N-Acetyl-2,5-diiodohistamine.—The reaction of 0.5 g of N-acetylhistamine with 1.52 g of I_2 was performed as described for the other compounds. After addition of KIO_3 and extraction of I_2, alkalinization to pH 8 produced a white voluminous precipitate. The compound was obtained in a final yield of 0.45 g (34%), melted at 214–216°, and gave one spot on tlc with R_f 0.80. *Anal.* ($C_7H_9I_2N_3O \cdot H_2O$) C, H, I, N.

Acknowledgments.—We wish to thank Professors P. C. Ferreira and M. Motidome for valuable advice and help in the preparation of N-acetylhistamine, Professor T. B. Paiva for the biological assays, and Mr. A. Hashimoto for the determination of nmr spectra.

Syntheses of Benzomorphan and Related Compounds. II.[1] The Debenzylation of Quaternary Ammonium Salts with Thiophenol[2]

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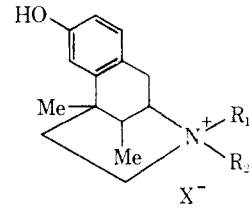
Shamma and his coworkers[3] had successfully employed sodium thiophenoxide in the demethylation of a variety of quaternary salts and proposed that the reaction proceeded by SN2-type displacement. In view of the fact that the benzyl or allyl are much better leaving groups than methyl in nucleophillic displacement, we have investigated the selective N-debenzylation or N-deallylation of a number of quaternary ammonium salts with thiophenol in the presence of 5–20% aqueous NaOH.

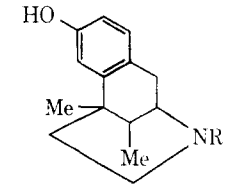
From various N-benzylammonium salts with other N-alkyl groups, the corresponding debenzylated tertiary amines were obtained selectively as shown in Table I. The cleavage of C–N single bond by pyrolysis[4] or by treatment with inorganic salts containing S[5] has been known in the case of both allylic and benzylic salts. Therefore, an investigation was made whether either selective debenzylation or deallylation would occur in the several N-allyl-N-benzylammonium salts and a greater ratio of deallylation to debenzylation was observed in all cases in Table II.

All the tertiary amines obtained in Tables I and II were found to be identical with authentic samples as free bases and/or their salts by mixture melting point, ir spectral, and tlc comparisons.[4-14] The unknown ammonium salts were confirmed by microanalysis. Quite naturally, benzyl phenyl thioether[15] and/or allyl phenyl thioether[16] were detected as by-products. In this case, NaOH is thought to react with an equimolar amount of thiophenol (*cf.* reaction 9 in Table II) in the first place, and the resulting thiophenoxide anion is an effective nucleophile but not basic enough to cause Hofmann degradation.

As an application of this method, a modified synthesis of pentazocine (I),[17,18] namely, 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3,3-dimethylallyl)-3-benzazocine, a very effective analgetic agent with no dependence liability, has been investigated. In the previous paper,[1] we have already reported the syntheses of several quaternary ammonium salts (II–IV) which were important intermediates for pentazocine. We also have reported that the reductive debenzylation of IV by catalytic hydrogenation afforded the expected pentazocine, but simultaneous reduction of the double bond occurred. Not surprisingly, treatment of two quaternary ammonium salts (II and III) with thiophenol in aqueous NaOH gave only V.[17] In the case of IV, the same treatment as above afforded a mixture of I (51.0%) and VI (24.4%) which were also formed in 58.7% (I) and 24.7% (VI) yields by heating of IV with excess sodium thiophenoxide in an organic solvent.



II, X = I; R_1 = Me; R_2 = CH_2Ph
III, X = I; R_1 = Me; R_2 = $CH_2CH{=}C(Me)_2$
IV, X = Br; R_1 = CH_2Ph; R_2 = $CH_2CH{=}C(Me)_2$



I, R = $CH_2CH{=}C(Me)_2$
V, R = Me
VI, R = CH_2Ph

Thus, this reaction seems to provide a useful method for debenzylation and deallylation. Further application of this reaction is in progress, especially aimed at the debenzylation of the compounds having other reducible functions together with an N-benzyl group.

Experimental Section[19]

N-Benzyl Quaternary Ammonium Salts. (1) Reaction of N-Alkyl Tertiary Amines with Benzyl Halide.—A mixture of 1 molar equiv of tertiary amine and benzyl halide in dry PhH or absolute EtOH was heated under reflux on a water bath for several hours. After cooling, excess Et_2O was added to the reaction mixture, which was set aside to precipitate the crystals. Collection by filtration, followed by recrystallization, gave the corresponding ammonium salts in 71–98% yields as shown in Table I.

(2) Reaction of N-Benzyl Tertiary Amines with Allyl Bromide.—A mixture of 1 molar equiv of tertiary amine and allyl bromide in dry PhH was refluxed on a water bath for 1–2 hr or kept at room temperature for 1–2 days; the precipitated crystals were

(1) Part I: T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, N. Wagatsuma, and K. Wakisaka, *J. Heterocyclic Chem.*, **6**, 43 (1969).

(2) This forms part CCLXXXXV of studies on the Syntheses of Heterocyclic Compounds. One part of this work is reported: T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, and K. Wakisaka, *Tetrahedron Letters*, 635 (1969).

(3) M. Shamma, N. C. Deno, and J. F. Remar, *ibid.*, 1375 (1966).

(4) D. S. Tarbell and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **65**, 231 (1943).

(5) H. R. Snyder and J. C. Speck, *ibid.*, **61**, 668, 2895 (1939).

(6) T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 1932 (1932).

(7) J. A. Barltrop and D. A. H. Taylor, *ibid.*, 108 (1951).

(8) J. L. Dunn and T. S. Stevens, *ibid.*, 1926 (1932).

(9) A. Partheil and H. von Broich, *Ber.*, **30**, 618 (1897).

(10) T. J. King, *J. Chem. Soc.*, 898 (1951).

(11) J. V. Braun, *Ber.*, **37**, 2920 (1904); F. Hasse and R. Wolffenstein, *ibid.*, **37**, 3232 (1904).

(12) I. N. Nazarov, V. N. Rakcheeva, and L. I. Shmonina, *Zh. Obshch. Khim.*, **22**, 611 (1952); *Chem. Abstr.*, **47**, 5369 (1953).

(13) A. McConbrey and D. W. Mathieson, *J. Chem. Soc.*, 2851 (1951).

(14) L. Claison, *J. Prakt. Chem.*, [2] **105**, 76 (1923).

(15) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

(16) S. D. Hurd and H. Greengard, *ibid.*, **52**, 3356 (1930).

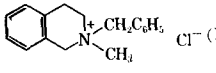
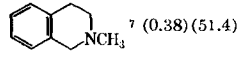
(17) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294, 1432 (1959).

(18) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pieson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

(19) All melting points and boiling points were not corrected.

TABLE I

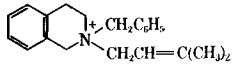
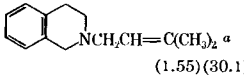
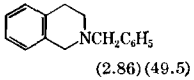
DEBENZYLATION OF QUATERNARY AMMONIUM SALTS

Reaction no.	Quaternary ammonium salts (g)	Mp, °C (solvent of recrystn)	Formula	Analyses	Thiophenol, g	Aq NaOH, ml (%)	Temp, °C	Time, hr	Tertiary amine (yield, g, %)
1	$(C_6H_5CH_2)_2{}^+N(CH_3)_2$ Cl^-[6] (2.61)	93–95 (*i*-PrOH)			5.5	10 (20)	90	5	$C_6H_5N(CH_3)_2$ (1.4) (85.1)
2	$(C_6H_5CH_2CH_2)(C_6H_5CH_2)^+N(CH_3)_2$ Cl^- (1.38)	169–172 (*i*-PrOH–Et_2O)	$C_{17}H_{22}ClN$	C, H, N	2.75	10 (20)	90	7	$C_6H_5CH_2CH_2N(CH_3)_2$ (0.52) (69.7)
3	$C_6H_5CH_2{}^+N(C_2H_5)_3$ Cl^- (1.9)	190–191 dec (*i*-PrOH–Et_2O)	$C_{13}H_{22}ClN$	C, H, N	3.0	10 (20)	90	10	$(CH_3CH_2)_3N$ (0.6) (22.1)
4	$(C_6H_5)(C_6H_5CH_2)^+N(CH_3)_2$ Br^-[7] (7.0)	110–111 (EtOH)			9.0	30 (10)	60	3.5	$C_6H_5N(CH_3)_2$ (2.8) (96.6)
5	cyclohexyl, $C_6H_5CH_2$ $>N^+(CH_3)_2$ Cl^- (4.0)	194–196 (Me_2CO)	$C_{15}H_{24}ClN\cdot0.75H_2O$[a,b]	C, N; H[d]	5.2	20 (10)	80	4	Cyclohexyl-$N(CH_3)_2$ (1.9) (95.0)
6	$(CH_2)_5N^+<CH_2C_6H_5$, CH_3 Cl^- (1.12)	243–245 dec (*i*-PrOH)	$C_{13}H_{20}ClN$	H, N; C[e]	1.1	2 (20)	90	5	$(CH_2)_5NCH_3$ (1.0) (60.9)
7	 Cl^- (1.37)	195–197 (*i*-PrOH)	$C_{17}H_{20}ClN\cdot0.2H_2O$[a,c]	C, H, N	5.5	4 (5)	70	7	 (0.38) (51.4)
8	$(CH_2)_5N^+<CH_2C_6H_5$, $(CH_2)_2CH_3$ I^- (5.0)	192–193 (*i*-PrOH)	$C_{15}H_{24}IN$	C, H, N	5.0	11 (10)	80	10	$(CH_2)_5NCH_2CH_2CH_3$ (1.4) (76.1)

[a] Since these compounds were very hygroscopic, the absorption of H_2O of crystallization was observed during weighing for microanalyses and the presence of H_2O of crystallization was confirmed by ir spectra since the mass spectrum of quaternary salts is meaningless. [b] λ_{max}^{KBr} 3450 cm^{-1} (H_2O of crystallization). [c] λ_{max}^{KBr} 3320 cm^{-1} (H_2O of crystallization). [d] H: calcd, 9.57; found, 10.01. [e] C: calcd, 69.15; found, 69.65.

TABLE II

DEBENZYLATION AND DEALLYLATION OF QUATERNARY AMMONIUM SALTS

Reaction no.	Quaternary ammonium salts (g)	Mp, °C (solvent of recrystn)	Formula	Analyses	Thiophenol, g	Aq NaOH, ml (%)	Temp, °C	Time, hr	Tertiary amines (yield, g, %) Debenzylated product	Tertiary amines (yield, g, %) Deallylated product
9	$C_6H_5{}^+N(CH_3)_2(CH_2CH{=}CH_2)$ Br^-[4] (1.4)	123–124 (AcOEt)			3.3	12 (10)	75	3	None	$C_6H_5N(CH_3)_2$ (0.6) (82.2)
10	$C_6H_5CH_2{}^+N(CH_3)_2(CH_2CH{=}CH_2)$ Br^-[8] (6.0)	99–100 (Me_2CO)			8.0	30 (10)	75	5	$(CH_3)_2NCH_2CH{=}CH_2$[9] (0.49) (28.3)	$C_6H_5CH_2N(CH_3)_2$ (1.53) (55.6)
11	$(CH_2)_5N^+<CH_2C_6H_5$, $CH_2CH{=}CH_2$ Br^- (4.5)	151–152 (*i*-PrOH–Me_2CO)	$C_{13}H_{22}BrN$	C, H, N	5.2	20 (10)	75	4	$(CH_2)_5NCH_2CH{=}CH_2$[10] (0.74) (34.0)	$(CH_2)_5NCH_2C_6H_5$[11] (1.33) (43.5)
12	$(CH_2)_5N^+<CH_2C_6H_5$, $CH_2CH{=}C(CH_3)_2$ Br^- (5.0)	156–159 (Me_2CO)	$C_{17}H_{26}BrN$	C, H, N	5.0	18 (10)	70	4	$(CH_2)_5NCH_2CH{=}C(CH_3)_2$[12] (0.5) (23.5)	$(CH_2)_5NCH_2C_6H_5$[11] (1.7) (69.5)
13	 I^- (10.8)	102–103 (Me_2CO–H_2O)	$C_{21}H_{26}IN$	C, H, N	8.5	32 (10)	70	4	 (1.55) (30.1)	 (2.86) (49.5)

[a] This compound was characterized as its hydrochloride as follows: colorless leaflets, mp 196–197° (*i*-PrOH–Et_2O). *Anal.* ($C_{14}H_{19}N\cdot HCl$) C, H, N.

collected and recrystallized to give the corresponding salts as shown in Table II.

(3) Reaction of N-Benzyl Tertiary Amines with 3,3-Dimethylallyl Bromide.—A mixture of 1 molar equiv of tertiary amine and 3,3-dimethylallyl bromide in dry Me_2CO was refluxed on a water bath for 1–5 hr in the presence of dry $NaHCO_3$.[20] After completion of the reaction, the solvent was distilled, and the residue was extracted with EtOH in order to remove an inorganic reagent and filtered. Evaporation of the filtrate gave the corresponding salts as shown in Table II.

(4) 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-3-(3,3-dimethylallyl)-3-benzazocinium Iodide (III).—A mixture of 0.36 g of I, 0.54 g of MeI, and 20 ml of dry PhH was refluxed on a water bath for 3 hr. After cooling, the solvent was distilled and the residue was triturated and washed (Et_2O) to give 0.34 g (63.1%) of colorless needles, mp 105–107° dec, which were used in the following reaction.

(5) 3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3,3-dimethylallyl)-3-benzazocinium Bromide (IV).—A mixture of 2 g of I, 20 ml of dry PhH, and 3 g of $PhCH_2Br$ was refluxed on a water bath for 40 min. After cooling, excess Et_2O was added to the reaction mixture, which was set aside to precipitate 3.1 g (97%) of a colorless powder. Recrystallization from EtOH–Et_2O afforded a colorless powder, mp 159–161° dec, identical with an authentic sample (VIII)[1] by mixture melting point and ir (KBr) spectral comparison.

Reaction of Quaternary Ammonium Salts with Thiophenol. (1) Reaction of N-Benzyl Quaternary Ammonium Salts with Thiophenol in Aqueous NaOH.—A mixture of N-benzyl derivatives (*cf.* reaction 1–8 in Table I), excess thiophenol, and aqueous NaOH solution was heated on a water bath with stirring. After cooling, the reaction mixture was extracted (Et_2O). The extract was washed (saturated NaCl solution) and then extracted with 5–10% HCl. In this case evaporation of the above Et_2O gave benzyl phenyl thioether as colorless plates (from EtOH), mp 41–42°.[13] The acidic solution was made basic with aqueous NaOH or concentrated NH_4OH and extracted with a large amount of Et_2O. The extract was washed (saturated NaCl solution), dried (Na_2SO_4), and evaporated to give the free bases, which were purified as such, and/or salts by recrystallization or distillation *in vacuo*.

(2) N-Allyl- and N-(3,3-Dimethylallyl)-N-benzyl Quaternary Ammonium Salts with Thiophenol in Alkaline Solution.—By the same conditions as above, reactions 9–13 in Table II were carried out to give a syrup, which showed two spots (except in case of 9) on its tlc (Wakogel B-5). Column chromatography on silicic acid using PhH, PhH–$CHCl_3$, $CHCl_3$, $CHCl_3$–MeOH, and finally MeOH as eluent, followed by purification, gave two compounds as shown in Table II, which were characterized by tlc and ir spectral comparisons with the authentic samples. Furthermore, benzyl phenyl thioether, mp 40–41°,[15] and allyl phenyl thioether, bp 83–87° (10 mm),[16] were obtained as insoluble substances in aqueous NaOH and aqueous HCl.

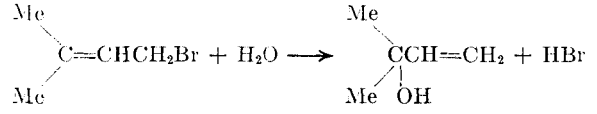
(3) Reaction of II and III with Thiophenol in Alkaline Solution.—A mixture of quaternary ammonium salts (II and III), thiophenol, and 5% aqueous NaOH was heated on a water bath at 40–50° with stirring for 5 hr. After cooling, the reaction mixture was mixed with Et_2O and extracted with 10% HCl. The acidic extract was made basic with concentrated NH_4OH and again extracted with $CHCl_3$ while salting out. The extract was washed (H_2O), dried (Na_2SO_4), and evaporated to give a colorless solid, whose recrystallization from EtOH gave V in 66.9–90.5% yields, identical with an authentic sample.[17]

(4) Reaction of IV with Thiophenol in Alkaline Solution.—A mixture of 3.9 g of IV, 9.4 g of C_6H_5SH, and 34 ml of 5% NaOH was heated with stirring on a water bath at 40–50° for 5 hr and treated as usual to give a colorless caramel-like substance, which was purified by chromatography using silicic acid. Removal of the Et_2O eluent gave 0.64 g (24.4%) of VI and evaporation of the Et_2O–$CHCl_3$ (95:5) eluent gave 1.24 (51%) of I, both of which were identical with the authentic samples.

(5) Reaction of IV with Sodium Thiophenoxide in Organic Solvents.—A mixture of 2 g of IV, 1.18 g of C_6H_5SNa,[21] and 50 ml of 2-butanone was heated on a water bath at 73–75° for 5 hr. After addition of 50 ml of H_2O to the reaction mixture, followed by extraction with $CHCl_3$, the $CHCl_3$ layer was evaporated to give a residue, which was extracted with 10% HCl. The resultant acidic solution was basified with saturated $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a brown caramel, which was purified by silicic acid chromatography using Et_2O, Et_2O–$CHCl_3$, $CHCl_3$, and MeOH as eluent. Removal of Et_2O gave 0.31 g (24.7%) of VI, whereas evaporation of ether–$CHCl_3$ afforded 0.79 g (58.7%) of I, both of which were identical with the authentic samples, respectively.

Acknowledgment. We thank Dr. K. Morita, Takeda Pharmaceutical Co. Ltd., and President A. Yanagisawa and Director O. Takagi of The Grelan Pharmaceutical Co. Ltd. for their encouragement. We also thank Miss R. Hasebe, Miss A. Kawakami, Miss Y. Tadano, Miss T. Yoshida, Miss K. Shima, and Miss R. Kato of Pharmaceutical Institute, Tohoku University, for ir and nmr spectral determinations and for microanalyses.

(20) Since 3,3-dimethylallyl bromide is decomposed in the presence of water, the HBr[14] formed seems to give the hydrobromide of the base. Therefore, this reagent was used.



(21) S. I. Miller, C. E. Orzech, C. A. Welch, G. R. Ziegler, and J. I. Dickstein, *J. Am. Chem. Soc.*, **84**, 2020 (1962).

Sulfamoylbenzoic Acid Ester Derivatives as Potential Local Anesthetics. I

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In view of the local anesthetic activity of the aromatic esters of the dialkylamino alcohols such as procaine, it was of interest to study the local anesthetic activity of sulfamoylbenzoic acid ester derivatives.

p-Dipropylsulfamoylbenzoic acid and *p*-dibutylsulfamoylbenzoic acid are widely used as uricosuric agents.[1] Some dialkylaminoethyl esters of *p*-dialkylsulfamoylbenzoic acids were reported to block the tubules in the kidneys, delaying secretion of therapeutic substances,[2,3] or forming crystalline salts with penicillin.[4] *p*-Dimethylsulfamoylbenzoic acid dimethylaminoethyl and diethylaminoethyl esters were found to be respiratory analeptics with low toxicity.[5]

In this work, aminoethyl esters of sulfamoylbenzoic acids were synthesized by the route outlined in Scheme I. The compounds prepared are tabulated in Table I and were subjected to local anesthetic screening. Rabbit's corneal application and subcutaneous injection in the guinea pig were used to determine their anesthetic activities.[6]

The preliminary assays showed that *p*-dipropylsulfamoylbenzoic acid dimethylaminoethyl ester hydrochloride (**9**), applied on the rabbits's cornea as a 1% solution, is as active as a 2% solution of cocaine hydro-

(1) C. S. Miller, U. S. Patent 2,608,507 (1952); *Chem. Abstr.*, **47**, 5440 (1953).

(2) Aktiebolaget Bofors, British Patent 797,794 (1958); *Chem. Abstr.*, **53**, 4218 (1959).

(3) Aktiebolaget Bofors, U. S. Patent 2,991,283 (1961); *Chem. Abstr.*, **56**, 4420 (1962).

(4) H. Sato, *J. Pharm. Soc. Japan*, **72**, 74 (1952).

(5) I. I. Krasil'nikov, *Farmakol. i. Toksikol.*, **29**, 163 (1966).

(6) The authors thank Dr. B. Djahanguiri, Faculty of Medicine, University of Tehran, for the local anesthetic activity testing.