changes in the polarization of bonds may create surface effects on the insoluble sodium alkyl aggregates which overrule the acidity influence.

A homogeneous system should greatly simplify a study of transmetalation reactions. As the complex formed by ethylsodium and diethylzinc is soluble in benzene,[5] its use as a metalating agent was attempted. For convenience a solution of the complex in diethylzinc was chosen which contained ethyl sodium and diethylzinc in a ratio of 1:1.84 and which could easily be prepared according to Hein.[6]

The complex, dissolved in benzene or 1,2-dimethoxyethane, metalated fluorene but not triphenylmethane at room temperature. Thus, the activity of the complex, relative to the hydrocarbon acidity series,[7] was intermediate between that of ethylsodium and diethylzinc. Complex formation does, therefore, decrease the activity of ethylsodium.

The complex seemed to be stable at room temperature, as a 2% solution in styrene did not give any visible signs of polymerization, which would be indicative of the presence of radicals according to Ziegler.[8] When the solution was warmed to 60°, a red color developed and the styrene was polymerized violently. This is in agreement with the thermal instability of the complex as reported by Wanklyn[5] and by Carothers and Coffman.[9] A transmetalation by the complex was attempted with thiophene which according to Schick and Hartough[10] cannot be metalated by sodium alkyls except in the presence of mercury, although Morton[11] has claimed lately that thiophene can be dimetalated by amylsodium in presence of sodium *t*-amylate.

On addition of the complex to thiophene a clear solution resulted, gas development began, and later two layers formed. After several hours the mixture was carbonated and thiophene-2-carboxylic acid was isolated in a 55% yield. The acidity rule predicted metalation by alkylsodium rather than by the less reactive complex. The separation of the solution into two phases suggested the formation of a compound of the complex with thiophene, which seemed to be responsible for the unexpected course of the reaction.

EXPERIMENTAL

Metalation of Fluorene by the Ethylsodium–Diethylzinc Complex. Fluorene, 0.248 g. (0.00149 mole), was treated with 0.408 g. of the ethylsodium–diethylzinc complex (containing 0.00145 mole NaC_2H_5) in 40 ml. of dry benzene under nitrogen at room temperature. Gas bubbles developed, and the solution became reddish orange. After 30 minutes the reaction mixture was carbonated by pouring into Dry Ice and ether, and worked up to give 0.125 g. (41.2%) of fluorene-9-carboxylic acid, m.p. 221–223°. A mixed melting point with an authentic sample of fluorene-9-carboxylic acid was not depressed.

The result was the same with 1,2-dimethoxyethane as solvent.

Diethylzinc did not affect fluorene under these conditions.

Reaction of the Ethylsodium-Diethylzinc Complex with Styrene. The complex (0.534 g., containing 0.0019 mole NaC_2H_5), dissolved in 20 ml. of freshly distilled styrene and kept under nitrogen at room temperature, gave no indication of reaction after 30 minutes. The flask was then heated to 60–65° with a water bath. At this temperature the solution became dark red and the styrene polymerized violently.

Metalation of Thiophene by the Ethylsodium-Diethylzinc Complex. The complex (2.99 g., containing 0.0106 mole NaC_2H_5) was dissolved in 25 ml. of dry thiophene under nitrogen at room temperature. Gas development was noted. After about 10 minutes a second phase, from which the gas bubbles appeared to originate, separated. After 4 hr. the reaction mixture was carbonated by pouring into Dry Ice and ether. 0.75 g. (55%) of thiophene-2-carboxylic acid was isolated, m.p. 127–128°. No depression of a mixed melting point with an authentic sample of thiophene-2-carboxylic acid was observed.

No reaction was observed between thiophene and diethylzinc under the same conditions.

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Synthesis of 4(5)-Imidazolylacetylcholine and 2-Pyridylacetylcholine

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The isolation from natural sources of β-[4(5)-imidazolyl]-acryloylcholine (murexine)[1,2] as well as the apparent isolation of 4(5)-imidazolylacetylcholine[3] from mammalian brain has led to numerous studies of the pharmacology of these choline esters as well as β-[4(5)-imidazolyl]-propionylcholine (dihydromurexine[4,5]). These compounds are potent ganglionic stimulants and neuromuscular blocking agents.[4] In order to study the pharmacology of

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compounds of this type we have synthesized 4(5)-imidazolylacetylcholine[6] and 2-pyridylacetylcholine. The pharmacology of 2-pyridylacetylcholine was of special interest since β-(2-pyridyl)-propionylcholine had been shown to be the most potent of a series of heterocyclic analogues of murexine and dihydromurexine in causing contraction of the frog rectus abdominus muscle.[7]

The preparation of the intermediate β-bromoethyl esters of 4(5)-imidazoleacetic acid and 2-pyridineacetic acid and their conversion to the corresponding choline esters was similar to the reported syntheses of murexine and dihydromurexine.[7-9]

Details of the pharmacological properties of these compounds have already been published.[4,10-12] In summary, it may be stated that as neuromuscular blocking agents the order of decreasing potency is as follows: dihydromurexine, murexine, 4(5)-imidazolylacetylcholine, and 2-pyridylacetylcholine; while as ganglionic stimulants the order is changed only in that 2-pyridylacetylcholine is more active than 4(5)-imidazolylacetylcholine.

EXPERIMENTAL[13]

4(5)-Imidazoleacetic acid hydrochloride was prepared by the method of Bauer and Tabor[14] modified to avoid any possibility of ester formation. Steam was passed through a boiling solution of 60.4 g. (0.56 moles) of 4(5)-imidazoleacetonitrile[14] and 40.0 g. (1.00 mole) of sodium hydroxide for 1 hr. at the end of which time ammonia evolution had ceased. The solution was cooled and 115 ml. of concentrated hydrochloric acid was added and the mixture taken to dryness *in vacuo*. The residue was triturated with 800 ml. of warm concentrated hydrochloric acid and the solution filtered through a sintered glass funnel to remove sodium chloride. The filtrate was taken to dryness *in vacuo* to leave a residue of 90.4 g. (99%) of 4(5)-imidazoleacetic acid hydrochloride, m.p. 220–225° (lit.[14] m.p. 223°).

β-Bromoethyl 4(5)-imidazolylacetate. A solution of 9.9 g. of 4(5)-imidazoleacetic acid hydrochloride in 100 ml. of ethylene bromohydrin was saturated with anhydrous hydrogen chloride and slowly distilled over a period of 90 min. to remove 50 ml. of solvent. The addition of ether to the cooled solution gave an oil which was separated and dissolved in ice water. The aqueous solution was extracted with methylene chloride, made alkaline with ammonia, and the precipitate taken up in methylene chloride. The organic layer was dried over anhydrous potassium carbonate, the solvent removed and the residue triturated with ether to give 9.9 g. of the crude ester, m.p. 74–80°. After several recrystallizations from acetone-ether the melting point was constant at 88–90°.

Anal. Calcd. for $C_7H_9N_2O_2Br$: C, 36.07; H, 3.89; N, 12.88. Found: C, 36.04; H, 3.49; N, 12.52.

4(5)-Imidazolylacetylcholine. The crude β-bromoethyl ester (prepared from 9.9 g. of 4(5)-imidazoleacetic acid hydrochloride), was dissolved in 100 ml. of acetone, the solution cooled with dry ice, 40 ml. of cold anhydrous trimethylamine added, and the solution shaken in a pressure bottle for 22 hr. at 28° (20 p.s.i.). The viscous oil which separated was washed with acetone, dissolved in absolute ethanol, and the solvent removed *in vacuo* at room temperature to remove traces of trimethylamine. The crude 4(5)-imidazolylacetylcholine bromide (11.1 g.) was again dissolved in absolute ethanol and converted to the hydrobromide salt with anhydrous ethanolic hydrogen bromide. After seeding the solution and allowing it to stand overnight at room temperature, the crystals which had separated were triturated with 50 ml. of absolute ethanol and collected to give 4.8 g. (21%) of 4(5)-imidazolylacetylcholine bromide hydrobromide as colorless crystals, m.p. 183–185°. The product was too hygroscopic to be recrystallized but was stable in a dry atmosphere.

Anal. Calcd. for $C_{10}H_{19}N_3O_2Br_2$: C, 32.19; H, 5.13; N 11.26. Found: C, 32.25; H, 4.89; N, 11.26.

The dipicrate of 4(5)-imidazolylacetylcholine crystallized from water as yellow crystals, m.p. 199–200°.

Anal. Calcd. for $C_{22}H_{23}N_9O_{16}$: C, 39.46; H, 3.46; N, 18.84. Found: C, 39.59; H, 3.62; N, 19.01.

β-Bromomethyl 2-pyridylacetate. The crude lithium salt of 2-pyridineacetic acid was prepared[15] from 97 ml. of α-picoline and dissolved in 1 kg. of ethylene bromohydrin. Anhydrous hydrogen chloride was passed into the cooled solution for 1 hr. After standing at room temperature for 4.5 days the solution was diluted to 4 l. with methylene chloride and extracted twice with a small volume of cold water. The cold aqueous solution was washed with ether, made alkaline with ammonia, and extracted with ether. The ether extract was washed once with water and dried over anhydrous potassium carbonate. The ether and unreacted α-picoline were removed *in vacuo* finally using a rotary evaporator at 45° and 1.0–2.0 mm. pressure. The residue was taken up in anhydrous ether and the solution filtered to remove a small amount of insoluble material and again evaporated *in vacuo* to give 23 g. of the crude ester as a yellow oil. A portion of the oil gave the picrate salt of β-bromoethyl 2-pyridylacetate as yellow crystals from aqueous ethanol, m.p. 126–128°.

Anal. Calcd. for $C_{15}H_{13}BrN_4O_4$: C, 38.07; H, 2.77; N 11.84. Found: C, 38.34; H, 2.45; N, 11.32.

2-Pyridylacetylcholine bromide hydrobromide. A solution of 20.0 g. of crude β-bromoethyl 2-pyridylacetate in 100 ml. of acetone was cooled in dry ice, 40 ml. of anhydrous liquid trimethylamine added and the mixture shaken in a pressure bottle at 26° (20 p.s.i.) for 17 hr. The precipitate was collected and washed with acetone to give 17.5 g. of a hygroscopic solid. The latter was dissolved in absolute ethanol and the solution acidified with alcoholic hydrogen bromide and cooled to give 18.5 g. of colorless crystals which melted at 120–130° with gas evolution. Two recrystallizations from absolute ethanol gave colorless platelets, m.p. 130–135°, which lost solvent of crystallization upon drying in high vacuum at 78° for 2 hr. and finally at 110° overnight; yield, 11.5 g.; m.p. 169–170°.

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Anal. Calcd. for $C_{12}H_{20}Br_2N_2O_2$: C, 37.52; H, 5.25; N, 7.29. Found: C, 37.46; H, 5.05; N, 7.01.

Anhydrous 2-pyridylacetylcholine bromide hydrobromide was kept for long periods over anhydrous calcium chloride but it rapidly absorbed water in a moist atmosphere.

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A Seven-Membered Heterocycle from *o*-Aminobenzenethiol and Chalcone[1]

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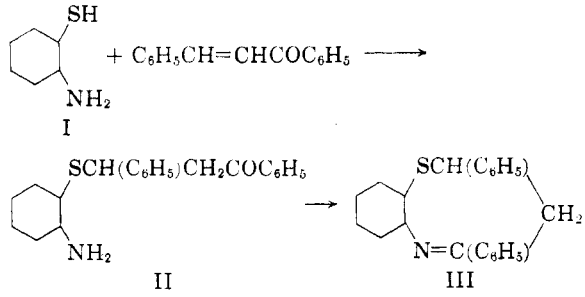
Herz and Tarbell found that the thiol group of a thiophenol could be blocked to permit operations elsewhere in the molecule by addition of the thiophenol to 3-nitrobenzalacetophenone, which subsequently could be removed.[2] When chalcone (benzalacetophenone)itself was used in essentially this procedure to protect the thiol group of *o*-aminobenzenethiol (I), prior to reactions of the amino group, two products were obtained. These proved to be the desired ketone (II) and a cyclized product (III).



Preparation of II (58% yield) could be achieved, however, by omitting acetic acid and using only piperidine in the procedure of Herz and Tarbell. Addition of acetic acid to the reaction mixture resulted in the isolation of the cyclized product (III) in 62% yield. Treatment of the isolated ketone II in methanol with acetic acid also converted it to III (78%).

The structures of II and III are supported by the elementary analyses and by the fact that II has a strong infrared-absorption band in the region expected for a carbonyl group, unlike III which lacks this band but has another in the region reasonably attributable to a C=N linkage. Further evidence is provided by the fact that since our work was completed Ried and Marx have demonstrated the same reactions with thiophene counterparts of chalcone; they reported the independent synthesis of a typical heterocyclic product.[3] It is interesting that the heterocyclic ring of III withstands the action of alkali, at least in water.

EXPERIMENTAL[4]

β-Phenyl-β-(o-aminophenylmercapto)propiophenone (II). Chalcone (5.00 g.) and *o*-aminobenzenethiol[5] (I, 3.00 g.) were dissolved in 50 ml. of boiling methanol. The heat was removed and piperidine (25 drops) was added. White needles of II precipitated upon cooling; yield, 4.64 g. (58%), m.p. 127–134°. Repeated recrystallization from hexane gave II with a constant m.p. of 134–135°. Strong infrared absorption at 1670 cm.$^{-1}$ is consistent with the presence of an aryl ketone linkage.

Anal. Calcd. for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74. Found: C, 75.42; H, 5.59.

2,4-Diphenyl-6,7-benzo-1-thia-5-aza-4,6-cycloheptadiene (III). Chalcone (5.00 g.) and I (3.00 g.) were dissolved in 25 ml. of boiling methanol. The heat was removed and piperidine (25 drops) was added. After the mixture had cooled to room temperature, an additional 25-ml. portion of methanol was added and the slurry heated until all material dissolved. Glacial acetic acid (10 ml.) then was added and the mixture allowed to stand overnight at 25°. Yellow crystalline III separated which amounted to 4.70 g. (62%), m.p. 111.5–115°. This material was repeatedly recrystallized from *t*-butyl alcohol to a constant m.p. of 114–115°. Strong infrared absorption occurred at about 1613 cm.$^{-1}$ (C=N), which was absent in the spectrum of II, with no other appreciable absorption from 1613–2940 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{17}NS$: C, 79.95; H, 5.43. Found: C, 79.64; H, 5.31.

When 1.00 g. of the III was heated at 70° for 2 days with 50 ml. of 10% aqueous sodium hydroxide, 0.98 g. of III was recovered, m.p. and mixture m.p. 111–114.5°.

Conversion of II *to* III. A mixture of 0.50 g. of II and 25 drops of glacial acetic acid was heated in 10 ml. of methanol on a steam bath for 20 min. After standing overnight, the mixture was concentrated to about one-half volume; yield of III, 0.28 g. (59%), m.p. and mixture m.p. (with III as prepared above), 114–115°. A second crop of 0.09 g. (19%), m.p. and mixture m.p. 112–115°, brought the total yield to 78%.

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