results in some self-quenching.[2] It has been previously noted in the case of dibenzofuran and dibenzo-*p*-dioxin[3] that the direct union of two benzene rings in a heterocycle, provides a more efficient scintillator nucleus than the corresponding heterocycle with an oxygen bridge. This is clearly confirmed in the comparison of derivatives of I and II. The 9-aryl carbazoles give values ranging from 0.24 to 0.93 (Compounds 5 through 9) while exactly analogous phenoxazine derivatives (Compounds 10, 14, 15, and 16) all fail to respond within the sensitivity of the instrument. The amine related to Compounds 5 and 9, triphenylamine, has been reported[4] to have a very low value (about 0.06 on our scale), markedly lower than that of 9-phenylcarbazole. 4-Biphenylyldiphenylamine (Compound 1) on the other hand has a slightly higher value than the corresponding carbazole derivative (Compound 6).

The synthetic methods employed in the preparation of these compounds are listed in the footnotes to Table I and appear to be completely general. An extension of these methods may prove rewarding in view of the fact that Compound 8 with six benzene rings is soluble to the extent of about 5 g./l. in toluene. A number of promising scintillator solutes, notably 1,4-di[2-(5-phenyloxazolyl)]benzene and 2,5-di(4-biphenylyl)oxazole,[5] have been relegated to use as secondary solutes because of poor solubility in toluene.

The values reported in Table I were measured in the pulse height analyzer previously described,[1] and all were measured at a concentration of 3 g./l. in toluene except compound 16, which, due to limited solubility, was measured as a saturated solution. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

EXPERIMENTAL[6]

10-(4-Biphenylyl)phenothiazine. Twenty grams (0.10 mole) of phenothiazine, 35 g. (0.15 mole) of 4-bromobiphenyl, 12 g. (0.11 mole) of anhydrous sodium carbonate, and 1 g. of copper powder were stirred at 150–160° for 16 hr. After this period the temperature was raised to 200° where it was maintained for an additional 4 hr. Steam distillation of the mixture afforded 15 g. (43%) of unreacted 4-bromobiphenyl. The undistilled residue was extracted with benzene, and this solution was chromatographed on alumina and eluted with more benzene. Evaporation of the eluate left 29 g. of hard resinous solid, melting at 140–170°. Two crystallizations from an acetone-water pair afforded 20 g. (57.5%) of pale yellow powder, melting at 174–178°.

Anal. Calcd. for $C_{24}H_{17}NS$: S, 9.12. Found: S, 9.24, 9.37.

p-Bis(10-phenothiazinyl)benzene. Twenty-four grams (0.12 mole) of phenothiazine, 16.5 g. (0.05 mole) of *p*-diiodobenzene, 12 g. (0.11 mole) of anhydrous sodium carbonate, and 1 g. of copper powder were stirred at 200° for 12 hr. During this period it was necessary to scrape the sublimed *p*-diiodobenzene from the sides of the reaction vessel in order to return it to the reacting mass. After cooling to room temperature the solid was crushed and extracted with five 200-ml. portions of benzene. The benzene was removed and the residue was extracted with three 20-ml. portions of absolute ethanol to remove unreacted *p*-diiodobenzene and phenothiazine. The remaining material was chromatographed on alumina using benzene as solvent and eluant. Removal of the solvent from the eluate left 18 g. of material melting at 248–250°. Recrystallization from benzene gave 16.5 g. (70%), m.p. 253–255°.

Anal. Calcd. for $C_{30}H_{20}N_2S_2$: S, 13.57. Found: S, 13.70, 13.70.

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[6] Melting points are uncorrected.

Rearrangement in the Reactions of *p*-Halotoluenes with Potassium Anilide[1]

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In recent years it has been shown that alkali amides in liquid ammonia[2-4] and refluxing piperidine[5,6] and organolithium compounds[7,8] react with non-activated aryl halides by the way of benzyne (I) intermediates. Strong bases and nucleophiles in liquid ammonia react with aryl halides in liquid

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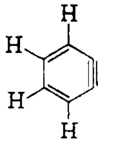

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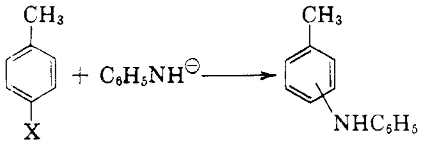
ammonia only in the presence of alkali amides.[9–13] Sodium and potassium hydroxides react with aryl halides only at very elevated temperatures[14–17] and when the reaction temperature and the base concentration are reduced, the reaction mechanism may change from elimination-addition to direct substitution.[14]

Sodium and potassium anilides do not react with halobenzenes in liquid ammonia, but potassium anilide and potassium diphenylamide are reported to react with bromobenzene at elevated temperatures[18] to give diphenylamine and triphenylamine, respectively. An improved procedure for this type of reaction has been developed and applied to the preparation of diphenylamine and tolylphenylamines. In order to gain some information regarding the mechanism of such a reaction, *p*-chloro-, *p*-bromo- and *p*-iodotoluenes were treated with potassium anilide in refluxing aniline. Mixtures of *p*- and *m*-tolylphenylamines resulted which were analyzed by means of infrared spectroscopy. The results are summarized in Table I.

TABLE I

PRODUCTS FROM THE REACTION OF *p*-HALOTOLUENES WITH POTASSIUM ANILIDE



X	Total Yield, %	Meta, %	Para, %
Cl	53	53 ± 3	47 ± 3
Br	50	53 ± 3	47 ± 3
I	43	52 ± 3	48 ± 3

If direct substitution were competing with elimination-addition, the ratios of the two isomers should be different for the three *p*-halotoluenes.[2] The fact that all three *p*-halotoluenes give essentially the same product mixtures is strong evidence that these substitutions proceed exclusively by the way of a benzyne-type intermediate. It cannot be excluded, however, that in the case of *p*-iodotoluene a small amount (about 2%) of direct displacement takes place; the analytical procedure, however, was not precise enough to verify this fact.

In order to determine whether alkoxides react with non-activated aryl halides by the way of a benzyne intermediate, the reaction between sodium cyclohexoxide and bromobenzene in refluxing cyclohexanol was investigated. It was found, however, that after 3 days the reaction had proceeded to an extent of less than 10%.

EXPERIMENTAL

Potassium anilide with bromobenzene. Potassium anilide was prepared by adding 4.2 g. (0.107 mole) of potassium metal to 250 ml. of refluxing aniline. Bromobenzene (20 g., 0.128 mole) was added and the solution heated under reflux for 2 hr. At the end of this time, the reaction mixture was allowed to cool and ethanol was cautiously added. Hexane and ether were added; the mixture was washed with water and the solvents evaporated. The residue was distilled through a semimicro column.[19] Diphenylamine (11.0 g., 60%), m.p. 49–52°, whose infrared spectrum was identical with the spectrum of an authentic sample of diphenylamine, was obtained.

Reaction of potassium m- and p-toluidides with bromobenzene. The reaction conditions were the same as above. Five grams (0.128 mole) of potassium and 30 g. (0.198 mole) of bromobenzene were used. The yield of crude *m*-tolylphenylamine was 14.5 g. (61.5%), the yield of *p*-tolylphenylamine was reduced by mechanical losses to 6.2 g. (26%). The products were purified by precipitation with anhydrous hydrogen chloride in ether, followed by treatment with water, extraction with ether, and recrystallization from pentane. The purified *m*-tolylphenylamine had m.p. 28.5–29.5°, lit.,[20] 30°. *p*-Tolylphenylamine had m.p. 87.5–88.5°, lit.,[20] 89°.

Reaction of potassium diphenylanilide with bromobenzene. To 25 g. (0.148 mole) of diphenylamine in 250 ml. of refluxing xylene was added 4.0 g. (0.10 mole) of potassium. The reaction was very slow, and even after 4 hr. of refluxing about 20% of the potassium was still unreacted. Bromobenzene (30 g., 0.198 mole) was added, and the reaction mixture was heated under reflux for 18 hr. Ethanol and a small amount of water were added; the organic layer was washed with water, dried over anhydrous magnesium sulfate, saturated with anhydrous hydrogen chloride, and filtered. The filtrate was evaporated and the residue recrystallized from ethyl acetate. Crude triphenylamine (1.0 g., 2.7%) was obtained. After several recrystallizations from ethyl acetate–ethanol, 500 mg. of pure product, m.p. 126–127°, undepressed by admixture with an authentic sample of triphenylamine, was obtained.

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Reaction of p-chloro-, p-bromo- and p-iodotoluenes with potassium anilide. Potassium (5.6 g., 0.144 mole) was added to 250 ml. of refluxing aniline. The appropriate *p*-halotoluene (0.10 mole) was added, and the reaction mixture was heated under reflux for 15 min. Water was cautiously added to decompose the unreacted bases. Ether was added, the organic layer was washed several times with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and saturated with anhydrous hydrogen chloride. The precipitate was washed with ether, treated with water, extracted with ether, and flash distilled to remove high-boiling tarry materials. The compositions of the distillates were determined by comparison of their infrared spectra in carbon disulfide solution at 11.75–14.00 μ with those of synthetic mixtures of *m*- and *p*-tolylphenylamines.

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Synthesis of 1-Alkyltryptophans

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Considerable effort has been expended on the synthesis of tryptophan analogs for use in the study of enzyme inhibition. This note describes a new general method for the synthesis of 1-alkyltryptophans, in particular the 1-methyl and 1-ethyl derivatives. The only 1-alkyltryptophan previously described is 1-methyltryptophan. This was obtained from 1-methylindole-3-aldehyde *via* the azlactone[1,2] and from 1-methylindole *via* 1-methylgramine.[3] Our starting material was ethyl-α-acetylamino-α-carbethoxy-β-(3-indole)-propionate.[4] This indole derivative was alkylated on refluxing in an inert solvent with alkyl *p*-toluenesulfonates in the presence of potassium carbonate. Subsequent steps in the synthesis were analogous to those used by Snyder and Smith[4] for the synthesis of DL-tryptophan, namely basic hydrolysis to the malonic acid derivative, decarboxylation to the 1-alkyl-*N*-acetyltryptophan and finally deacetylation by refluxing with dilute hydrochloric acid.

The alkylation of indole using our conditions has led to both 1- and 3-alkyl derivatives[5,6] and since, in our reaction, there was also the possibility of alkylation of the actylamino group, the alkyltryptophans were decarboxylated in molten fluorene at 240–270°. The products were 1-alkyltryptamines, characterized as their phthalimides, hydrochlorides, and picrates. Furthermore, the infrared spectrum of our 1-methyltryptophan was quite different from the spectrum of the isomeric L-abrine [α-methylamino-β-(3-indole)propionic acid]. Our 1-methyltryptophan had a melting point of 250°–251° (dec.). Melting points previously reported for this compound were 289°,[1] 285°,[2] and 223–225°.[3] This variation may be due to partial solvation of the amino acid since a lower melting point was observed in the compound was not extensively dried *in vacuo* at 100°.

EXPERIMENTAL[7]

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-methylindole)propionate (I). Ethyl-α-acetylamino-α-carbethoxy-β(3-indole)-propionate[4] (17.3 g., 0.05 mole) was refluxed in 200 ml. of dry xylene with methyl *p*-toluenesulfonate (10.0 g., 0.06 mole) and anhydrous potassium carbonate (15 g., 0.11 mole) for 5 hr. The mixture was filtered, the residue was washed with benzene, and the combined filtrates evaporated to dryness *in vacuo*. The residue was titurated with ether yielding crystals of I (12.6 g., 70% yield), m.p. 124°. Crystallization from ethanol afforded colorless rhombic crystals, m.p. 125–126°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.70; N, 7.57.

The methylation was also carried out successfully in refluxing *o*-dichlorobenzene resulting in a 62% yield.

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-ethylindole)propionate (II). This 1-ethyl derivative was prepared by substituting ethyl *p*-toluenesulfonate (12.0 g., 0.06 mole) for the methyl ester in the previous synthesis. The crude product (7.0 g., 54% yield), m.p. 107–108°, was crystallized from ethanol to yield short colorless prisms, m.p. 115–116°.

Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00. Found: C, 64.10; H, 6.89.

α-Acetylamino-α-carboxy-β(3-N-methylindole)propionic acid (III). The ester I (18 g., 0.05 mole) was refluxed with 100 ml. of 10% sodium hydroxide solution for 4 hr. The cooled, filtered solution was acidified with concentrated hydrochloric acid. The malonic acid derivative (III) which separated was crystallized from 50% aqueous ethanol to yield colorless rhombic plates (14.1 g., 93% yield), m.p. 147–148°. The crystals became pink on exposure to air.

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 7.77. Found: C, 58.91; H, 5.56; N, 7.57.

α-Acetylamino-α-carboxy-β(3-N-ethylindole)propionic acid (IV). Hydrolysis of II as in the previous preparation yielded IV as colorless prisms (from ethanol) in 85% yield, melting at 128–129°.

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70. Found: C, 60.22; H, 5.94.

1-Methyl-N-acetyltryptophan (V). The malonic acid derivative III (7.6 g.) was heated in a nitrogen atmosphere at 180–190° for 15 min. The pale yellow glass which remained on cooling was crystallized from ethanol (charcoal) to yield large colorless prisms of V (5.6 g., 86% yield), m.p. 169.5–170.5° (lit.[3] 171–172°).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.58; H, 6.20. Found: C, 64.59; H, 6.44.

1-Ethyl-N-acetyltryptophan (VI). The decarboxylation of IV carried out as in the previous preparation yielded colorless plates of VI (from ethanol) in 82% yield, m.p. 185–187°.

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