TABLE I
A VALUE OF ND_2 AS A FUNCTION OF CONCENTRATION AND SOLVENT AT −93°

Solvent	Concn, mol/l.	K[a]	A value, kcal/mol
CD_3OD	0.5	34 ± 5	1.3 ± 0.1
	1.0	42 ± 7	1.3 ± 0.1
	1.5	56 ± 9	1.4 ± 0.1
	2.0	55 ± 9	1.4 ± 0.1
50% Pyridine–50% CH_2CHCl (v/v)	2.0	26 ± 4	1.2 ± 0.1
50% CD_2Cl_2–50% toluene-d_8 (v/v)	2.0	55 ± 10	1.4 ± 0.1

[a] According to eq 1; the error assigned to K is the maximum deviation in the measured value.

not change appreciably with concentration in CD_3OD (Table I), K (eq 1) does increase at increasing concentrations of **1**, suggesting an increasing degree of self-association by **1** in preference to complexation by CD_3OD. In those solvents which do not form as strong hydrogen bonds, *e.g.*, 50% pyridine–50% CH_2CHCl (v/v), the equatorial ND_2 conformational preference is reduced slightly in agreement with previous results.[4]

It is then instructive to compare the A value of the amino group to other functionalities having nitrogen bonded to the cyclohexane ring (Table II).[7] Although

TABLE II
PERTINENT A VALUES

Group	A Value, kcal/mol
$-ND_2$	1.2[a]
$-NO_2$	1.1[b]
$-N{=}C{=}N\text{-}C_6H_{11}$	1.0[b,c]
$-N{=}C{=}O$	0.51[b]
$-N{=}C{=}S$	0.28[b]
$-N{\equiv}C$	0.21[b]

[a] 2.0 M in 50% pyridine–50% CH_2CHCl at −93°. [b] 2.0 M in CS_2 at −80° except NO_2 at −90°; see ref 7. [c] See ref 8.

unique hybridization of nitrogen in the case of –NCO, –NCS, and $-N{\equiv}C$ apparently leads to more substituent cylindrical symmetry and a relatively low A value,[8] the A value for ND_2 is only slightly larger than that for $-NO_2$ or $-N{=}C{=}N{-}C_6H_{11}$ (Table II). Indeed, the higher A value for $-ND_2$ as compared to $-NO_2$ may reflect stronger solvent complexation of $-ND_2$ *via* hydrogen bonding and an effectively larger group.

Experimental Section

Nmr spectra were obtained using a Varian Associates HR-60A spectrometer equipped with a custom-built variable temperature probe or using a Varian HA-100 spectrometer equipped with the Varian variable temperature probe and accessories. Temperature measurement was performed using a copper–constantan thermocouple inserted into the sample (HA-100) or permanently in place in the probe (HR-60A) and is accurate to ±0.3° at the sample.

Registry No.—Cyclohexylamine-$N,N,2,2,6,6$-d_6, 33885-12-0.

Acknowledgment.—We are grateful to U. S. Army Natick Laboratories for use of a Varian HA-100 nmr spectrometer.

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Studies on the Syntheses of Heterocyclic Compounds. CDLX.[1] Benzyne Reaction. XIII.[2] Benzyne Reaction of Halogenobenzenes with *N*-Alkylmorpholines

T. KAMETANI,* K. KIGASAWA, M. HIIRAGI, AND T. AOYAMA

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan, and Research Laboratories, Grelan Pharmaceutical Company, Ltd., Tokyo, Japan

Received October 28, 1971

In previous papers,[3-5] we reported the benzyne reaction of a number of ortho-substituted halogenobenzenes with acetonitrile or phenylacetonitrile in various organic solvents together with the appropriate amines in the presence of sodium amide to give the desired meta-substituted phenylacetonitriles in addition to the meta-substituted amino compounds. During these investigations, when *N*-methylmorpholine was used as solvent in the benzyne reaction of *o*-chloroanisole, 3-methoxy-*N*-methylaniline (**7b**)[3] was obtained as an unusual product in comparatively good yield. Although the formation of Stevens type[6-11] or Sommelet type[12] rearranged products by the reaction of amines with benzyne has been reported, formation of the *N*-alkylaniline derivative by the benzyne reaction of halogenobenzene with N-substituted alicyclic amines has not previously been described, and we have therefore studied several other cases of this reaction.

The benzyne reaction of bromobenzene, *o*-chloroanisole, and *o*-benzyloxychlorobenzene with *N*-methyl-, *N*-ethyl-, *N*-propyl-, *N*-benzylmorpholine, *N*-methylpiperidine, and *N,N'*-dimethylpiperazine was examined and found to give *N*-alkylaniline derivatives. Furthermore, in the case of the benzyne reaction of the halogenobenzenes with *N*-alkylmorpholines, 2-(*N*-alkyl-*N*-phenyl)aminoethanols were obtained in addition to the desired products. All the known products were identified with authentic specimens by comparison of spectroscopic data. The structures of the unknown products were determined by microanalyses and nmr, ir, and mass spectra. These results are shown in Table I. In the benzyne reaction of bromobenzene with *N*-methylmorpholine, when a mixture of bromo-

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(2) Part XII: T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.*, 2712 (1971).
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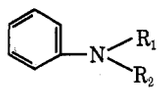
TABLE I

BENZYNE REACTION PRODUCTS OF BROMOBENZENE WITH *N*-ALKYLMORPHOLINE, *N,N'*-DIMETHYLPIPERAZINE, AND *N*-METHYLPIPERIDINE[a]



Amine	Compd	R_1	R_2	Yield, %[b]
N-Methylmorpholine	**7a**	CH_3	H	12.8[c]
	8a	CH_3	CH_2CH_2OH	13.1
N-Methylmorpholine	**7a**	CH_3	H	13.4[d]
	8a	CH_3	CH_2CH_2OH	13.8
N-Methylmorpholine	**7a**	CH_3	H	32.8[e]
	8a	CH_3	CH_2CH_2OH	21.6
N-Ethylmorpholine	**7c**	CH_2CH_3	H	24.4
	8e	CH_2CH_3	CH_2CH_2OH	12.4
N-*n*-Propylmorpholine	**7d**	$CH_2CH_2CH_3$	H	21.9
	8f	$CH_2CH_2CH_3$	CH_2CH_2OH	3.2
N-Benzylmorpholine	**7e**	CH_2Ph	H	19.4
	8g	CH_2Ph	CH_2CH_2OH	6.2
	4	CH_2Ph	$CH_2CH_2OCH{=}CH_2$	12.1
N,N'-Dimethylpiperazine	**7a**	CH_3	H	1.2
	8c	CH_3	$CH_2CH_2NHCH_3$	9.6
	9	$-CH_2CH_2N(CH_3)CH_2CH(CH_3)-$		2.5
N-Methylpiperidine	**10**	$-(CH_2)_5-$		3.2

[a] All the reactions were carried out under reflux, although *N*-benzylmorpholine was allowed to react at 145–155°. The reaction time was 4 hr in all reactions except that with *N*-methylpiperidine which was 6 hr. [b] Ratio of bromobenzene:amine:$NaNH_2$: (c) 1:2:1.5; (d) 1:2:2; (e) 1:4:4.

benzene, *N*-methylmorpholine, and sodium amide (1:4:4) was used, *N*-methylaniline (**7a**) and 2-(*N*-methyl-*N*-phenyl)aminoethanol (**8a**) were formed in better yield than under other conditions.

In the case of the benzyne reaction of 2-benzyloxychlorobenzene with *N*-methylmorpholine, *N*-methyl-*N*-(2-vinyloxyethyl)aniline (**4a**), and 2-[*N*-methyl-*N*-(3-methylphenyl)]aminoethanol (**8b**) were obtained in addition to the desired product, 3-benzyloxy-*N*-methylaniline (**7f**). Benzyne reaction of bromobenzene with *N,N'*-dimethylpiperazine afforded *N*-methyl-*N*-(β-methylaminoethyl)aniline (**8c**) together with **7a** and the Stevens type rearranged product, 2,4-dimethyl-1-phenylpiperazine (**9**). Furthermore, piperidinobenzene was obtained on the benzyne reaction of bromobenzene with *N*-methylpiperidine as reported by Wittig.[6]

The mechanism to explain the formation of these products remained unclear but would involve the reaction of the base with the quaternary salt (**2**) as shown in Scheme I.

Thus, *N*-alkylanilines and *m*-alkoxy-*N*-alkylanilines were obtained by application of the benzyne reaction of bromobenzene and *o*-alkoxyhalogenobenzenes with the appropriate tertiary cyclic amines.

Experimental Section[13]

***N*-Methylaniline (7a) (Benzyne Reaction of Bromobenzene with *N*-Methylmorpholine).**—To a stirred mixture of 25 g of *N*-methylmorpholine and 10 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued under reflux for 3 hr, the excess sodium amide was decomposed with saturated ammonium chloride solution under ice cooling. After the addition of water, the mixture was extracted with ether. The organic layer was extracted with 10% HCl. The acidic extract was made basic with 10% NaOH and extracted with ether. The ethereal 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 first fraction afforded 2.3 g (32.8%) of **7a** as a pale yellowish oil, which was identified by comparison of spectroscopic data with those of the authentic sample. Removal of the second fraction gave 2.07 g (21.6%) of **8a** as a pale yellowish oil, the spectroscopic data of which were identical with those of the authentic specimen:[14] nmr (CCl_4) δ 2.68 (3 H, s, NCH_3), 3.08 (2 H, t NCH_2CH_2OH), 3.38 (2 H, t, NCH_2CH_2OH), 6.10–6.81 (5 H, m, aromatic protons).

3-Methoxy-*N*-methylaniline (7b).—To a stirred mixture of 28 g of *N*-methylmorpholine and 11 g of sodium amide, 10 g of *o*-chloroanisole was added under reflux and the mixture was refluxed with stirring for 4 hr. After the reaction, the mixture was worked up as usual and the crude product was chromatographed on silicic acid using chloroform as an eluent. The first eluent gave 2.1 g (21.9%) of **7b** as a yellow oil, which was identical in ir and nmr spectral comparison with the authentic sample.[3] The second eluent afforded 2.7 g (21.1%) of **8d** as a yellow oil: nmr (CCl_4) δ 2.98 (3 H, s, NCH_3), 3.42 (2 H, t, CH_2CH_2OH), 3.72 (2 H, t, CH_2CH_2OH), 3.78 (3 H, s, OCH_3), 6.02–7.00 (4 H, m, aromatic protons). The oxalate gave colorless needles from ethanol–ether, mp 87–88°. *Anal.* Calcd for $C_{10}H_{15}NO_2 \cdot C_2H_2O_4$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.28; H, 6.00; N, 5.21.

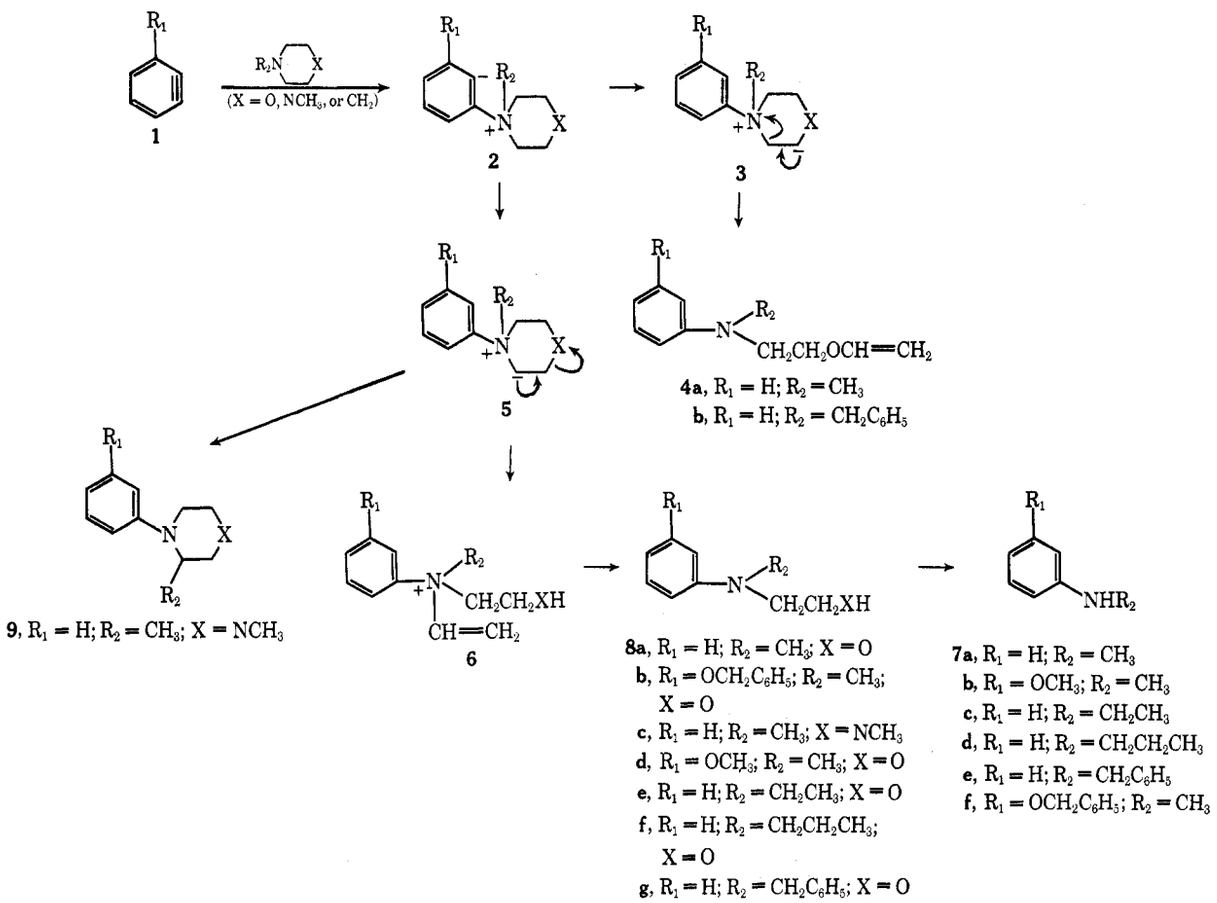
***N*-Ethylaniline (7c) (Benzyne Reaction of Bromobenzene with *N*-Ethylmorpholine).**—To a stirred mixture of 25 g of *N*-ethylmorpholine and 8.4 g of sodium amide was dropwise added 8.5 g of bromobenzene under reflux. After the stirring had been continued under reflux for 4 hr, the mixture was worked up as usual and the crude product was subjected to silicic acid chromatography. The first chloroform eluent gave 1.6 g (24.4%) of **7c** as a pale yellowish oil, bp 75–80° (15 mm), the hydrochloride of which was recrystallized from ethanol–ether to afford colorless needles, mp 174–177°; this was identical with the authentic specimen by comparison of spctroscopic data and melting point. The second eluent gave 1.1 g (12.4%) of **8e** as a pale yellow oil: nmr (CCl_4) δ 1.12 (3 H, t, CH_2CH_3), 3.41 (2 H, q, CH_2CH_3), 3.43 (2 H, t, CH_2CH_2OH), 3.78 (2 H, t, CH_2CH_2OH), 6.55–7.41 (5 H, m, aromatic protons). The picrate formed yellow prisms from ethanol–ether, mp 103.5–104°. *Anal.* Calcd for for $C_{10}H_{15}NO \cdot C_6H_3N_3O_7$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.62; H, 4.56; N, 14.05.

***N*-*n*-Propylaniline (7d).**—To a stirred mixture of 2.8 g of *N*-*n*-propylmorpholine and 8.4 g of sodium amide was added 8.5 g

(13) Melting points and boiling points are not corrected; ir and nmr spectra were determined on a Shimazu spectrometer and JNM-MH-60 with tetramethylsilane as internal reference, respectively.

(14) W. Wilson, *J. Chem. Soc.*, 3524 (1952).

SCHEME I



of bromobenzene under reflux. After the stirring had been contined under reflux for 4 hr, the mixture was worked up as usual to give 1.6 g (21.9%) of **7d** as a pale yellowish oil, from the first chloroform eluent, bp 81–84° (16 mm), the hydrochloride of which was recrystallized from ethanol–ether to afford colorless needles, mp 145–147°; this was identified with the authentic specimen by comparison of spectroscopic data and melting point. The second chloroform eluent afforded 0.3 g (3.2%) of **8f** as a yellow oil: nmr (CCl_4) δ 0.91 (3 H, t, $CH_2CH_2CH_3$), 1.60 (2 H, sextet, $CH_2CH_2CH_3$), 3.31 (2 H, t, $CH_2CH_2CH_3$), 3.46 (2 H, t, CH_2CH_2OH), 3.75 (2 H, t, CH_2CH_2OH), 6.55–7.43 (5 H, m, aromatic protons). This sample was identical with the authentic sample prepared by Wilson's method[14] in ir and nmr spectral comparison.

***N*-Benzylaniline (7e).**—To a stirred mixture of 18 g of *N*-benzylmorpholine and 4 g of sodium amide was added 4 g of bromobenzene at 145–155°. After the stirring had been continued for 4 hr at the same temperature, the mixture was worked up as usual and the resulting oil was chromatographed on silicic acid using chloroform as an eluent. The first eluent gave 0.9 g (19.4%) of **7e** as a yellow oil, bp 170–190° (7 mm), the hydrochloride of which was recrystallized from ethanol to yield colorless plates, mp 212–214°; this was identical with the authentic specimen by comparison of spectroscopic data.

Evaporation of the second eluate afforded 0.7 g (12.1%) of *N*-benzyl-*N*-(2-vinyloxyethyl)aniline (**4b**) which was recrystallized from ethanol to afford colorless prisms: mp 88–89.5°; nmr (CCl_4) δ 2.05–2.62 (2 H, m, NCH_2–), 3.30–4.02 (4 H, m, $-CH_2OCH{=}CH_2$), 3.85 (2 H, s, NCH_2Ph), 4.48–4.95 (1 H, m, $CH{=}CH_2$), 6.35–7.40 (10 H, m, aromatic protons); mass spectrum *m/e* 253 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.23; H, 7.20; N, 5.71.

This third eluent gave 0.4 g (6.2%) of **8g** as a yellow oil: ir ν_{max}^{liquid} 3390 cm^{-1} (OH); nmr (CCl_4) δ 3.47 (2 H, t, CH_2CH_2OH), 3.66 (2 H, t, CH_2CH_2OH), 4.53 (2 H, s, CH_2Ph), 6.50–7.41 (10 H, m, aromatic protons).

***N*-Methyl-3-benzyloxyaniline (7f).**—To a stirred mixture of 16 g of *N*-methylmorpholine and 4.1 g of sodium amide was added dropwise 15.3 g of 2-benzyloxychlorobenzene under reflux. After the stirring had been continued for 4.5 hr under reflux, the mixture was worked up as usual, and the crude product was distilled *in vacuo* to give an oil, bp 170–190° (0.3 mm), which was chromatographed on silicic acid using chloroform as an eluent. Evaporation of the first elution gave 1.6 g (10.8%) of **7f** as a pale yellowish oil: nmr (CCl_4) δ 2.67 (3 H, s, NCH_3), 4.96 (2 H, s, OCH_2Ph), 5.98–7.50 (9 H, m, aromatic protons). The picrate was recrystallized from ethanol to give yellowish prisms, mp 137.5–138.5° (lit.[15] mp 138–138.5°). Removal of the second elution afforded 550 mg (3%) of **8b** as a pale yellowish oil: nmr (CCl_4) δ 2.78 (3 H, s, NCH_3), 3.26 (2 H, t, NCH_2CH_2OH), 3.57 (2 H, t, NCH_2CH_2OH), 4.93 (2 H, s, OCH_2Ph), 6.10–7.45 (9 H, m, aromatic protons). The hydrobromide was recrystallized from isopropyl alcohol–ether to give colorless needles, mp 78–80°. *Anal.* Calcd for $C_{16}H_{19}NO_2 \cdot HBr$: C, 56.81; H, 5.96; N, 4.14. Found: C, 56.55; H, 5.91; N, 4.41.

***N*-Phenylpiperidine (10).**—To a mixture of 12.5 g of *N*-methylpiperidine and 3.7 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued for 6 hr under reflux, the mixture was worked up as usual to give **10**, which was purified as its picrate to give 450 mg (1.9%) of yellow prisms, mp 144–145° (lit.[16] mp 145–146°).

Benzyne Reaction of Bromobenzene with *N*,*N*′-Dimethylpiperazine.—To a stirred mixture of 20 g of *N*,*N*′-dimethylpiperazine and 10 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued for 4 hr under reflux, the mixture was worked up as usual and the crude product was chromatographed on silicic acid. Removal of the elution with chloroform afforded 80 mg (1.2%) of **7a**, the spectroscopic data of which were identical with those of the authentic specimen. Evaporation of the successive elution with 5% ethanol–chloroform gave 300 mg (2.5%) of 2,4-dimethyl-1-phenylpiperazine (**9**): nmr (CCl_4) δ 1.08 (3 H, d, $CHCH_3$), 2.01–2.95 [4 H, m, $-CH_2N(CH_3)CH_2-$], 2.30 (3 H, s, NCH_3),

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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.

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