using a procedure previously described.[5] The partition coefficient was calculated from the concentration of aryl compound in each phase (ratio of octanol solubility to aqueous phase solubility).

Molecular Orbital Theory Calculations.—The matrix equations for Hückel molecular orbital treatment of the aryl π-electron framework were solved with the use of an IBM 1130 computer. Coulomb and bond integrals were obtained from Streitwieser.[6] Methyl substituents were treated as heteroatoms. Charge density (Q_r) and electrophilic superdelocalizability (S_r) values for aryl atoms were calculated from the appropriate equations also given by Streitwieser.[6]

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Iodinated Derivatives of Histamine and N-Acetylhistamine

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Although it has been reported that histamine loses its biological activity by reaction with iodine, probably by iodination,[2] and kinetic studies have indicated iodine substitution in its imidazole ring,[3] iodinated derivatives of histamine have not yet been described. With the purpose of obtaining authentic iodinated derivatives for the chromatographic estimation of reaction products in studies of the kinetics of iodination of histamine and N-acetylhistamine, the following compounds were prepared: 5-iodohistamine dihydrochloride, 2,5-diiodohistamine, N-acetyl-5-iodohistamine, and N-acetyl-2,5-diiodohistamine. The position of the iodine atom in the imidazole ring of these compounds was determined from their nmr spectra. The limited iodination of histamine resulted in only one of the two possible isomers of monoiodohistamine, in which the iodine atom is in the 5 position, in analogy with what has been reported for monoiodoimidazole[4a] and monoiodohistidine.[4b]

None of the four compounds described here showed any spasmogenic activity upon the isolated guinea pig ileum in doses up to 10^4 times higher than an effective concentration of histamine on the same preparation. Slight antihistaminic activity was present only in N-acetyl-2,5-diiodohistamine and in 2,5-diiodohistamine. The latter was the more active of the two; at a concentration of 2×10^{-8} M it caused 50% reversible inhibition of the contraction produced by 5.5×10^{-5} M histamine on the isolated guinea pig ileum.

Experimental Section

Microanalyses for C, H, N, I, and Cl were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.[5] Melting points were determined on the Kofler micro melting point apparatus and are reported uncorrected. Nmr spectra were obtained at 60 Mc on a Varian T-60 or a Perkin-Elmer R-10 spectrometer, using D_2O as the solvent and Me_2CO-d_6 as an internal standard. Tlc was performed on silica gel G (E. Merck, A.G., Darmstadt) plates and the solvent system most adequate for separation of the iodinated compounds was n-BuOH saturated with 9 N NH_4OH, in which histamine had an R_f value of 0.08. Biological activity was tested by four-point assays on the isolated guinea pig ileum using histamine as standard. Antihistaminic activity was tested by the inhibition of response to histamine using acetylcholine as a control for specificity.

5-Iodohistamine Dihydrochloride.—A solution of 2.0 g of histamine dihydrochloride in 200 ml of 0.5 N NaOH and 100 ml of n-C_6H_{14} was cooled in an ice bath, and 2.76 g of I_2 dissolved in 300 ml of n-C_6H_{14} was added dropwise (90 min) with vigorous stirring. The stirring was continued for 10 min after the addition of I_2, and then 0.56 g of KIO_3, dissolved in 20 ml of H_2O and 10 ml of concentrated HCl, was added, followed by the extraction of I_2 with n-C_6H_{14}. The solution was concentrated to dryness *in vacuo* at 35°. The residue was suspended in 200 ml of absolute EtOH and 10 ml of concentrated HCl and refluxed for 30 min. The addition of a large volume of Me_2CO produced a white voluminous precipitate which was collected and, after charcoal decolorizing, crystallized from Me_2CO–H_2O as the dihydrochloride, yielding 1.5 g (45%) of a white solid that melted at 211–213° dec and was very soluble in H_2O, sparingly soluble in EtOH, and insoluble in Me_2CO. This product gave only one spot on tlc with R_f 0.33. *Anal.* ($C_5H_8IN_3 \cdot 2HCl$) C, H, N, Cl, I.

2,5-Diiodohistamine.—To 1.0 g of histamine dihydrochloride, dissolved in 200 ml of 0.25 N NaOH and 100 ml of n-C_6H_{14}, was added 3.04 g of I_2 dissolved in 240 ml of n-C_6H_{14}, as described in the preceding section. After addition of 0.50 g of KIO_3, dissolved in 20 ml of H_2O and 5 ml of concentrated HCl, I_2 was removed by extraction with n-C_6H_{14} and the solution was concentrated *in vacuo*, at 35°, to 35 ml. When the pH was brought to 9 by addition of concentrated NH_4OH a yellowish precipitate was formed. This was purified by repeated dissolution in concentrated HCl, treatment with charcoal, and precipitation by adding concentrated NH_4OH to bring the pH to 9, yielding 0.85 g (43%) of a white powder that melted at 163–164° dec, and gave one spot on tlc with R_f 0.52. *Anal.* ($C_5H_7I_2N_3$) C, H, N; I: calcd, 69.93; found, 69.44.

N-Acetylhistamine was prepared according to van der Merwe,[6a] but the mixture of histamine and Ac_2O was not refluxed, which prevented darkening of the product and afforded better yields. The light yellow oily residue, obtained after evaporation of the solvent, was dissolved in absolute EtOH and passed through a column of neutral alumina. On concentration of the eluate white crystals were obtained in a yield of 73%. The product melted at 145–147° (lit.[6b] mp 147–148°) and gave one spot on tlc with R_f 0.47.

N-Acetyl-5-iodohistamine.—The reaction of 1.0 g of N-acetylhistamine with 1.66 g of I_2 was performed as described above. After addition of KIO_3, extraction of I_2, and concentration *in vacuo*, at 40°, to 10 ml, alkalinization to pH 8 produced a white precipitate that was repeatedly dissolved in H_2O and reprecipitated by adjusting to pH 8. The final product, obtained in a yield of 0.78 g (44%), melted at 188–190°, and gave one spot on tlc with R_f 0.66. *Anal.* ($C_7H_{10}IN_3O$) C, H, I, N.

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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.

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

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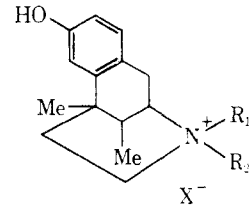
Shamma and his coworkers[3] had successfully employed sodium thiophenoxide in the demethylation of a variety of quaternary salts and proposed that the reaction proceeded by SN2-type displacement. In view of the fact that the benzyl or allyl are much better leaving groups than methyl in nucleophillic 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.

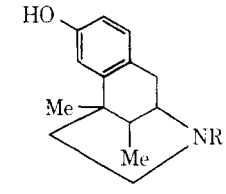
From various N-benzylammonium salts with other N-alkyl groups, the corresponding debenzylated tertiary amines were obtained selectively as shown in Table I. The cleavage of C–N single bond by pyrolysis[4] or by treatment with inorganic salts containing S[5] has been known in the case of both allylic 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

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