product was fractionally distilled at atmospheric pressure. The first fraction boiling at 81–83° consisted of benzene. The product boiling at 130–132° (5.62 g.) was shown to be chlorobenzene. The semisolid residue from the steam distillation was extracted with benzene, washed neutral and was dried by distillation with benzene. It weighed 28.07 g. The dry residue was sublimed at 160–200° (2 mm.). The sublimate, dissolved in a minimum amount of Skellysolve C, was adsorbed on aluminum oxide. A blue fluorescent band visible in ultraviolet light was developed and eluted with the same solvent. It yielded 12.70 g. of anthracene, m. p. 212–214°. A brown band, eluted with benzene, contained 7.40 g. of triphenylcarbinol, m. p. 160–162° (from Skellysolve B).

The isomeric methoxy-, chloro- and hydroxybenzaldehydes treated in the same way, yielded phenol and chlorobenzene as volatile products. The non-volatile material consisted of anthracene, triphenylcarbinol and tar. The yields of both volatile and non-volatile substances for aldehydes with equivalent configurations were in the order $CH_3O < Cl < OH$.

Nitrotriphenylmethanes.—Each nitrobenzaldehyde (25 g.) was added slowly to a mixture of 50.6 g. of aluminum chloride and 150 cc. of thiophene-free benzene. The mixture was allowed to react as described for *o*-chlorobenzaldehyde, decomposed and steam distilled. The residual material was dissolved in benzene, dried by distillation with benzene and distilled under reduced pressure. The distillates were crystallized from Skellysolve B.

o-Nitrotriphenylmethane was obtained in 65.5% yield, b. p. 200–210° (2 mm.), m. p. 88–89°. It depressed the melting point of the *m*- and *p*-isomers. Its melting point is reported as 93–94°.[13]

m-Nitrotriphenylmethane boiled at 200–210° (2 mm.) and melted at 91.5–93°, yield 82.4%. The literature melting point is 90°.[14]

The yield of *p*-nitrotriphenylmethane was 67.4%, b. p. 200–210° (2 mm.), m. p. 90–91°. The melting point could be raised to 93–94° by adsorption of the substance on aluminum oxide from Skellysolve C solution. It did not depress the melting point of a sample prepared according to Baeyer and Lohr.[15]

The Reaction with Disubstituted Benzaldehydes.—2,4-Dichloro-, 3,4-dichloro-, 2,3-dimethoxy-, 2-hydroxy-3-methoxybenzaldehyde and veratric aldehyde (0.18 mole each) were treated with benzene and aluminum chloride as described before. The volatile products consisted of *o*- and *m*-dichlorobenzene and guaiacol. The non-volatile material from the disubstituted aldehydes with exception of veratric aldehyde contained anthracene and triphenylcarbinol. Veratric aldehyde gave 15.48 g. of pure vanillin, m. p. 79–80°, as the only non-volatile product.

The Reaction with Toluene.—Benzaldehyde (0.24 mole) aluminum chloride (67 g.) and toluene (150 cc.) yielded 14.9 g. of chromatographically uniform non-volatile material which melted at 215–217° (from Skellysolve C). The substance is regarded as a mixture of 2,6- and 2,7-dimethylanthracenes.[8]

Summary

The reaction of aromatic aldehydes with aluminum chloride and aromatic hydrocarbons has been further investigated. The reaction with the nitrobenzaldehydes represents a simple way to prepare nitrotriphenylmethanes.

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[13] Kliegl, *Ber.*, **40**, 4941 (1907).

[14] Tschacher, *ibid.*, **21**, 188 (1888).

[15] Baeyer and Lohr, *ibid.*, **23**, 1621 (1890).

COLUMBIA, MO. RECEIVED OCTOBER 25, 1948

[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

A Synthesis of N-(3-Methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine

BY K. E. HAMLIN AND ARTHUR W. WESTON

The synthesis of N-(3-methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine (I) was undertaken to determine its identity with α-fagarine, an alkaloid from the plant *Fagara coco*.[1,2] A comparison of physical data has shown I to be different from α-fagarine, thus confirming the results recently reported by Surrey[3] and by Redemann, Wisegarver and Icke.[4] Inasmuch as our synthesis of 3-methoxy-4,5-methylenedioxyphenethylamine (II) is novel and more direct than those previously reported, we wish to describe it as well as certain other unreported experimental data involved in the synthesis of I. The synthesis of II by the rhodanine method of Gränacher[5,6] has been carried out also. Since it nearly duplicates the work of Redemann and co-workers, only where variations occur in the physical data obtained for the compounds prepared in this synthesis, are such differences indicated in the experimental section.

As shown in the accompanying flow sheet, the starting material used was myristicinaldehyde which was obtained in 51% yields by the oxidation of isomyristicin using a modification of the method of Milas.[7] The required isomyristicin was obtained from the isomerization of myristicin by ethanolic potassium hydroxide. A fractionation of heavy oil of nutmeg provided the myristicin.

Myristicinaldehyde was converted to the corresponding nitrostyrene by means of nitromethane. Reduction by lithium aluminum hydride[8] provided a ready synthesis of III. The N-(3-methoxybenzyl)-3-methoxy-4,5-methylenedioxyphenethylamine (III) was prepared by catalytic hydrogenation[3,4] of the Schiff base from II and 3-methoxybenzaldehyde. Methylation by the lithium aluminum hydride reduction[8] of the formyl derivative of III resulted in the formation of I in good yield. The isolation and characterization of I and III as free bases, as well as the above mentioned Schiff base, are described.

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[1] Stuckert, *C. A.*, **29**, 2298 (1935).

[2] Deulofeu, Labriola and De Langhe, THIS JOURNAL, **64**, 2326 (1942).

[3] Surrey, *ibid.*, **70**, 2887 (1948).

[4] Redemann, Wisegarver and Icke, *J. Org. Chem.*, **13**, 886 (1948).

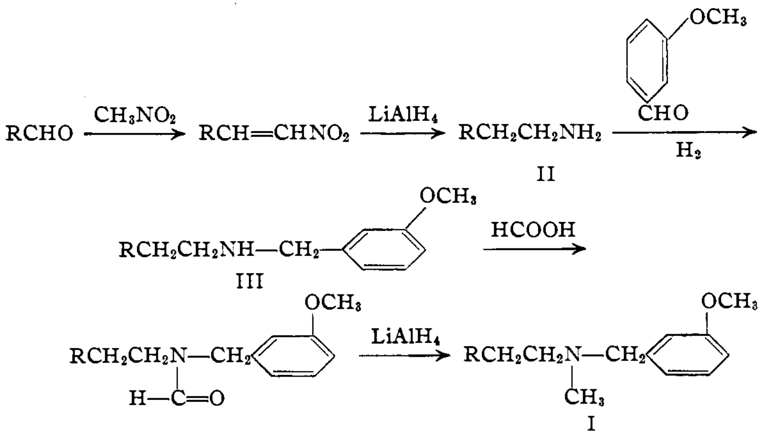
[5] Gränacher, *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923).

[6] Julian and Sturgis, THIS JOURNAL, **57**, 1126 (1935).

[7] Milas, *ibid.*, **59**, 2342 (1937).

[8] Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

FLOW SHEET



R = 3-methoxy-4,5-methylenedioxyphenyl

Experimental

Myristicinaldehyde.—Fractionation of heavy oil of nutmeg obtained from Fritzsche Brothers, Inc., yielded 7.5% myristicin, b. p. 118–120° (2 mm.), $n^{25}\text{D}$ 1.5385. This was rearranged to isomyristicin with ethanolic potassium hydroxide in 89% yield; b. p. 110–115° (1 mm.); m. p. 42–44° (lit.[9] 44°). The method of Milas[7] for the oxidation of isoeugenol and anethole by means of hydrogen peroxide and vanadium pentoxide was applied to isomyristicin. In this manner, myristicinaldehyde, m. p. 130–131°, was obtained in an average yield of 51%.

α-Thiono-β-(3-methoxy-4,5-methylenedioxyphenyl)-propionic Acid.—By means of the hydrolysis of 5-myristicinalrhodanine, a quantitative yield of the thiono acid was obtained. Crystallization from methanol yielded a compound melting at 156–158°. On recrystallization from methanol, the melting point suddenly jumped to 220°. An additional recrystallization from dioxane gave yellow crystals, m. p. 227–228° dec. Redemann, *et al.*,[4] give a melting point of 153–154° dec. from methanol.

Anal. Calcd. for $C_{11}H_{10}O_5S$: C, 51.96; H, 3.96. Found: C, 52.04; H, 3.82.

α-Oximino-β-(3-methoxy-4,5-methylenedioxyphenyl)-propionic Acid.—Treatment of the above thiono acid with hydroxylamine gave a 92% yield of the oximino acid, m. p. 159–160° from toluene (lit.[4] 150–151°).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38; N, 5.53. Found: C, 51.98; H, 4.63; N, 5.41.

3-Methoxy-4,5-methylenedioxy-β-nitrostyrene.—A mixture of 9 g. of myristicinaldehyde, 3 g. of nitromethane, 0.43 g. of *n*-amylamine and 60 cc. of 95% ethanol was permitted to stand protected from light at room temperature for one week. The yellow crystalline precipitate was filtered and washed with additional ethanol. The yield of dried material, m. p. 208–210°, was 10 g. (90%); after recrystallization from butanol, m. p. 210–211°.

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.07; N, 6.28. Found: C, 53.72; H, 3.95; N, 6.23.

3-Methoxy-4,5-methylenedioxyphenethylamine (II).—A solution of 6 g. of 3-methoxy-4,5-methylenedioxy-β-nitrostyrene in anhydrous ether (Soxhlet extraction technique[10]) was added at a rapid reflux rate to a well-stirred solution of 4.2 g. of lithium aluminum hydride in 200 cc. of anhydrous ether, nearly twenty-four hours being required for complete addition. The complex was decomposed by 10% sulfuric acid and the acid fraction was separated from the ether layer. The acid solution was made strongly alkaline with cooling and the resulting mixture extracted well with ether. After the ether extract was dried, the amine was obtained by distillation, b. p. 132° (1 mm.), $n^{25}\text{D}$ 1.5507; yield 2.5 g. (49%). A picrate was prepared and melted at 192–193° (lit.[11] 193°). The hydrochloride melted at 164.5° (lit.[3] 167–168°).

N-(3-Methoxybenzal)-3-methoxy-4,5-methylenedioxyphenethylamine.—A solution of 8.5 g. of 3-methoxy-4,5-methylenedioxyphenethylamine and 6 g. of freshly distilled 3-methoxybenzaldehyde in 50 cc. of ethanol was refluxed for one-half hour and then distilled. The expected product boiled at 215° (0.75 mm.) and solidified to a waxy material, m. p. 39–41°; yield 11 g. (82%).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.98; H, 6.09; N, 4.47.

N-(3-Methoxybenzyl)-3-methoxy-4,5-methylenedioxyphenethylamine (III).—A solution of 10.5 g. of the N-(3-methoxybenzal)-3-methoxy-4,5-methylenedioxyphenethylamine in 50 cc. of methanol was hydrogenated using 1.5 g. of Raney nickel catalyst at 2 atmospheres pressure. After filtration of the catalyst, the solution was distilled to yield 8.5 g. (80%) of viscous base,[12] b. p. 210–215° (0.75 mm.), $n^{25}\text{D}$ 1.5726.

Anal. Calcd. for $C_{18}H_{21}NClO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.62; H, 6.38; N, 4.37.

The hydrochloride salt was prepared and after recrystallization from ethyl acetate, it melted at 142–143° (lit.[3] 144–145°).

Anal. Calcd. for $C_{18}H_{22}NO_4$: C, 61.44; H, 6.30; N, 3.98. Found: C, 61.23; H, 6.14; N, 3.95.

The oxalate salt was prepared from the base with ethereal oxalic acid, m. p. 222° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{23}NO_8$: C, 59.25; H, 5.72; N, 3.46. Found: C, 58.91; H, 5.52; N, 3.53.

N-Formyl-N-(3-methoxybenzyl)-4,5-methylenedioxyphenethylamine.—A solution of 6 g. of N-(3-methoxybenzyl)-4,5-methylenedioxyphenethylamine in 60 cc. of anhydrous formic acid was refluxed for forty-eight hours. After removing the excess formic acid *in vacuo*, the residue was treated with water and extracted with ether. The ether extract was washed with 1% hydrochloric acid and water and dried over anhydrous magnesium sulfate. After removal of the ether, 5 g. of an orange viscous oil remained. A small sample of this became crystalline after considerable manipulation; m. p. 88–90° after several recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{19}H_{21}NO_5$: N, 4.08. Found: N, 4.02.

Seeding with the pure material failed to cause crystallization of the above oil.

N-(3-Methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine (I).—To a stirred solution of 2.2 g. of lithium aluminum hydride in 200 cc. of anhydrous ether was added dropwise a solution of 5 g. of the crude amide described above in 200 cc. of anhydrous ether. After the addition of the amide, the mixture was refluxed an additional six hours. Water was added until the complex and excess lithium aluminum hydride were decomposed. After filtration, the inorganic material was washed with ether and the filtrate extracted well with ether. The ether extracts were combined, dried and then treated with ethereal hydrogen chloride to precipitate the crystalline hydrochloride; yield 4.6 g. (87%), m. p. 157–165°. After recrystallization from ethanol, the product melted at 170–171° (lit.[3] 170.4–171.2° cor.).

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(9) Power and Salway, *J. Chem. Soc.*, **91**, 2055 (1907).

(10) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(11) Decker and Becker, *Ann.*, **395**, 329 (1913).

(12) The same product was obtained in 81% over-all yield from 3-methoxy-4,5-methylenedioxyphenethylamine by hydrogenation in the presence of 3-methoxybenzaldehyde.

The base was liberated from the hydrochloride and distilled as a colorless viscous oil, which failed to crystallize; b. p. 198–200° (0.5 mm.); $n^{25}D$ 1.5643.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.53; H, 6.77; N, 4.29.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg and the members of the Microanalytical Department for the microanalyses and Mr. Morris Freifelder for his assistance in the hydrogenation experiments.

Summary

A new synthesis of N-(3-methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine is reported and additional physical data for this compound and its intermediates are described.

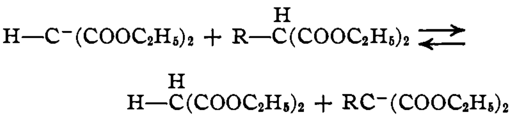
NORTH CHICAGO, ILLINOIS RECEIVED JANUARY 13, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Alkylation of Malonic Ester

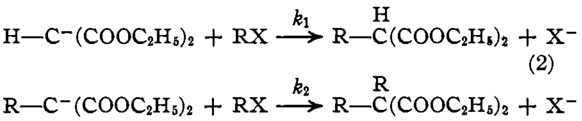
BY RALPH G. PEARSON

The relative amounts of mono- and dialkylation obtained in the reaction of equivalent amounts of malonic ester, sodium alcoholate and an alkyl halide depends on two factors: first, the relative acidities of the substituted and unsubstituted malonic esters; and, secondly, the rates of reaction of the two ester anions with the alkyl halide



$$H{-}C^-(COOC_2H_5)_2 + R{-}\overset{H}{C}(COOC_2H_5)_2 \rightleftarrows H{-}\overset{H}{C}(COOC_2H_5)_2 + RC^-(COOC_2H_5)_2$$

(1)



$$H{-}C^-(COOC_2H_5)_2 + RX \xrightarrow{k_1} R{-}\overset{H}{C}(COOC_2H_5)_2 + X^-$$
$$R{-}C^-(COOC_2H_5)_2 + RX \xrightarrow{k_2} R{-}\overset{R}{C}(COOC_2H_5)_2 + X^-$$

(2)

Presumably the effect of an alkyl group is acid weakening so that the equilibrium in (1) lies well to the left. The effect of an alkyl group on the rate of (2) is not known for malonic ester.

This paper presents the results of attempted measurements of the acid ionization constants of malonic ester and ethylmalonic ester in absolute ethanol, and of the rates of reaction of the sodium salts with ethyl bromide in the same medium. These quantities were determined for malonic ester but the acidity of ethylmalonic ester proved too low for either measurement to be made accurately.

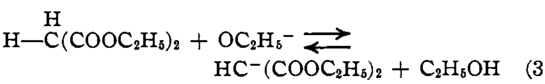
Experimental

Diethyl malonate was purified by two fractionations through a ten-plate column, $n^{25}D$ 1.4112, d^{25}_4 1.0490. Ethyl diethylmalonate was made by standard procedures[1] and repeatedly fractionated, $n^{25}D$ 1.4141, d^{20}_4 0.9982. C. P. ethyl bromide was fractionated and a constant-boiling, middle-fraction taken. Ethyl alcohol was dried by the method of Manske[2] and protected from moisture as far as possible. Solutions of sodium ethoxide were made by dissolving freshly cut sodium metal in dry alcohol and analyzed by titration. Both the acidities and the rates of reaction were measured by utilizing the large changes in electrical resistance that occur when malonic ester is converted to its sodium salt and when the sodium salt reacts with ethyl bromide. Selected volumes of the reactants were mixed at the reaction temperature, placed in a conductivity cell and thermostated at 25.0 ± 0.02°. Measurements of the resistances were made with a Jones–Josephs bridge.

The solutions of sodium ethoxide were not stable and were prepared fresh for each run. Ethyl bromide stock solutions in alcohol were alcoholyzed very slowly and could be kept for several days in the cold room.

Calculations and Results

The method of obtaining acid ionization constants is similar to that of Goldschmidt[3] who measured the hydrolysis of salts of weak acids in ethanol. Resistances of solutions containing a fixed concentration of sodium ethoxide and varying amounts of malonic ester were measured. The resistance increased with the concentration of malonic ester because of the replacement of ethoxide ion by the less mobile malonic ester anion. Because of the weak acidity of the ester this change is not complete for any solution experimentally available. However, if R_0 is the resistance when the malonic ester concentration is zero and R the resistance when the concentration is c then a plot of $R/(R - R_0)$ against $1/c$ gives a straight line which can be extrapolated to $1/c$ equal to zero. This gives a value of R_∞ which is the resistance of a hypothetical solution of infinite ester concentration and in which all of the sodium ethoxide has been converted to sodiomalonic ester. From values of R_∞, R_0 and R the fraction of ethoxide ion converted to ester anion can be found for any solution (by assuming the ionic conductivities are additive) and the concentration equilibrium constant K_1 for (3) determined.



$$H{-}\overset{H}{C}(COOC_2H_5)_2 + OC_2H_5^- \rightleftarrows HC^-(COOC_2H_5)_2 + C_2H_5OH$$

(3)

The experimental and calculated results are given in Table I. The effect of malonic ester on a neutral electrolyte, potassium iodide, was also checked. The relatively small increase in resistance for the latter is due to viscosity effects and a correction of the same magnitude was applied to the measured resistances with sodium ethoxide before calculations were made. Table II gives

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[1] "Organic Syntheses," Coll. Vol. I, (1941), p. 250.

[2] Manske, THIS JOURNAL, 53, 1106 (1931).

[3] Goldschmidt, *Z. physik. Chem.*, 99, 116 (1921).