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THE BISULFITE ADDITION COMPOUNDS OF CODEINE KETONES

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THE BISULFITE ADDITION COMPOUNDS OF CODEINE KETONES[1]

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A recent statement[2] that dihydrocodeinone forms a bisulfite addition compound was of considerable interest to us, since if true, this observation suggests a potentially valuable and easy method for separating ketonic from non-ketonic material in the morphine series. Previously, attempts to remove the corresponding nitrogen-free ketone, 6-keto-13-vinyloctahydromethylmorphenol, from benzene by extraction with aqueous sodium bisulfite had failed,[3] and this difference in behavior led us to re-examine the successful results reported[2] with dihydrocodeinone.

The reported extraction of dihydrocodeinone, which has a pK_a' of 7.95[4] does not necessarily prove formation of a bisulfite adduct since the 40% sodium bisulfite solution used has a pH of 5 and at this pH the ratio for dihydrocodeinone of ammonium salt form to free base is 910 to 1. Thus the extraction of dihydrocodeinone from benzene into saturated aqueous bisul-

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(1) Supported (in part) by the U. S. Atomic Energy Commission.

(2) M. M. Baizer, A. Loter, K. S. Ellner, and D. R. Satriana, J. Org. Chem., 16, 543 (1951).

(3) G. B. Payne, Thesis, 1950, University of California; H. Rapoport and G. B. Payne, J. Am. Chem. Soc., 74, 2630 (1952).

(4) N. Schoorl, Pharm. Weekblad, 76, 1497 (1939).

fite can be explained merely by salt formation. Since most codeine derivatives are of fairly similar basic strength, the use of aqueous bisulfite under these conditions would be non-selective, and all of these substances would be extracted because of salt formation. This was clearly demonstrated by the quantitative removal of both dihydrocodeinone and codeine from benzene solutions using 40% aqueous bisulfite.

Definitive evidence as to whether carbonyl bisulfite addition compounds are actually formed has been sought by the following two procedures. The effect of the presence of bisulfite ion on the specific rotation at a given pH has been observed. If a carbonyl adduct is formed, an appreciable change in optical rotation would be expected, since a new center of asymmetry is formed as well as a different environment created for those already present. Also, the effect on the apparent partition coefficient of adding bisulfite ion has been measured. A carbonyl adduct would be expected to increase greatly the compound's water-solubility and thus markedly change its partition in favor of the aqueous phase.

Table I summarizes the optical rotation data. For both ketonic (dihydrocodeinone and codeinone) and non-ketonic (thebaine and codeine) compounds, there was essentially no variation in rotation as the pH was changed from 1 to 5 in the absence of bisulfite. This is to be expected, since in this range of acidity these compounds are completely in the ammonium salt form. Addition of bisulfite caused no change in the rotation of the non-ketonic compounds, as was anticipated, since the anion is in no way contributing to the rotation. However, in the case of the ketonic com-

pounds, there is a marked change in rotation in the presence of bisulfite, and this change can best be explained by the formation of bisulfite adducts.

The partition coefficient data are given in Table II. Apparent partition coefficients were determined experimentally for several ketonic and non-ketonic codeine derivatives between benzene and aqueous phosphate and bisulfite solutions buffered at pH7 and of the same ionic strength. Whereas the non-ketonic compounds exhibited only very minor differences in apparent partition coefficient in the two systems, dihydrocodeinone and codeinone show a tremendous increase in solubility in the aqueous phase as the buffer is changed from phosphate to bisulfite. This increase in solubility of the ketonic compounds in the presence of bisulfite again can best be explained by the formation of bisulfite adducts. Thus the behavior of the specific rotation and aqueous solubility of codeinone and dihydrocodeinone upon addition of bisulfite constitutes proof that these substances form bisulfite adducts.[5]

It was also of interest to see if the ketones could be recovered from their aqueous bisulfite solutions, since this would be a necessary corollary if the bisulfite procedure was to be used successfully in purification. When a solution of dihydrocodeinone in aqueous bisulfite was made alkaline with sodium carbonate and extracted with benzene, a

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(5) An explanation for the lack of bisulfite-adduct formation in the case of 6-keto-13-vinyloctahydromethylmorphenol (ref. 3) may be its extreme insolubility in water.

quantitative recovery of dihydrocodeinone was obtained on evaporation of the benzene. However, this same procedure with codeinone left all the codeinone in the aqueous phase. If basification was accomplished instead with sodium hydroxide and the alkaline (pH13) solution shaken continuously over a 20 hour period with chloroform (replacing the chloroform with fresh portions four times), codeinone could be recovered in 87% yield (crude) from the chloroform extracts. This stability to carbonate and decomposition by sodium hydroxide is a behavior frequently encountered with the bisulfite adducts of α,β-unsaturated carbonyl compounds when addition has taken place at the conjugate carbon-carbon double bond,[6] and in the case of codeinone indicates that addition has at least occurred at the 7,8 double bond.

The above data suggest that aqueous bisulfite solutions may be of value for separating ketonic from non-ketonic substances in the morphine series, and also for separating α,β-unsaturated from saturated ketones.

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(6) F. Tiemann, Ber., 31, 3297 (1898); E. Knoevenagel, ibid., 37 4038 (1904).

Table I

Specific Rotations of Some Ketonic and Non-ketonic Codeine Derivatives in the Absence and Presence of Bisulfite

Compound	pK_a'	pH 1.0		pH 1.5		pH 5		
		1M $KHSO_4$		1M $KHSO_4$+1M $NaHSO_3$			1M HOAc+1M NaOAc	1M $NaHSO_3$
		NH^+/N[a]	$[\alpha]_D^{25}$	NH^+/N[a]	$[\alpha]_D^{25}$	NH^+/N[a]	$[\alpha]_D^{25}$	$[\alpha]_D^{25}$
Dihydrocodeinone	7.95[b]	9.1×10^6	-143	2.9×10^6	-156	9.1×10^2	-143	-163
Codeinone	7.36[c]	2.3×10^6	-195[d]	7.3×10^5	-321[d]	2.3×10^2	-195[d]	-100[d]
Thebaine	8.15[e]	1.4×10^7	-204[f]	4.5×10^6	-203[f]	1.4×10^3	-204[f]	-203[f]
Codeine	8.04[c]	1.1×10^7	-131	3.5×10^6	-131	1.1×10^3	-133	-129

[a] Ratio of ammonium salt form to free base; [b] Ref. 4; [c] Determined by solution in excess hydrochloric acid and potentiometric titration with sodium hydroxide; [d] Initial value--on standing the rotation changed due to conversion to other products (S. P. Findlay and L. F. Small, J. Am. Chem. Soc., 73, 4001 (1951); [e] I. M. Kolthoff, Biochem. Ztschr., 162, 289 (1951); [f] Initial value--on standing rotation slowly changed.

Table II

Partition Coefficients of Some Ketonic and Non-ketonic Codeine Derivatives in the Absence and Presence of Bisulfite

Compound	$K_1' = \frac{\text{conc. in benzene}}{\text{conc. in } H_2PO_4^-,\ HPO_4^{=}}$ [a]	$K_2' = \frac{\text{conc. in benzene}}{\text{conc. in } HSO_3^-,\ SO_3^{=}}$ [a]	K_1'/K_2'
Dihydrocodeinone	3.0	0.20	15
Codeinone	7.4	0.30	24.7
Δ^6-Dihydrothebaine	13.7	12.9	1.1
Codeine	1.04	0.62	1.7
Dihydrocodeine	0.33	0.20	1.7

[a] pH7.