2.98–3.31 (2 H, m, CH_2NPh), 3.52–4.00 (1 H, m, $CHCH_3$), 6.55–7.35 (5 H, m, aromatic protons). The hydrochloride was recrystallized from ethanol–ether to give a colorless powder, mp 208–212° dec. *Anal.* Calcd for $C_{12}H_{18}N_2 \cdot 2HCl$: C, 54.76; H, 7.66; N, 10.64. Found: C, 54.53; H, 7.88; N, 10.47.

Finally, the elution with 10% ethanol–chloroform was evaporated to leave 1.1 g (9.7%) of *N*-metahyl-*N*-(2-methylaminoethyl)aniline (**8c**): nmr (CCl_4) δ 2.45 (3 H, s, $NHCH_3$), 2.78 (2 H, t, CH_2NHCH_3), 2.98 (3 H, s, $PhNCH_3$), 3.44 (2 H, t, $PhNCH_2$), 6.45–7.3 (5 H, m, aromatic protons). The hydrochloride was recrystallized from ethanol–ether to give pale yellowish needles, mp 159–160°. *Anal.* Calcd for $C_{10}H_{16}N_2 \cdot HCl$: C, 59.84; H, 8.54; N, 13.96. Found: C, 59.69; H, 8.69; N, 13.74.

The Reaction of 2-(*N*-Methyl-*N*-phenyl)aminoethanol (8a) with Sodium Amide.—A mixture of 1.5 g of **8a** and 0.78 g of sodium amide was stirred for 4 hr at 150–160° in the presence of 2.4 g of *N*-methylmorpholine as solvent. After cooling, the excess sodium amide was decomposed with saturated ammonium chloride solution under ice cooling and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed on silicic acid using chloroform as an eluent. Evaporation of the solvent afforded 45 mg (4.2%) of **7a**, the spectroscopic data of which were identical with those of the authentic specimen.

Registry No.—**4b**, 33905-37-2; **7f**, 33905-38-3; **8b**, 33905-39-4; **8b** HBr, 33905-40-7; **8c**, 2412-49-9; **8c** HCl, 33905-42-9; **8d**, 33905-43-0; **8d** oxalate, 33905-44-1; **8e**, 92-50-2; **8e** picrate, 33905-46-3; **8g**, 33905-47-4; **9**, 33905-48-5; **9** HCl, 33905-49-6; bromobenzene, 108-86-1; *o*-chloroanisole, 766-51-8; *o*-benzyloxychlorobenzene, 949-38-2; *N*-methylmorpholine, 109-02-4; *N*-ethylmorpholine, 100-74-3; *N*-propylmorpholine, 23949-50-0; *N*-benzylmorpholine, 10316-00-4; *N*-methylpiperidine, 626-67-5; *N,N'*-dimethylpiperazine, 106-58-1.

Acknowledgments.—We thank President A. Yanagisawa and Director O. Takagi of the Grelan Pharmaceutical Co., Ltd., for their encouragement. We also thank Dr. K. Fukumoto and Dr. S. Shibuya, Pharmaceutical Institute, Tohoku University, for their kind suggestions.

A Bisulfite Mediated Oxidation of Thebaine. Formation of 6-*O*-Demethylsalutaridine[1]

LEONARD F. BJELDANES AND HENRY RAPOPORT*

Department of Chemistry, University of California, Berkeley, California 94720

Received October 14, 1971

A method for removal of ketonic compounds from thebaine and other nonketonic alkaloids involves treatment of such a mixture with an aqueous sodium bisulfite solution.[2] Water-soluble bisulfite addition products are readily separated from the thebaine by simple extraction. We have noted, however, that in certain instances the yields of recovered thebaine (**1**) were unexpectedly low. Further study indicated that thebaine was consumed under the extraction conditions only when the process was carried out in the presence of oxygen.

Thus, by reaction with aqueous sodium bisulfite (pH 4) and oxygen, thebaine (**1**) is oxidized to 6-*O*-demethylsalutaridine ($\Delta^{8(14)}$-7-oxothebainone) (**7**). The identity of the product was established by direct comparison with material obtained by the action of alkali on 14-bromocodeinone.[3,4] Thebaine is unaffected by a sodium phosphate buffer, pH 4, in the presence of oxygen, or sodium bisulfite buffer, pH 4, in the absence of oxygen. Furthermore, when oxygen is excluded, thebaine is unaffected by a bisulfite solution which has been previously shaken for 2 hr in the presence of oxygen. The possibility that the production of **7** is dependent on the alkaline treatment in the isolation procedure was eliminated, since, on omitting this process, **7** was produced in undiminished yield.

To determine the origin of the oxygen functions, ^{18}O tracer techniques were applied. An initial series of experiments was conducted to determine the extent of exchange of the carbonyl functions with water. The product **7** was subjected to the conditions under which it was formed except that the bisulfite solution used was prepared with ^{18}O-enriched water. Mass spectrometric analysis[5] of the reisolated product indicated that exchange at both carbonyls had occurred to the extent of about 10% after 1 hr, 40% after 3 hr, and 95% after 24 hr. Therefore, isotopic studies became definitive if the reaction time was reduced to 1 hr, a process which was feasible since the product **7** was still isolated in sufficient yield (15%).

The possibility that either water or molecular oxygen was the source of the oxygen functionalities in **7** was explored by conducting the oxidation reaction first with ^{18}O-enriched water and then with ^{18}O-enriched O_2. Mass spectrometric analysis indicated that the ^{18}O enrichment of the product obtained from the first experiment was due only to exchange of the carbonyl oxygen atoms with the $H_2{}^{18}O$. The product obtained from the reaction in an $^{18}O_2$ atmosphere showed no ^{18}O enrichment.

The remaining possible source of the oxygen which is incorporated into 6-*O*-demethylsalutaridine is bisulfite. Since it was previously established that water is not incorporated into the product, testing the bisulfite hypothesis was somewhat simplified. Thus, to prepare ^{18}O-labeled bisulfite a 1 *N* sodium bisulfite solution was prepared using ^{18}O-enriched water, and it was stirred under nitrogen for 28 hr. Thebaine was then added to this solution and allowed to react as usual. Analysis of the product indicated a 100% isotopic enrichment of one oxygen atom. The initial bisulfite $H_2{}^{18}O$ exchange period was then increased to 48 hr and subsequent oxidation of thebaine in this solution produced a product which was again 100% isotopically enriched for one oxygen atom. The fact that the same enrichment was obtained with solutions in which exchange was allowed to occur for different periods establishes that the HSO_3^-–$H_2{}^{18}O$ exchange was complete within 28 hr. Furthermore, it eliminates the possibility that the result obtained with the 28-hr exchange solution could have been due to a 50% isotopic enrichment of both carbonyl oxygens in the product.

(1) Supported in part by Grant MH 12797 from the National Institute of Mental Health, U. S. Public Health Service.

(2) H. Rapoport, C. H. Lovell, H. R. Reist, and M. E. Warren, Jr., *J. Amer. Chem. Soc.*, **89**, 1942 (1967).

(3) W. Fleischhacker, F. Vieböck, and F. Zeidler, *Monatsh. Chem.*, **101**, 1215 (1970).

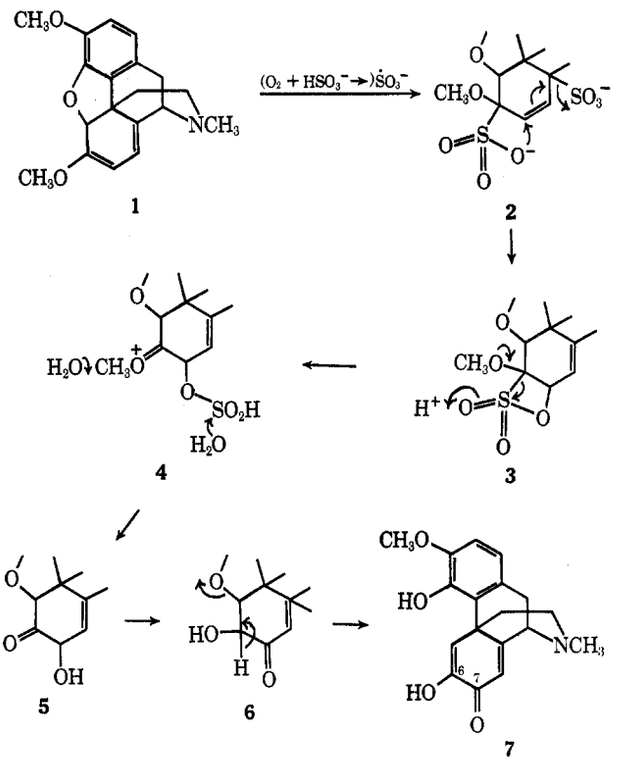
(4) D. E. Rearick and M. Gates, *Tetrahedron Lett.*, 507 (1970).

(5) C. D. Snyder and H. Rapoport, *Biochemistry*, **7**, 2318 (1968); **9**, 2033 (1970).

For mechanistic considerations, since only one oxygen atom is incorporated, it is reasonable to assume that it is the oxygen atom at C-7 of **7** which is incorporated from bisulfite. Any mechanism proposed for this transformation must be consistent with the following observations: (a) thebaine is unaffected by a bisulfite solution in the absence of O_2; (b) molecular oxygen must be present during the course of the reaction in order for the conversion to occur; and (c) the source of the oxygen atom which is incorporated into the product is bisulfite.

These conditions have been incorporated in the mechanism proposed in Scheme I. The postulated first

SCHEME I



step is the 1,4 addition of two bisulfite radical ions to form the disulfonate **2**. The radical ions in turn are proposed as formed by the action of oxygen on aqueous bisulfite, conditions which are well documented to convert olefins to sulfonates and disulfonates[6] *via* radical intermediates. Reaction then proceeds *via* displacement of the sulfonate at position 14 to form the β-sultone **3**. The latter then collapses to **4** which is hydrolyzed to the α-hydroxy ketone **5**. Tautomeric rearrangement to **6** is followed by β elimination to form the morphinandienone, 6-*O*-demethylsalutaridine (**7**). Clearly, alternatives exist for the route from β-sultone **3** to dienone **7** involving essentially the same principles.

Experimental Section

6-*O*-Demethylsalutaridine (7).—A solution of 9 g of thebaine (**1**) in 250 ml of 1 *N* sodium bisulfite was shaken for 3 hr under an atmosphere of oxygen. The solution was then brought to pH 11 with 30% aqueous sodium hydroxide and extracted with two 75-ml portions of benzene–hexane, 1:1. After drying (Na_2SO_4) and removal of the solvent, the first extract produced 0.67 g of a 2:1 mixture of thebaine and **7** and the second extract produced 0.14 g of a 3:2 mixture of the thebaine and **7**. The aqueous phase was adjusted to pH 8.0 with concentrated HCl and extracted with methylene chloride (four 75-ml portions). The extracts were combined and dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield **7**, 5.10 g (64%) based on thebaine consumed, as a white solid after crystallization from benzene, mp 184–186° turning red-brown, identical with material prepared by the action of alkali on 14-bromocodeinone.[3,4]

Isotopic Experiments. A. ^{18}O Determinations.—Reactions were carried out for 1 hr in the presence of $H_2{}^{18}O$, $^{18}O_2$, or $NaHS^{18}O_3$, and the purified product was examined for ^{18}O by nonoxidative pyrolysis as previously described.[5] The ^{18}O content of the carbon monoxide produced was determined by mass spectrometry. Pyrolysis of an equal amount of unlabeled product provided a natural abundance background determination. The ^{18}O content of the $H_2{}^{18}O$ and O_2 used are 2.0 and 1.6%, respectively. All isotope assays were performed using a Consolidated Electrodynamics Corp. Model 130 mass spectrometer.

B. Apparatus.—The oxidations were conducted in an apparatus[7] which is commonly used for hydrogenation at atmospheric pressure, fitted for the introduction of oxygen instead of hydrogen. All experiments using isotopically enriched materials were conducted with this apparatus.

Registry No.—**7**, 27669-33-6.

(6) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965, p 150.

(7) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 228.

A Novel Intramolecular Rearrangement of a 1,4 Dipole

KENNETH B. WAGENER, S. RICHARD TURNER, AND GEORGE B. BUTLER*

Department of Chemistry, University of Florida, Gainesville, Florida 32601

Received September 14, 1971

While cycloaddition reactions of 1,4 dipoles are well documented,[1,2] intramolecular rearrangements of these dipoles have rarely been observed.[1] We wish to report experimental evidence for a unique 1,4-dipolar intramolecular rearrangement resulting from the reaction of 4-phenyl-1,2,4-triazoline-3,5-dione[3] (**1**) with vinyl esters.

Equimolar quantities of **1** and vinyl acetate (**2**) react in methylene chloride at 60° yielding 1-formyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**3**) exclusively. Isopropenyl acetate (**4**) reacts in a similar manner to give 1-acetylmethyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**5**).

A plausible mechanism for these reactions would involve the unusually stable 1,4 dipole[4] (**6**) as the reactive intermediate, formed *via* initial reaction of the electron-poor nitrogen double bond with the electron-rich double bond of the vinyl ester. The 1,4 dipole, once formed, could undergo an intramolecular nucleophilic attack by nitrogen on the carbonyl carbon displacing the ester oxygen (path a, Scheme I). Intramolecular nucleophilic attack by nitrogen is sterically hindered by large R_2 groups, decreasing the relative yield of the product

(1) R. Huisgen, *Z. Chem.*, **8**, 290 (1968).

(2) E. K. Von Gustorf, D. V. White, B. Kim, K. Hess, and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970).

(3) J. C. Stickler and W. H. Pirkle, *ibid.*, **31**, 3444 (1966).

(4) 1,4 dipoles of a similar nature have previously been reported.[5]

(5) (a) Ref 2; (b) S. R. Turner, L. J. Guilbault, and G. B. Butler, *J. Org. Chem.*, **36**, 2838 (1971).