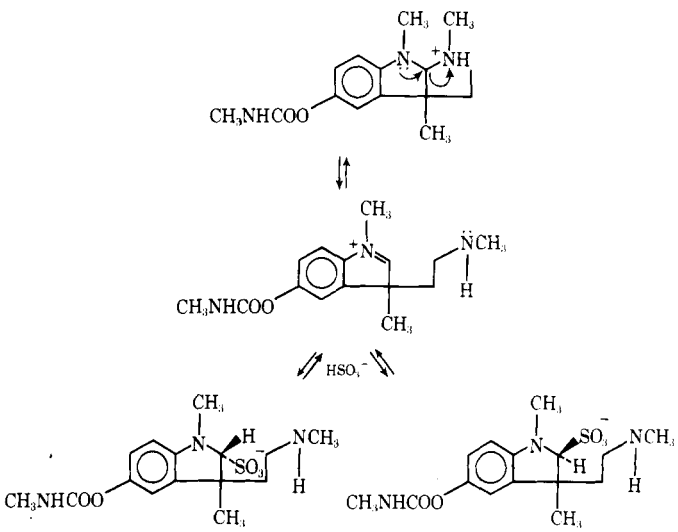


Figure 5—*Plot showing the change in the optical rotation of physostigmine in the presence of varying amounts of bisulfite at pH 5.5.*



Scheme I

The equilibrium constant K = [phys − bisulf]$_{eq}$/[phys]$_{eq}$[bisulf]$_{eq}$ calculated from both the spectrophotometric and polarimetric data (Figs. 3 and 5) was 38 ± 2 M^{-1} at pH 5.5. The second-order rate constant for the reaction, calculated from the data of Fig. 2, was 0.103 M^{-1} sec^{-1} at pH 5.5. The reverse rate k_{-1} at pH 5.5, calculated from the intercept of Fig. 2, was 0.67 × 10^{-2}. The equilibrium constant calculated from the ratio of K_1[bisulfite]/k_{-1} was 30 M^{-1}, close to the value calculated from the direct measurements of the equilibrium constant.

Reaction Scheme I is consistent with these data. The significance of these findings in regard to the biological activity of physostigmine as well as the elucidation of the overall mechanism of these reactions is being investigated.

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