absolute ether was treated with 30 ml. of thionyl chloride and three drops of pyridine. After standing for fifteen hours, the volatile constituents were removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 600 ml. of dry thiophene-free benzene and chilled until the solvent began to crystallize. Then a solution of 40 ml. of stannic chloride in 40 ml. of benzene was added rapidly with shaking and the mixture allowed to stand in the ice-bath for fifteen minutes. The yellow complex was destroyed by pouring upon a mixture of 50 ml. of ether, 100 ml. of concentrated hydrochloric acid, and ice. The organic layer was then separated and washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. Drying, followed by evaporation of the solvent, left an oil which was distilled at reduced pressure. The fraction boiling at 192–198° (0.4 mm.) was collected as product; the yield was 42.2 g. (71%). The pale yellow oil solidified on standing and melted at 67–68° after recrystallization from cyclohexane–petroleum ether.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.30; H, 6.98. Found: C, 67.14; H, 6.89..

Nitrosation of the Tetralone XII.—Various conditions and methods were tried without good results. Nitrosation with an ester of nitrous acid in the presence of dry hydrogen chloride produced only resinous products. In the presence of sodium alkoxides with either freshly prepared butyl or isopropyl nitrite, small amounts of the desired oximinoketone XIII were obtained. The yields in all cases were too low to warrant continuance of the synthesis along this path. The following procedure is an example of a successful experiment. A solution of 1.5 g. (0.005 mole) of XII and 0.23 g. of sodium in 50 ml. of absolute ethanol was prepared. Then, 1.5 g. (0.0075 mole) of freshly prepared *n*-butyl nitrite was added, and the mixture was allowed to stand at 5° for two days. The alcohol solution was diluted with an equal volume of cold water and extracted twice with 30-ml. portions of ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted three times with 30-ml. portions of ether. Drying, followed by evaporation of the solvent, left 1.5 g. of a red oil which partially solidified on standing. Trituration with ether provided 0.15 g. of pale yellow **2-nitroso-4-cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XIII)** which melted with darkening at 154–155° after three recrystallizations from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_{17}H_{20}O_5N_2$: C, 61.43; H, 6.07. Found: C, 61.33; H, 5.81.

Summary

A method leading to a compound containing a fused-ring tetralin–piperidine system, similar to part of the morphine ring system, has been developed.

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The Preparation of the C_{10} Monocyclic Aromatic Hydrocarbons

BY S. F. BIRCH, R. A. DEAN, F. A. FIDLER AND R. A. LOWRY

Introduction

A comparatively elaborate program has been carried out over a number of years to produce a supply of hydrocarbons in a high degree of purity required in connection with spectroscopic analysis and other analytical problems. Although interest in the aromatic series at first centered primarily round the hydrocarbons in the C_6 to C_9 range, it was later found desirable to include the C_{10} compounds. At the time this work was commenced, no source of these hydrocarbons was available, and the physical data reported in the literature were extremely scanty and contradictory.

The present paper describes in general the methods and techniques employed in these laboratories for their preparation. Possibly its chief interest is on account of the steps taken at each stage to ensure that the intermediate compounds were satisfactorily purified before proceeding to the next step in the synthesis. Particular emphasis was placed on the determinations of the physical constants and purities of the intermediates at all stages of their purification and as a result the densities, refractive indices and freezing points of many compounds of known purity are recorded for the first time. At any point at which an intermediate proved relatively impure, it was possible to continue purification until a satisfactory product had been obtained. Only when a following stage permitted the easier separation of impurities was the synthesis continued without satisfactory purification being attained. Thus in some cases it was more satisfactory to purify the carboxylic acid than the nitrile from which it was obtained.

The scale of the preparation was based upon a quantity of 1500 to 2000 ml. of final hydrocarbon in a satisfactory state for purification. This quantity is appreciably smaller than that generally made available to Rossini and his co-workers for purification at the National Bureau of Standards and it would have been desirable to increase this quantity two- or three-fold. Unfortunately, the effort necessary for preparations on this scale was not available. It was felt, however, that taking considerable care in the purification of the intermediates would in great measure offset the smaller quantity of hydrocarbon available for final treatment.

The methods chosen as being most satisfactory were made as general as possible so that they would be applicable to the preparation of more than one hydrocarbon. By so doing, not only was the working out of new techniques largely avoided but the same apparatus could frequently be employed for a number of preparations. Routes were selected which enabled readily available and easily purified starting materials to be employed for the synthesis. Thus it will be observed that amines formed the most common class of starting materials, since these can readily be purified in bulk by crystallization of their salts or acyl derivatives.

Care was taken to avoid reactions in which the possibility of isomerization was likely to occur at any stage or in which impurities separated only with difficulty from the final products, would be formed. Thus, the Friedel–Crafts method for preparing substituted ketones, *e.g.*, *p*-ethylacetophenone from acetyl chloride and ethylbenzene with aluminium chloride, was avoided, since previous experience had shown that this reaction tends to produce a mixture of isomers. Also, an early batch of *n*-butylbenzene was prepared by the Wurtz–Fittig reaction using bromobenzene and *n*-butyl bromide. The purification of the hydrocarbon obtained by this method proved so difficult, owing to the presence of halogen compounds in the product, and the yield was so poor, that this reaction was avoided in further syntheses. The low yield obtained in this reaction is in agreement with the findings of Karabinos, Serijan and Gibbons[1]. Still another reaction which was avoided was that exemplified by the Grignard condensation of benzylmagnesium chloride and diethyl sulfate for the production of *n*-propylbenzene. This preparation had been carried out several years ago in these laboratories but the purification of the hydrocarbon proved extremely difficult with the columns then available. At the time, this was assumed to be due to halogen substitution in the benzene ring but a recent publication[2] has shown that in this reaction, a certain amount of rearrangement occurs giving *p*-ethyltoluene as well as *n*-propylbenzene.

A further point which influenced the choice of route was that, as far as possible, the stages involved should be adaptable to relatively large-scale laboratory operation. Thus the reactions which were found to be most applicable and were repeatedly used included the diazo reaction, Grignard condensations, ketonization by passage of mixed acids over a thoria catalyst and Clemmensen reductions.

Experimental

For simplicity, since more than one hydrocarbon was often prepared by the same route, the general method adopted is described once only and details of physical properties and yields of intermediates are quoted for each individual hydrocarbon. Thus the route

$$\text{Amine} \longrightarrow \text{Nitrile} \longrightarrow \text{Acid} \longrightarrow \text{Ketone} \longrightarrow \text{Hydrocarbon}$$

was used for *p*-diethylbenzene, 1,2-dimethyl-3-ethylbenzene, 1,2-dimethyl-4-ethylbenzene, and 1,4-dimethyl-2-ethylbenzene while the route

$$\text{Amine} \longrightarrow \text{Nitrile} \longrightarrow \text{Ketone} \longrightarrow \text{Hydrocarbon}$$

was employed for *o*-diethylbenzene, 1,3-dimethyl-4-ethylbenzene, 1,3-dimethyl-5-ethylbenzene and the three methyl-*n*-propylbenzenes.

Conversion of Amines to Ketones via Nitriles and Acids.—The procedures used for the conversion of the various toluidines, xylidines and ethylanilines to their corresponding ketones through the nitriles and carboxylic acids followed very closely on those described in Organic Syntheses.[3] The hydrolysis of the nitriles to carboxylic acids by 75% sulfuric acid worked perfectly satisfactorily in all the cases tried except for *m*-2-xylonitrile. When this nitrile was heated with the acid, the only recoverable product was *m*-xylene.

Since pumice was unobtainable when much of the work was carried out (1942), the thoria catalyst used for the conversion of the carboxylic acids into substituted acetophenones was supported on unglazed porcelain (approximately 0.25 inch). Furthermore, owing to the low solubility of many of the acids in glacial acetic acid, it was necessary to increase the mole ratio of acetic acid to carboxylic acid to 8 to 1. Even so, in certain instances it was essential to provide the dropping funnel with a heating jacket in order to prevent crystallization and subsequent blockage. A reaction tube 48 inches long and 1.5 inches in diameter, and holding approximately 500 ml. of the impregnated unglazed porcelain, was employed. With a new batch of catalyst it was found that no more than about 500 to 600 ml. of the mixed acids could be put through the reactor tube in eight hours, otherwise a considerable portion passed through unchanged. However, when the catalyst had been in use for several days, the rate could be almost doubled. The most satisfactory method of arranging the processing and regeneration was to carry out the ketonization during the day and regenerate the catalyst each night by drawing through air at a temperature of between 500 and 550°.

Reaction of Nitriles with Alkylmagnesium Halides.—In the production of an arylalkyl ketone from a nitrile and a Grignard reagent, it has been observed that the best yield is obtained by the use of an aryl nitrile and aliphatic Grignard rather than an aromatic Grignard and alkyl nitrile.[4] The procedure adopted for the Grignard condensations described here was based on a private communication received from Dr. G. Baddeley.

A quantity of methylmagnesium (or ethylmagnesium) chloride was prepared in the usual manner by passing methyl (or ethyl) chloride into a stirred suspension of magnesium turnings in absolute ether. The nitrile (1 mole to each 1.2 moles of Grignard) was then added with stirring over a period of one hour. During the addition, the reaction product became yellow but no temperature rise was observed.

After stirring for seventeen to twenty hours, the magnesium complex was decomposed to the ketimine by pouring on to crushed ice and the precipitated magnesium compounds were dissolved by the subsequent addition of dilute sulfuric acid. During this process, the ethereal layer changed in color giving a green solution. The combined aqueous and ethereal layers were heated on a steam-bath for one and a quarter hours during which time the ether distilled off and the ketimine was hydrolyzed to give an upper layer of ketone.[5]

The ketone was separated off, the aqueous layer extracted with ether and the combined ketone and extract dried. After removal of the solvent the residue was distilled under reduced pressure.

Clemmensen Reduction of the Ketones to Hydrocarbons.—The method which was found most satisfactory and which gave good yields of hydrocarbons from the ketones was the modification of the Clemmensen reduction described by Brady and Day.[6]

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[1] Karabinos, Serijan and Gibbons, THIS JOURNAL, **68**, 2107 (1946).

[2] Burtle and Shriner, *ibid.*, **69**, 2059 (1947).

[3] "Organic Syntheses," Coll. Vol. I, 1943, p. 500; Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943 pp. 389 and 588.

[4] Baddeley, *J. Chem. Soc.*, **147**, 232 (1944).

[5] An evolution of ammonia at this stage indicated that an insufficient quantity of acid had been used and that more should be added.

[6] Brady and Day, *J. Chem. Soc.*, **137**, 114 (1934).

Purification.—In almost all cases the purification of the hydrocarbons obtained in the last stages of the syntheses comprised refluxing over sodium for several hours, distilling to as small a residue as possible and fractionating in 50- or 100-plate columns. Recently, the 100-plate columns have been modified to operate at reduced pressures and, as a result, some of the higher boiling aromatic hydrocarbons have been fractionated at 50 mm. or 100 mm. instead of at 760 mm. From these distillations, the final "best" samples were obtained by bulking fractions of constant boiling point and constant refractive index. In a number of cases, freezing points of individual fractions were used as an additional check.

Tetramethylbenzenes

1,2,4,5-Tetramethylbenzene (Durene).—The alkylation of a mixed coal-tar *meta/para*-xylene cut was carried out as described by Smith.[7] The yield of tetramethylbenzenes obtained from a number of runs varied from 8.3% to 43% based on the xylene taken while the yield of crude durene varied from 2% up to 15.3%. The average yield of tetramethylbenzene cut from nine thirty mole runs was 17% theoretical.

Cooling the mixture to −10° brought about the crystallization of the durene, which was filtered off and crystallized three times from ethanol and finally from benzene. The mother liquors were used for the preparation of prehnitene and isodurene (see below). The yield of pure durene (no. 1129) from 28.6 kilograms of xylene was 1470 g.

1,2,3,4-Tetramethylbenzene (Prehnitene).—The experimental procedure for the conversion of durene and isodurene sulfonic acids by the Jacobsen reaction into prehnitene sulfonic acid varied slightly from that given in "Organic Reactions."[8] It was found that the reaction between the acid and hydrocarbon was too violent to allow shaking in a separating funnel, and consequently the sulfonation was carried out in a wide-mouthed bottle with efficient stirring. The starting material for this preparation was the mother liquors from the tetramethylbenzenes, obtained by the alkylation of xylenes, after filtration of the durene.

The prehnitene sulfonic acid from 750 g. of hydrocarbon was hydrolyzed by dissolving in 2 liters of water and allowing this aqueous solution to drip into sulfuric acid (600 ml. of 96% acid and 400 ml. of water) which was maintained at 140–150°. During the hydrolysis, a stream of super-heated steam was blown through the reaction mixture, the prehnitene thus being steam distilled over as rapidly as formed. The yield of crude prehnitene thus obtained was 1564 g. from 2350 g. of mixed durene–isodurene. Final purification was effected by distillation in a 100-plate column at 48 mm. pressure.

1,2,3,5-Tetramethylbenzene (Isodurene): **First Method, via Bromomesitylene.**[9]—The bromination of mesitylene proceeded satisfactorily and the crude bromo-compound, which was obtained in 75 to 80% yields, was fractionated in a 20-plate column under reduced pressure. The fractions, which were bulked together, boiled at 135.5° at 50 mm. pressure and had a constant refractive index $n^{20}\text{D}$ of 1.5520.

Table I

Physical Constants of Durene, Prehnitene and Isodurene

				Isodurene	
		Durene no. 1129	Prehnitene no. 1130	From bromomesitylene no. 1131	By fractionation no. 1134
B. p.	°C.	196.85	205.10	198.15	198.15
	Mm.	760	760	760	760
	°C.	....	115.3	104.5	120.0
	Mm.	....	49	36	73
$n^{20}\text{D}$		....	1.5203	1.5130	1.5130
d^{20}		....	0.9046	0.8905	0.8904
F. p., °C.		79.09	−6.33	−23.81	−23.77
Estimated purity, wt. %		99.6	99.8	99.8	99.88

Reaction of the Grignard compound of the bromomesitylene with dimethyl sulfate[9] gave a 55% yield of crude isodurene (600 g.) which on fractionation in a 50-plate column at 36 mm. pressure gave 308 g. of hydrocarbon. The purity of this hydrocarbon as indicated by its freezing point was 99.8% by weight.

Second Method, by Alkylation of Xylene.—The mother liquors, after filtration of crude durene from the tetramethylbenzene fractions, were twice fractionated in a 100-plate column at 100 mm. pressure.

Ethylxylenes

1,3-Dimethyl-4-ethylbenzene

***m*-4-Xylidine** (1,3-Dimethyl-4-aminobenzene): **2,4-Dimethylbenzonitrile.**—Approximately 15 kilograms of technical *m*-4-xylidine acetate was crystallized once from petroleum ether which served to remove most of the attached oil. The amine was then regenerated from the acetate, distilled at 30 mm. pressure and converted to the hydrochloride. Crystallization of this salt from 5% hydrochloric acid gave a final material (7,931 g.) of melting point 161–162°. The yield of nitrile from the hydrochloride *via* the Sandmeyer reaction was 52.4%.

2,4-Dimethylacetophenone.—The product from the Grignard reaction contained a mixture of the ketone and unchanged nitrile and these proved very difficult to separate by distillation. However, trial Clemmensen reductions on the mixture indicated that although the ketone was reduced to hydrocarbon, the nitrile remained unaffected. Consequently the whole of the mixture (2,473 g.) was reduced and the reaction product distilled at a pressure of 140 mm. The hydrocarbon boiled at 130° at this pressure and the residue which remained consisted almost entirely of unreacted nitrile.

1,2-Dimethyl-4-ethylbenzene

4-Nitro-*o*-xylene. (**1,2-Dimethyl-4-nitrobenzene**).—*o*-Xylene (19,150 g., purity 99.92%) was nitrated according to the method of Emerson and Smith.[10] The crude nitroxylenes (21,622 g.) were fractionated in a 7-ft. all-glass helix-packed column under reduced pressure when the 3-nitro compound (11,020 g.) was taken overhead and the 4-nitro-*o*-xylene left as a residue. The latter was distilled from a Claisen flask at 12 mm. pressure, the distillate solidifying on cooling. Final purification was effected by crystallization from ethanol, the recrystallized 4-nitro-compound weighing 8,122 g.

***o*-4-Xylidine** (**1,2-Dimethyl-4-aminobenzene**).—Reduction of the nitro compound was carried out with hydrogen in a stirred autoclave using a Raney nickel catalyst, the pressure employed being 1500 lb. per sq. in. As soon as the reaction commenced, usually at 90 to 100°, the temperature rose very rapidly due to the strongly exothermic nature of the reaction, and the external heating was stopped. By regulation of the hydrogen pressure and the rate of stirring, the temperature was maintained at 150 ± 2°.[11] Before the amine solidified, the product was removed from the autoclave, steam distilled and then distilled under reduced pressure. Crystallization of the crude amine from 60–80° petroleum ether gave 4,930 g. of purified *o*-4-xylidine.

3,4-Dimethylbenzonitrile: **3,4-Dimethylbenzoic Acid.**—The Sandmeyer reaction on *o*-4-xylidine gave a 43.5% yield of nitrile (2,015 g.) and hydrolysis of this material gave a 70% yield of acid melting at 164°.

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(7) "Organic Syntheses," Coll. Vol. II, p. 248.

(8) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 382.

(9) "Organic Syntheses," Coll. Vol. II, pp. 95 and 360.

(10) Emerson and Smith, This Journal, **62**, 141 (1940).

(11) It is important that the temperature is not allowed to fall below 145° whilst the hydrogenation is proceeding otherwise the reaction rate slows down considerably and can only be raised again with difficulty.

3,4-Dimethylacetophenone.—The acetic acid solution of the 3,4-dimethylbenzoic acid (150 g. in 500 ml. of acetic acid) was maintained at a temperature of approximately 60° to avoid crystallization of the xylic acid. The pure ketone (906 g.), obtained from 1,560 g. of acid, had the physical properties given in Table II.

1,3-Dimethyl-5-ethylbenzene

***m*-5-Xylidine (1,3-Dimethyl-5-aminobenzene).**—The most satisfactory method for the preparation of this amine was by the direct amination of 1,3,5-xylenol. Amination of this xylenol, with ammonia and ammonium chloride under pressure, had previously been studied by Morgan and Pratt[12] who found that treatment with ammonia alone at 350° for eight hours gave a 20% yield of the required xylidine.

Various catalysts have been recommended to increase the production of *m*-5-xylidine, chiefly chlorides of such metals as zinc, iron, etc., but a preliminary experiment using ferric chloride (5% by weight) yielded mostly the secondary base and very little xylidine. To avoid formation of the secondary amine, it was therefore decided to use no catalyst at all but merely to heat the xylenol with ammonia, recover the unchanged starting material from the base and reaminate.

The aminations were kindly carried out by Dr. Hardy at the Chemical Research Laboratory, Teddington, England, in an 18-liter autoclave equipped with a stirrer. Commercially "pure" 1,3,5-xylenol (6,530 g.) and liquid ammonia (2,025 g.) were weighed into an autoclave and stirring was commenced whilst cold and continued throughout the warming up period. The time taken to reach the reaction temperature of 350° was approximately six hours and at this temperature the pressure was of the order of 200 to 250 atmospheres. The autoclave was maintained at 350 to 360° for eight hours and was then allowed to cool. At the end of each run, the excess of ammonia was blown to waste and the autoclave flushed out with a current of air.

The crude product was dissolved in 60–80° petroleum ether at 35 to 40°, and washed several times with dilute hydrochloric acid until all the amine had been extracted. The acid extracts were neutralized with caustic soda and the amine, which was recovered by steam distillation, was distilled under reduced pressure. Approximately 25% of the amination product was recovered as crude xylidine. The unchanged xylenol crystallized out from the petroleum ether solution on cooling and was filtered off.

A further batch of xylidine was prepared employing only xylenol recovered from the earlier runs. On working up the product, it was discovered that the yield of xylidine had increased to 70 to 75%, the weight of crude xylidine obtained from 7,138 g. of xylenol being 4,900 g. This increased yield of amine obtained indicated that the recovered xylenol must have contained some material which was capable of catalyzing the amination reaction.[13]

The crude *sym*-xylidine (11,400 g.) was converted to the formyl-derivative, which was crystallized from methanol to constant melting point (76%). The final amine (9,274 g.) was obtained by steam distilling the pure formxylidide (11,680 g.) from caustic soda solution.

3,5-Dimethylbenzonitrile.—The yield of nitrile based on amine was 45% of the theoretical.

3,5-Dimethylacetophenone.—A preliminary experiment was carried out using the conditions employed for the *m*-4-xylonitrile, but the yield of ketone was only of the order of 50%. In addition to the expected ketone, a small amount of yellow solid separated during the decomposition of the ketimine. Analysis showed this material to be trixylyldiazine produced from two molecules of nitrile and one of ketimine. It was found that the best method of carrying out the Grignard reaction on symmetrical xylonitrile was to use a considerable excess of methylmagnesium iodide over that theoretically required. Using a 2.5 to 1 mole ratio of Grignard to nitrile, the yield of ketone was 63%. The yield of ethylxylene from the ketone was 82%. A high-boiling residue, obtained from the fractionation of the crude hydrocarbon, was shown to contain a solid hydrocarbon (m. p. 277.5°) believed to be trixylylbenzene.

1,4-Dimethyl-2-ethylbenzene

***p*-Xylidine (1,4-Dimethyl-2-aminobenzene): 2,5-Dimethylbenzonitrile.**—The hydrochloride of this base was obtained by crystallization of a batch of commercial *p*-xylidine hydrochloride (as obtained by treatment of coal-tar xylidines with hydrochloric acid) from dilute hydrochloric acid. The free base regenerated from the hydrochloride (m. p. 223°) had the physical properties shown in Table II. The yield of nitrile from amine in this case was only 38%.

Although the purity of this nitrile was only 96.0%, no further purification was attempted since it was considered that this could be most satisfactorily carried out at the next stage.

2,5-Dimethylbenzoic Acid.—Hydrolysis of the nitrile (2,600 g.) by the standard procedure gave 2,5-dimethylbenzoic acid, which was crystallized to a constant melting point of 132°.

2,5-Dimethylacetophenone.—Ketonization of the above acid with acetic acid over thoria produced 2,5-dimethylacetophenone in 69% yield

1,2-Dimethyl-3-ethylbenzene

***o*-3-Xylidine (1,2-Dimethyl-3-aminobenzene): 2,3-Dimethylbenzonitrile.**—This was obtained by reduction of 3-nitro-*o*-xylene, the preparation of which has already been described, with hydrogen in the presence of Raney nickel under conditions similar to those used for *o*-4-xylidine. Purification of the amine was effected through its sulfate, the *o*-3-xylidine sulfate being much less soluble in water than the *o*-4-salt.[14] The amine was regenerated from the purified sulfate for the diazotization and Sandmeyer reaction. The yield of nitrile from amine was 27%.

Again, further purification was considered easier at the next stage of the synthesis.

2,3-Dimethylbenzoic Acid.—The yield of xylic acid, which was purified to a constant melting point of 143.5°, was 68% based on the nitrile.

2,3-Dimethylacetophenone.—The ketone was prepared in the usual way by passage of *o*-3-xylic acid with acetic acid over thoria.

1,3-Dimethyl-2-ethylbenzene

***m*-2-Xylidine (1,3-Dimethyl-2-aminobenzene).**—When the preparation of this amine was commenced, it was realized that the most satisfactory method would have been by the nitration of pure *m*-xylene, separation of the 2-nitro-*m*-xylene and 4-nitro-*m*-xylene by fractionation, followed by reduction of the former in a manner similar to that employed for the *o*-xylidines.[15] Unfortunately, at the time, an insufficient supply of pure *m*-xylene was available and the raw material used was a commercially available xylidine mixture even though it was known that the desired amine was present only to a small extent in this product and was contaminated with isomeric amines derived from ethylbenzene, *o*-xylene and *p*-xylene. The separation of *m*-2-xylidine from this mixture was however, relatively easily if tediously effected.

A quantity (80 gallons) of "Xylidine residues," which is the material obtained from coal-tar xylidines after removal of the bulk of the *m*-4- and *p*-xylidines as acetate and hydrochloride respectively, was made available through the kindness of Imperial Chemical Industries, Ltd. (Dyestuffs Division). The method of separation adopted was also suggested by I. C. I. and depended on the isolation of

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(12) Morgan and Pratt, *J. Soc. Chem. Ind.*, **51**, 283(T) (1932).

(13) Further work on this process has since been carried out and is covered in British Patent Application No. 17,719/46.

(14) The solubility of *o*-3-xylidine sulfate was approximately 200 g. in 3-liters of water at the boiling point.

(15) A report describing German work on the nitration of *m*-xylene and the separation of the nitro-*m*-xylenes at Leverkusen has recently been issued (British Intelligence Objectives Subcommittee Final Report 1146. Published by H. M. Stationery Office, London, 1947).

TABLE II

PHYSICAL CONSTANTS OF THE SIX ISOMERIC ETHYLXYLENES TOGETHER WITH THOSE OF THEIR INTERMEDIATES

Ethylxylene	1,3-Dimethyl-4-ethyl	1,2-Dimethyl-4-ethyl	1,3-Dimethyl-5-ethyl	1,4-Dimethyl-2-ethyl	1,2-Dimethyl-3-ethyl	1,3-Dimethyl-2-ethyl
Nitro-compound						
B. p., °C. (mm.)	....	130(12)	....	....	116(10) 106(5)	....
M. p., °C.	....	+28.5	....	....	+14.2	....
n^{20}D	....	....	....	....	1.5441	....
d^{20}	....	....	....	....	1.1402	....
Estimated purity, wt. %	....	99.5	....	....	99.6	....
Amine						
F. p., °C.	−14.3	+48.9	+9.8	+14.2	+3.5[a]	+11.2
n^{20}D	1.5576	....	1.5581	1.5596	1.5684	1.5610
d^{20}	0.9763	....	0.9706	0.9755	0.9931	0.9842
Estimated purity, wt. %	99.0	99.4	99.6	99.0	99.3	98.9
Nitrile						
B. p., °C. (mm.)	112(21)	....	....	104–105(18)	112(25)	....
F. p., °C.	+23.9	+65.7	+42.9	+11.0	+16.4	....
Estimated purity, wt. %	99.1	99.5	99.6	96.0	92.7	....
Ketone						
B. p., °C. (mm.)	....	132(19)	129(22) 122(17)	127(31)	108(13)	....
F. p., °C.	....	−5.1	+22.9	−18.1	−14.3	....
n^{20}D	....	1.5400	(n^{25}D) 1.5276	1.5306	1.5334	....
d^{20}	....	1.0042	(d^{25}) 0.9879	0.9955	1.0079	....
Estimated purity, wt. %	....	99.1	99.6	99.4	99.65	....
Hydrocarbon, no.	1085	1087	1088	1098	1102	1103
Sunbury determinations						
B. p., °C. at 760 mm.	188.45	189.55	183.65	186.45	193.80	189.95
M. p., °C.	−63.01	−67.09	−84.43	−53.74	−49.54	−16.34
n^{20}D	1.5039	1.5032	1.4981	1.5043	1.5117	1.5107
d^{20}	0.8759	0.8741	0.8644	0.8777	0.8920	0.8905
Estimated purity, wt. %	>99.6	>99.6	>99.7	>99.8	>99.6	99.84
N. B. S. determinations[b]						
B. p., °C. at 760 mm.	188.41	189.75	183.75	186.91	193.91	190.01
dt/dP at 760 mm., °C./mm.	0.055	0.0563	0.0542	0.0533	0.0554	0.0561
n^{20}D	1.50383	1.50311	1.49810	1.50435	1.51172	1.51072
n^{25}D	1.50156	1.50086	1.49583	1.50199	1.50950	1.50850
d^{20}	0.87627	0.87452	0.86479	0.87717	0.89209	0.89043
d^{25}	0.87230	0.87058	0.86078	0.87317	0.88814	0.88642

[a] M. p. of formyl derivative 102°. [b] Determinations of the physical constants on the six ethylxylenes, whose preparations are described here, were kindly carried out by Dr. Rossini at the National Bureau of Standards and these are included together with the values obtained at Sunbury.

the *m*-2-xylidine as the nitrate after a preliminary treatment of the residues with sulfuric acid.

The crude amine was purified through its formyl derivative. The total amount of xylidine residues treated was 311 kg. from which 9,510 g. of *m*-2-formxylidide of melting point 164° was obtained. The amine was regenerated in the usual manner by steam distillation in the presence of caustic soda whereby 6,990 g. of *m*-2-xylidine was obtained from 8,750 g. of formyl compound.

While the above work on the isolation of *m*-2-xylidine from the residues was proceeding, it was decided to investigate whether any individual xylidines could be separated from this material by means of fractionation alone. It was found that it was possible by distillation of the residues at a pressure of 10 mm. in a 20-plate column to obtain a low boiling fraction rich in *m*-2-xylidine and a high boiling fraction rich in *o*-4-xylidine. Further work along these lines is given in British Patent Application 15,840/46.

It was found that neither of the schemes already described for going from the amine to the hydrocarbon could be applied to the 1,3-dimethyl-2-ethylbenzene. Using the Grignard technique, no reaction occurred with *m*-2-xylonitrile and the latter was recovered completely unchanged. An attempt was also made to prepare the carboxylic acid from the nitrile but it was found, rather surprisingly, that on hydrolysis the —CN group was eliminated and the only product recoverable was *m*-xylene. The method finally adopted was the conversion of the amine to the iodo compound which in turn was treated with magnesium, the Grignard compound thus formed being then treated with diethyl sulfate.

2,6-Dimethyliodobenzene.—The method adopted for the conversion of the amine to the iodo compound was based on that of Hickinbottom.[16] Diazotization of the amine was carried out in the presence of sulfuric acid and the diazo solution reacted with potassium iodide solution at 0°. After allowing to stand overnight, the product was worked up in the usual manner. Fractionation of the crude iodoxylene gave a final material (5857 g. from 6137 g. of *m*-2-xylidine) which was used for the Grignard reaction. Physical properties of 2,6-dimethyliodobenzene; b. p. 102.3° (14 mm.); f. p. + 11.2°; n^{20}D 1.6035; d^{20} 1.6518; estimated purity 99.6% by wt.

1,3-Dimethyl-2-ethylbenzene.—The iodoxylene was converted to the magnesium compound which in turn was treated with diethyl sulfate. The crude hydrocarbon obtained from this reaction was given a purification by reflux-

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(16) Hickinbottom, "Reaction of Organic Compounds," Longmans-Green, London, 1936, p. 341.

ing for one hour with alcoholic soda followed by steam distillation. Fractionation in a 40-plate column gave a material boiling at 188° and having a refractive index of 1.5110. Further purification of the hydrocarbon, which was yellow in color, was effected by stirring with 20% caustic potash for two hours followed by sodium treatment and fractionation.

Diethylbenzenes

o-Diethylbenzene

o-Nitroethylbenzene.—Ethylbenzene was nitrated according to the method of Cline and Reid.[17] The crude nitration product was distilled under reduced pressure from an oil-bath, care being taken that the temperature of the liquid did not exceed 150°. The isomeric nitro compounds were then fractionated in a 7-ft. glass helix-packed column under reduced pressure. Fractions containing the *o*-nitroethylbenzene from several distillations boiling at 119° at 19 mm. were bulked and refractionated, fractions of the distillate of constant refractive index being bulked prior to reduction. Nitration of 12 kg. of ethylbenzene produced 12,104 g. of crude nitroethylbenzenes from which was isolated 4,650 g. of the pure *ortho* isomer.

o-Ethylaniline.—The reduction of the nitroethylbenzene was carried out under conditions similar to those employed for the reduction of the nitro-*o*-xylenes.

o-Ethylacetophenone.—Trial runs indicated that reaction of *o*-ethylbenzonitrile with an excess of methylmagnesium iodide gave a product which was a mixture of ketone and unchanged nitrile in approximately equal proportions and these two compounds proved to be separable by vacuum fractionation. The procedure therefore adopted was to treat the whole of the nitrile with methylmagnesium iodide and separate the unchanged nitrile by fractionation. The latter then reacted further until the final yield of ketone based on reacted nitrile was 62% of the theoretical.

m-Diethylbenzene

Fractionation of Commercial Diethylbenzene.—A commercial diethylbenzene cut, which was kindly given by the Distillers Co., Ltd., was fractionated in a 100-plate column and the fractions boiling between 180.6 and 181.5° and having refractive indices of 1.4954 or 1.4955 were bulked, refluxed with sodium and refractionated. Separation of the *o*- and *p*-isomers from this material could not be effected by fractionation owing to the similarity in their boiling points.

p-Diethylbenzene

p-Nitroethylbenzene.—The *p*-nitroethylbenzene was obtained with the *ortho* derivative in the product from the nitration of ethylbenzene, this isomer distilling at 125° at 12 mm. Attempts to isolate the *meta* isomer from the intermediate boiling fractions failed. From the 12 kg. of ethylbenzene which was nitrated, the final yield of *p*-nitroethylbenzene was 4,750 g.

p-Ethylaniline.—The amine obtained by the catalytic reduction of the above nitro compound appeared from its freezing point to be relatively impure (92.5%) and further purification was effected through its acetyl derivative (m. p. 89.5° to 90.5°).

p-Ethylbenzoic Acid.—The *p*-ethylbenzoic acid, which was obtained on hydrolysis of the nitrile, was crystallized to a constant melting point of 112°. The yield of pure acid based on nitrile was 85% theoretical.

p-Ethylacetophenone.—*p*-Ethylbenzoic acid and glacial acetic acid (300 g. per liter of acetic acid) were passed over a thoria catalyst at 450° and the resulting product was fractionated in a 25-plate column at a pressure of 20 mm.

Methyl-*n*-Propylbenzenes

Methylpropiophenones.—The three ketones were prepared from the corresponding nitriles and ethylmagnesium chloride using the procedure already described. The reaction was usually carried out in 12-liter flasks, 350 g. of the nitrile being added to the Grignard reagent from 168 g. of magnesium in 3-liters of ether. The crude ketones were fractionated at reduced pressures from which fractions of constant refractive index and constant boiling point were bulked.

TABLE III

PHYSICAL CONSTANTS OF *o*- AND *p*-DIETHYLBENZENES TOGETHER WITH THOSE OF THEIR INTERMEDIATES

Diethylbenzene	*Ortho*	*Para*
Nitro-compound		
B. p., °C. (mm.)	119(19)	125(12)
$n^{20}D$	1.5354	1.5455
F. p., °C.	....	−12.3
d^{20}	....	1.1183
Estimated purity, wt. %	....	98.4
Amine		
B. p., °C. (mm.)	108(30)	111(22)
F. p., °C.	−46.6	−5.85
$n^{20}D$	1.5588	1.5550
d^{20}	0.9810	0.9690
Estimated purity, wt. %	99.3	97.8
Nitrile		
B. p., °C. (mm.)	115(29)	*ca.* 121(24)
F. p., °C.	−23.6	−24.2
$n^{20}D$	1.5232	1.5274
d^{20}	0.9781	0.9716
Estimated purity, wt. %	96.5	97.0
Yield, % theoretical on amine	50	38
Ketone		
B. p., °C. (mm.)	118(29)	125(20)
F. p., °C.	−19.0	−20.6
$n^{20}D$	1.5249	1.5298
d^{20}	0.9918	0.9985
Estimated purity, wt. %	96.0	99.3
Hydrocarbon, no.	1099	1100
B. p., °C. at 760 mm.	183.30	183.60
F. p., °C.	−31.44	−43.25
$n^{20}D$	1.5034	1.4947
d^{20}	0.8805	0.8619
Estimated purity, wt. %	99.85	99.65

TABLE IV

PHYSICAL CONSTANTS OF *m*-DIETHYLBENZENE

B. p., °C. at 760 mm.	181.25
F. p., °C.	−83.82
$n^{20}D$	1.4956
d^{20}	0.8641
Estimated purity, wt. %	99.98

Methylisopropylbenzenes (Cymenes)

***o*- and *m*-Cymenes.**—These two isomers were synthesized by identical routes. The toluic acids, obtained from the toluidines *via* the nitriles, were converted to the acid chlorides which in turn were converted to the tertiary alcohols by reaction with methylmagnesium chloride. These reactions were carried out in 10-liter cylindrical copper pots. The products, after working up in the usual way, were mixtures of the olefins and alcohols. Dehydration was completed by distillation at atmospheric pressure through a column packed with short lengths of glass tubing.

m-Isopropenyltoluene.—B. p. 184°; $n^{20}D$ 1.5321, yield 81%.

o-Isopropenyltoluene.—B. p. 170–171°; **yield,** 79.5%.

The olefins were hydrogenated in an autoclave using a Raney nickel catalyst. Reaction commenced at room

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[17] Cline and Reid, THIS JOURNAL, **49**, 3150 (1927).

TABLE V

PHYSICAL PROPERTIES OF *o*-, *m*- AND *p*-METHYL-*n*-PROPYLBENZENES AND *o*-, *m*- AND *p*-METHYLPROPIOPHENONES

	Ortho	*Meta*	*Para*
Ketone			
B. p., °C. (mm.)	127.5(38)	134(32)	135(30)
F. p., °C.	−27.6	− 4.4	+ 7.2
$n^{20}D$	1.5250	1.5249	1.5278
Estimated purity, wt. %	99.3	99.0	97.3
Yield, % based on nitrile	65	82	97
Hydrocarbon, no.	1120	1124[a]	1119
B. p., °C. at 760 mm.	184.75	181.75	183.10
F. p., °C.	−60.44	....	−63.77
$n^{20}D$	1.4998	1.4936	1.4918
d^{20}	0.8744	0.8610	0.8585
Estimated purity, wt. %	99.4	....	99.6

[a] This hydrocarbon set to a glass on cooling and consequently an estimate of its purity was not possible.

temperature with a hydrogen pressure of 1700 lb./sq. in. and the temperature then rose rapidly to 90° at which it was maintained until hydrogenation was complete. Under these conditions no hydrogenation of the aromatic ring occurred. Yields based on toluic acids; *m*-cymene, 67%; *o*-cymene, 65%.

TABLE VI

PHYSICAL PROPERTIES OF *o*-, *m*- AND *p*-CYMENES

	Ortho, 1073	*Meta*, 1076	*Para* From technical cymene. 1044	*Para* From camphor. 1054
B. p., °C. at 760 mm.	178.35	175.20	177.25	177.10
F. p., °C.	−71.71	−63.89	−68.21	−70.13
$n^{20}D$	1.5006	1.4930	1.4909	1.4910
d^{20}	0.8766	0.8610	0.8573	.08575
Estimated purity, wt. %	99.96	99.96	99.8	95.8

***p*-Cymene: First Method, from Technical Cymene.**—The commercial material, a by-product from the wood-pulp industry, was fractionated after the following series of refining treatments:[18] (1) steam distillation after refluxing with 10% by weight of powdered sulfur; (2) treatment with small amounts of sulfuric acid followed by chlorosulfonic acid and an alkali wash; (3) shaking for three hours with potassium permanganate solution; (4) refluxing for five hours over sodium.

Fractions of constant refractive index ($n^{20}D$) were bulked to give 1,013 g. of "best" *p*-cymene.

Second Method, from Camphor.—A quantity of *p*-cymene was prepared from camphor and phosphorus pentoxide.[19] The yield of purified material was poor (30%) and the product rather impure.

Butylbenzenes

***n*-Butylbenzene: First Method, *n*-Butyrophenone.**—*n*-Butyrophenone was prepared in the usual manner by the reaction of *n*-butyryl chloride and benzene in the presence of aluminium chloride. Properties of ketone: b. p. 142° at 50 mm., 128° at 27 mm., $n^{20}D$ 1.5198–1.5199.

The hydrocarbon obtained by reduction of the ketone was extremely sensitive to oxidation by air and had to be freshly distilled before the physical constants were determined.

Second Method, Bromobenzene.—The product from the reaction of bromobenzene and *n*-butyl bromide[20] was obtained in poor yield and was of low purity.[21]

Isobutylbenzene.—Isobutyrophenone was prepared from isobutyryl chloride and benzene as for *n*-butyrophenone. The pure ketone, which was obtained by fractionation of the product at 50 mm. pressure, amounted to 1,653 g. Properties of ketone; b. p. 131.0° at 50 mm.; $n^{20}D$ 1.5176.

***s*-Butylbenzene: First Method, by Alkylation.**—The conditions used for the alkylation of benzene with 2-butanol were those given by Meyer and Bernhauer.[22] The yield of crude *s*-butylbenzene (1,710 g.) on benzene taken was 52% of the theoretical.

Purification was effected by vigorous stirring with concentrated sulfuric acid (1% by volume of 96% acid) followed by removal of the acid, neutralization with sodium hydroxide solution, refluxing with sodium and finally fractionation.

The purity of the hydrocarbon could not be estimated accurately owing to the peculiar shape of the freezing curve but it was not less than 99.75%. The fact that only one isomer is formed by this method of alkylation confirms the findings of both Meyer and Bernhauer and of Nightingale and Smith.[23]

Second Method, Methylethylphenylcarbinol.—This carbinol was obtained in 85% yield from acetophenone and

TABLE VII

PHYSICAL PROPERTIES OF THE BUTYLBENZENES

	B. p., °C. at 760 mm.	F. p., °C.	$n^{20}D$	d^{20}	Estimated purity, wt. %
n-Butylbenzene					
(a) From butyrophenone, no. 1094	183.35	−87.54	1.4897	0.8603	Not less than 99.9
(b) From bromobenzene, no. 1070	183.10	−87.82	1.4897	.8603	Not less than 98.9
Isobutylbenzene					
From isobutyrophenone, 1092	172.85	−51.59	1.4865	.8535	99.98
s-Butylbenzene					
(a) By alkylation, no. 1093	173.30	−75.39	1.4898	.8619	Not less than 99.75
(b) From acetophenone, no. 1082	173.30	−75.30	1.4902	.8622	Not less than 99.75
t-Butylbenzene					
(a) By alkylation, no. 1002	169.5	−58.09	1.4926	.8666	99.92
(b) By disproportionation, no. 1001	169.45	−58.34	1.4927	.8667	99.66

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(18) Le Fèvre, Le Fèvre and Robertson, *J. Chem. Soc.*, **138**, 480 (1935).

(19) Fittig, *Ann.*, **172**, 307 (1874).

(20) Read and Foster, THIS JOURNAL, **48**, 1606 (1926).

(21) Since this work was completed, it has been observed that 1-phenylbutadiene-1,3 can be obtained in satisfactory yields from cinnamaldehyde. This diene would probably be an excellent starting material for preparing further quantities of *n*-butylbenzene in a high state of purity.

(22) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721 (1929).

(23) Nightingale and Smith, THIS JOURNAL, **61**, 101 (1939).

ethylmagnesium chloride. Properties of carbinol: b. p. 140° at 25 mm.; $n^{20}\mathrm{D}$ 1.5198.

The carbinol was dehydrated over activated alumina at 300-350°, and the olefin hydrogenated as for *o*- and *m*-cymenes.

t-Butylbenzene: **First Method, by Alkylation.**—*t*-Butyl chloride (1.108 g.) was added to a stirred mixture of benzene (5.320 g.) and powdered anhydrous aluminum chloride over a period of two hours. Stirring was continued for a further thirty minutes after which the hydrocarbon was decanted from the catalyst and worked up in the usual manner. The residue in the flask was used as catalyst for eleven similar runs with addition of 20 g. of fresh aluminium chloride in between each batch.

A total quantity of 11 gallons of fractionated hydrocarbon was prepared.

Second Method. By Disproportionation of *p*-Di-*t*-Butylbenzene and Benzene.—The conditions used for this reaction were those described by Ipatieff and Corson,[24] approximately 2 kg. of *t*-butylbenzene being prepared by this method. The yield of final hydrocarbon was 85% based on *p*-di-*t*-butylbenzene initially taken.

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Summary

Selected methods for the preparation of the twenty-two monocyclic C_{10} aromatic hydrocarbons are described. Selection was based upon readily available starting materials, which could be conveniently purified, and upon reactions easy to carry out on a relatively large scale. Excepting where a required hydrocarbon could be readily separated from a commercially available material by fractionation, *e.g.*, *m*-diethylbenzene, syntheses have been chosen to avoid the presence of impurities in the final hydrocarbon which would prove difficult to separate.

Physical constants have been determined on the hydrocarbons and on most of the amines, nitriles, ketones and nitro compounds which were obtained as intermediates in the syntheses.

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(24) Ipatieff and Corson, THIS JOURNAL, **59**, 1417 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE]

Interaction of Homologous Alkyl Sulfates with Bovine Serum Albumin

BY FRED KARUSH[1] AND MARTIN SONENBERG

The study of the structure of the protein molecule as it exists in aqueous solution meets formidable difficulties not only because of the complexity of the structure but also because of the absence of any really direct and general experimental method. It is true, of course, that important structural information has come and more will undoubtedly follow from X-ray diffraction investigations with protein crystals and that much of this knowledge can be carried over to the dissolved molecule. However, it is still an open question whether the diffraction method can disclose the fine details of protein structure, particularly those associated with the configuration of side chains. These elements of structure are undoubtedly of crucial significance in the determination of specificity. In any case, it would appear that the environment of the protein molecule in the crystal is sufficiently different from that in solution that significant limits on the extrapolation from solid to solution must be imposed. It seems very likely that distinctive structural properties would accrue to the protein molecule in the transition from the crystalline to the dissolved state.

One experimental approach which offers promise of obtaining information which can be interpreted in terms of protein configuration is the study of complex formation of protein with small organic ions or molecules of known structure. In the specialized field of immunochemistry this method has been intensively employed[2] and has led to considerable clarification with regard to the problem of serological specificity. It is particularly applicable to the study of serum albumins since these proteins are able to combine reversibly with a great variety of compounds of known structure, in particular, organic anions.[3-7]

In the investigation described here we have studied the reversible binding by bovine serum albumin of an homologous series of straight chain alkyl sulfates. These compounds offer the possibility of distinguishing between polar and nonpolar contributions to the binding. The work was conducted with a view to obtaining the maximum amount of thermodynamic information about the binding process. Earlier studies[8] of the interaction of serum albumin and alkyl sulfates, as well as other synthetic detergents, have involved much higher concentrations of detergent

(1) Investigation conducted during tenure of a Fellowship in Cancer Research of the American Cancer Society, recommended by the Committee on Growth of the National Research Council; present address: Sloan-Kettering Institute for Cancer Research, New York.

(2) K. Landsteiner, "The Specificity of Serological Reactions," Harvard University Press, Cambridge, Mass., 1945.

(3) B. D. Davis, *J. Clin. Invest.*, **22**, 753 (1943).

(4) B. D. Davis, *Am. Scientist*, **34**, 611 (1946).

(5) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

(6) I. M. Klotz and J. M. Urquhart, *J. Biol. Chem.*, **173**, 21 (1948).

(7) J. D. Teresi and J. M. Luck, *ibid.*, **174**, 653 (1948).

(8) F. W. Putnam, *Adv. Prot. Chem.*, **4**, 79 (1948).