TABLE III

MISCELLANEOUS MANNICH DERIVATIVES OF SYMMETRICAL BIPHENOLS[a]

| Substituents on each *o*-cresol ring | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| | | From 4,4′-bi-*o*-cresol | | | | | | |
| 6-Methyl-α-dimethylamino[b] | 144[c] | $C_{20}H_{28}N_2O_2$ | 73.23 | 73.40 | 8.60 | 8.86 | 8.54 | 8.65 |
| 6-Methyl-α-diethylamino[d] | 75[e] | $C_{24}H_{36}N_2O_2$ | 75.06 | 75.02 | 9.45 | 9.60 | 7.29 | 7.47 |
| 6-Methyl-α-1-pyrrolidyl | 135[c] | $C_{24}H_{32}N_2O_2$ | 75.75 | 75.73 | 8.48 | 8.78 | 7.36 | 7.35 |
| 6-Methyl-α-1-piperidyl | 181[c] | $C_{26}H_{36}N_2O_2$ | 76.53 | 76.66 | 8.89 | 8.92 | 6.86 | 6.98 |
| 6-Methyl-α-4-morpholinyl | 203[c] | $C_{24}H_{32}N_2O_4$ | 69.96 | 70.09 | 7.83 | 7.89 | 6.80 | 6.99 |
| | | From 4,4′-oxy-bis-(2-chlorophenol) | | | | | | |
| 6-Chloro-α-dimethylamino[f] | 132[e] | $C_{18}H_{22}Cl_2N_2O_3$ | 56.11 | 56.35 | 5.76 | 5.87 | 7.27 | 6.99 |
| 6-Chloro-α-pyrrolidyl | 159.5[e] | $C_{22}H_{26}Cl_2N_2O_3$ | 60.46 | 60.47 | 6.00 | 6.15 | 6.41 | 6.55 |
| 6-Chloro-α-piperidyl | 166.5[c] | $C_{24}H_{30}Cl_2N_2O_3$ | 61.99 | 62.08 | 6.50 | 6.65 | 6.02 | 6.16 |
| 6-Chloro-α-4-morpholinyl | 161.5[c] | $C_{22}H_{26}Cl_2N_2O_5$ | 56.34 | 56.52 | 5.59 | 5.83 | 5.95 | 5.66 |
| | | From 4,4′-sulfonyl-bis-(2-acetamidophenol) | | | | | | |
| 6-Acetamido-α-diethylamino[g] | 178[h] dec. | $C_{26}H_{38}SN_4O_6$ | 58.40 | 58.58 | 7.16 | 7.25 | 10.48 | 10.36 |

[a] All derivatives obtained as free bases. [b] Full name of compound: 6,6′-dimethyl-bis-(α,α′-dimethylamino)-4,4′-bi-*o*-cresol. [c] From ethanol. [d] The dihydrochloride of this compound was reported by Burckhalter and co-workers,[3] m.p. 215°. [e] From methanol. [f] Complete name: 4,4′-oxy-bis-(6-chloro-α-dimethylamino-*o*-cresol). [g] Full name: 4,4′-sulfonyl-bis-(6-acetamido-α-diethylamino-*o*-cresol). [h] Yellow crystals from isopropyl alcohol–ether.

TABLE IV

DIMETHYLAMINOMETHYL DERIVATIVES OF *p*-ANILINOPHENOL[a]

| Name of compound | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| 4-Anilino-2-dimethylamino-methylphenol | 98.5[b] | $C_{15}H_{18}N_2O$ | 74.35 | 74.48 | 7.49 | 7.28 | 11.56 | 11.31 |
| 4-Anilino-2,6-bis-(dimethyl-aminomethyl)-phenol | 117[c] | $C_{18}H_{25}N_3O$ | 72.29 | 72.19 | 8.43 | 8.72 | 14.03 | 13.71 |
| 4-(N-Acetyl-anilino)-2,6-bis-(dimethyl-aminomethyl)-phenol[d] | 113[e] | $C_{20}H_{27}N_3O_2$ | 70.43 | 70.35 | 7.97 | 7.98 | 12.32 | 12.60 |

[a] Intermediate phenol was obtained from B. F. Goodrich Chemical Co. [b] From methanol. [c] From benzene–petroleum ether first, then two recryst. from benzene. [d] *p*-Anilinophenol was acetylated with $Ac_2O$ before introduction of two Mannich groups. [e] Flesh colored crystals from benzene–petroleum ether.

methanol produced a pink or flesh-colored product, m.p. 164–165°. *Anal.* Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.17. Found: C, 73.93; H, 5.63; N, 6.25.

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# Acetoxymethylation of Aromatic Compounds[1]

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Methoxymethyl acetate in acetic acid reacted with mesitylene, isodurene, pentamethylbenzene, *m*-xylene, anisole or diphenyl ether, in the presence of a trace of strong acid. With mesitylene, the products were 2,4,6-trimethylbenzyl acetate (up to 37%), bis-(2,4,6-trimethylphenyl)-methane (up to 15%), polymer (up to 72%) and recovered mesitylene. Lower temperatures or shorter reaction times led to optimum yields of the monomeric ester. Higher temperatures led to polymer as the almost exclusive product. Compared to chloromethylation, this acetoxymethylation reaction differs chiefly in the greater tendency toward polymer formation. This limits the utility of acetoxymethylation as a preparative method for the monomeric esters. The polymer is readily obtained in good yield. Isodurene gave 18%, and pentamethylbenzene 20%, of the monomeric esters. The other aromatic compounds mentioned gave largely polymer, as did mesitylene with methylene diacetate or with paraformaldehyde in acetic acid.

Solutions of chloromethyl methyl ether in acetic acid conceivably contain methoxymethyl acetate. The latter compound has been isolated after attempts to chloromethylate terpenes with such solutions.[2] Also, the preparation of α-butoxyethyl acetate in 85% yield by heating α-chloroethyl butyl ether with acetic acid has been described.[3] Acetic

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[1] Presented at the 124th Meeting of the American Chemical Society, Chicago, 1953; see Abstracts of Papers, p. 71-O.

[2] J. Allard, *Bull. soc. chim.*, 731 (1947).

[3] M. F. Shostakovskiĭ and A. V. Bogdanova, *Zhur. Obshcheĭ Khim.*, **17**, 565 (1947).

acid solutions have been employed in various studies[4,5] of the chloromethylation reaction. It has been reported that when the reagent was chloromethyl methyl ether, the acetic acid solutions underwent a change, the nature of which was not investigated.[4b] This change probably involves the formation of methoxymethyl acetate in these solutions, and it seemed of interest to determine whether methoxymethyl acetate would itself react with aromatic nuclei.

Such reactions do occur quite readily. The products from methoxymethyl acetate and mesitylene, for example, include 2,4,6-trimethylbenzyl acetate (up to 37%), bis-(2,4,6-trimethylphenyl)-methane (up to 15%), and polymer (up to 72%). Table I shows some of the experimental results.

TABLE I

REACTIONS OF AROMATIC COMPOUNDS WITH METHOXYMETHYL ACETATE[a]

| Reactant | Time, hr. | Temp., °C. | Recovery of starting material, % | Yield of monomeric ester, % | Undistilled residue,[b] g./0.1 mole of aromatic reactant |
|---|---|---|---|---|---|
| Mesitylene | 46 | 27 | 38 | 32 | 3.2[c] |
| Mesitylene | 24 | 27 | 32;46;53[d] | 26;27;23[d] | 2.9;3.2;2.2[d,e] |
| Mesitylene[f] | 24 | 27 | 33 | 16 | 5.2[g] |
| Mesitylene | 1 | 50 | 62 | 6 | 1.3[h] |
| Mesitylene | 2 | 65 | 12;10[d] | 25;27[d] | 6.2[c];6.5[c,d] |
| Mesitylene[i] | 2 | 65 | 16 | 37 | 6.5[c] |
| Mesitylene[j] | 2 | 65 | 0 | [k] | 10.0[l] |
| Mesitylene[m] | 2 | 65 | 30 | 18 | [n] |
| Mesitylene[o] | 2 | 65 | 0 | 12[p] | 6.1 |
| Mesitylene[q] | 6 | 85 | 0 | [k] | 11.1[l,r] |
| Mesitylene[s] | 7 | 85 | [t] | [t] | 13.8[l,u] |
| Isodurene | 48 | 27 | 17 | 18;19[d] | 6.6;5.9[d] |
| *m*-Xylene | 48 | 65 | 11 | 9[p] | |
| Anisole | 34 | 28 | 0 | 4[p] | 10.2 |
| Anisole | 1 | 65 | 0 | 3[p] | 11.8 |
| Diphenyl ether | 12 | 65 | 11 | [v] | 9.5[w] |
| Pentamethylbenzene | 26 | 30 | 5[t] | 29[t] | 8.3[t,x] |
| Pentamethylbenzene | 4 | 85 | [t] | 20[t] | 8.0[t,y] |

[a] In proportion of 1.0 mole of the aromatic compound and 2.0 moles of methoxymethyl acetate in 1000 ml. of glacial acetic acid containing 4.0 ml. of concentrated sulfuric acid. Most runs employed 0.1 to 0.2 mole of the aromatic compound. [b] Polymer plus substituted diphenylmethane. [c] Crystallized in part only. [d] Duplicate experiments. [e] Consisted, in the third experiment, of the substituted diphenylmethane in 6% yield, plus (by difference) 1.24 g. of polymer per 0.1 mole of mesitylene (about 11% yield of polymer). [f] Concentration of mesitylene and of methoxymethyl acetate doubled. [g] Very little crystallized (mostly polymer). [h] Essentially all substituted diphenylmethane, yield 10%. [i] Used 4.0 moles of methoxymethyl acetate per mole of mesitylene. [j] Used methylene diacetate, 1.0 mole, in place of the methoxymethyl acetate. [k] Trace. [l] Essentially all polymer. [m] Used 2.0 moles of mesitylene per 1.0 mole of methoxymethyl acetate. [n] Gave the substituted diphenylmethane in 15% yield. [o] Used paraformaldehyde, 2.0 moles, in place of the methoxymethyl acetate. [p] Not well characterized, possibly impure. [q] Used *p*-toluenesulfonic acid in place of the sulfuric acid. [r] Approximately 83% yield. [s] Mole ratio mesitylene:methoxymethyl acetate 1:1. [t] Worked up differently; see Experimental part. [u] Gave 9.5 g. per 0.1 mole of mesitylene or approximately 72% yield, of purified polymer. [v] Uncertain; see Experimental part. [w] Waxy. [x] All substituted diphenylmethane, yield 54%. [y] All substituted diphenylmethane, yield 52%.

This acetoxymethylation reaction is closely analogous to chloromethylation. The main difference, in practice, lies in the greater tendency toward polymer formation during acetoxymethylation. This polymer formation can be minimized, but it cannot be avoided entirely, and it limits the utility of the procedure as a preparative method for the monomeric ester. The polymer can be obtained readily in good yield under proper reaction conditions.

The polymer from higher-temperature reactions solidified on cooling. Such a sample from a reaction carried out at 85° was a brittle resin, with softening temperature about 125°, which contained 1.44% oxygen. For a structure such as I, *n* would have to be about 12, in view of this oxygen analysis.

$$C_9H_{11}—CH_2—(C_9H_{10}—CH_2)_n—C_9H_{10}—CH_2OCOCH_3 \quad (I)$$

$$C_9H_{11}—CH_2—(C_9H_{10}—CH_2)_m—C_9H_{10}—CH_3 \quad (II)$$

This would require an average molecular weight of about 1900, but the value found (cryoscopic, in benzene), was about 880. This result suggests that some of the chains must be terminated by non-oxygenated groups, and that the polymer may be a mixture of structures such as I and II. Analogous compositions have been indicated previously for polymers derived from benzyl chloride[6] or from benzyl alcohol.[7]

Anisole and diphenyl ether gave mostly polymer, as did mesitylene with methylene diacetate.[8] Paraformaldehyde in acetic acid reacted with mesitylene in a similar fashion.[9]

Acetoxymethylation, then, might conceivably proceed concurrently with chloromethylation when the latter is carried out with chloromethyl methyl ether in acetic acid. Our experiments have not, however, demonstrated any 2,4,6-trimethylbenzyl acetate in the product of chloromethylation of mesitylene by this procedure. It seems possible that any substituted benzyl acetate formed might be split rapidly by the hydrogen chloride or chloromethyl ether.

## Experimental[10,11]

Methoxymethyl acetate was prepared[12] from anhydrous sodium acetate and chloromethyl methyl ether. Other starting materials were redistilled reagent grade chemicals, or were prepared by standard methods.

**General Procedure.**—A typical reaction with mesitylene was carried out as follows: methoxymethyl acetate, 104.1 g. (1.00 mole) and 60.1 g. (0.50 mole) of mesitylene were dissolved in 500 ml. of glacial acetic acid containing 2.0 ml. of concentrated sulfuric acid. The mixture was stirred for 24 hours at 27°, protected from atmospheric moisture. It was then poured into about 700 ml. of water in a separatory funnel and was extracted with 150 ml. of chloroform. The chloroform solution was washed twice with water, then with 5% sodium bicarbonate solution and again with water, dried

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[4] (a) G. Vavon and J. Bolle, *Compt. rend.*, **204**, 1826 (1937); (b) G. Vavon, J. Bolle and J. Calin, *Bull. soc. chim.*, [5] **6**, 1025 (1939).

[5] See also H. C. Brown and K. LeR. Nelson, THIS JOURNAL, **75**, 6292 (1953); H. H. Szmant and J. Dudek, *ibid.*, **71**, 3763 (1949); H. H. Szmant, H. F. Harnsberger and J. B. Chow, Abstracts of Papers, 121st Meeting, American Chemical Society, Buffalo, N. Y., 1952, p. 45K.

[6] R. A. Jacobson, THIS JOURNAL, **54**, 1513 (1932).

[7] R. L. Shriner and A. Berger, *J. Org. Chem.*, **6**, 305 (1941).

[8] See A. Baeyer, *Ber.*, **5**, 1094 (1872).

[9] See G. B. Frankforter and V. R. Kokatnur, THIS JOURNAL, **36**, 1529 (1914).

[10] M.p.'s are uncorrected.

[11] Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill.

[12] F. E. Clark, S. F. Cox and E. Mack, THIS JOURNAL, **39**, 712 (1917); J. W. Farren, H. R. Fife, F. E. Clark and C. E. Garland, *ibid.*, **47**, 2419 (1925).

on Drierite and distilled. The chloroform was taken off through a helix-packed column, in order to avoid loss of mesitylene. The residue was then distilled through a Vigreux column under reduced pressure, and gave 31.7 g. (53% recovery) of mesitylene, b.p. 42–47° (10 mm.) and 21.8 g. (23%) of product fraction, b.p. 97–112° (2 mm.). This latter fraction was redistilled through a Wheeler semimicro concentric-tube column, and a main fraction of 17.7 g., b.p. 97–98° (1.5 mm.), $n^{23}_{\rm D}$ 1.5091, was obtained. Reported[13] b.p. of 2,4,6-trimethylbenzyl acetate is 136–137° (15 mm.).

*Anal.* Calcd. for $C_{10}H_{13}OCOCH_3$: sapn. equiv., 192.2. Found: sapn. equiv., 194.9, 194.8.

This ester saponified easily. The alcohol, after recrystallization from aqueous ethanol, had m.p. 85–87°; reported[14] m.p. 88–89°.

The undistillable residue from the reaction mixture weighed 11.2 g., and deposited crystals on cooling, but did not solidify entirely. It was treated with 30 ml. of cold ethanol and filtered. The remaining crystals (4.1 g., 6%), after recrystallization from glacial acetic acid, had m.p. 129–131°; reported[8] value for bis-(2,4,6-trimethylphenyl)-methane is 130°. The polymer formed was (by difference in the undistillable residue) 7.2 g. (approximately 11%). About 93% of the mesitylene was therefore accounted for.

The same general procedure, with variations in temperature and reaction time, was followed in carrying out most of the reactions listed in Table I, except those reactions intended to produce samples of polymer of as high a degree of polymerization as possible. Information concerning particular reactions which is not apparent from Table I is given below.

The procedure described above represents the best conditions for the preparation of 2,4,6-trimethylbenzyl acetate by acetoxymethylation of mesitylene.

**Polymer.**—Methoxymethyl acetate, 15.6 g. (0.15 mole) and 18.0 g. (0.15 mole) of mesitylene were dissolved in 100 ml. of glacial acetic acid and heated to 80°. Then 0.5 ml. of concentrated sulfuric acid was added, and the mixture was stirred at 85–90° for 7 hours, in a reaction flask equipped with a reflux condenser protected by a drying tube (there was almost no refluxing). The mixture was allowed to cool, with stirring, to 50°, and the acetic acid was decanted off the precipitated polymer. The polymer was stirred at 80° for five minutes with about 100 ml. of fresh acetic acid, and the latter was again decanted off after cooling to about 40 or 50°. The slightly grayish, brittle material remaining in the flask was easily broken out and weighed 20.7 g. after drying in air for 10 days. It was powdered in an agate mortar, extracted with methanol for 8 hours in a Soxhlet extractor and dried, finally over sodium hydroxide for 20 hours at 1 mm. and 40°. This left as product 14.3 g. of nearly white powder, which softened to a viscous, tacky liquid at about 125° and did not set on further heating (to 250°).

*Anal.* Calcd. for $(C_{10}H_{12})_n$: C, 90.85; H, 9.15. Calcd. for $C_{10}H_{13}(C_{10}H_{12})_{13}OCOCH_3$: C, 89.25; H, 9.07; O, 1.67; mol. wt., 1911. Found: C, 89.18, 89.14; H, 9.12, 9.05; O, 1.44; mol. wt. (cryoscopic, in benzene), 871, 896.

This polymer was soluble in chloroform and in benzene.

Samples of polymer prepared under different conditions varied considerably in properties. A sample obtained from the reaction of methylene diacetate (16.2 g., 0.10 mole) with mesitylene (12.0 g., 0.10 mole) for two hours at 65° had properties similar to those described above. Determination of the saponification equivalent gave a value of 1571, which is a rough check on the oxygen analysis above. The saponification determination is not to be considered very reliable, because of the insolubility of the sample in alcoholic sodium hydroxide.

**Isodurene.**—The two duplicate experiments gave nearly identical results. The 2,3,4,6-tetramethylbenzyl acetate had b.p. 109–112° (1.2 mm.), $n^{20}_{\rm D}$ 1.5191.

*Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.82; H, 8.68.

Saponification gave the alcohol, m.p. 93–94°.

*Anal.* Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.43; H, 9.73.

***m*-Xylene.**—This reaction gave, from 0.15 mole of *m*-xylene, 2.3 g. of a fraction, b.p. 100–110° (5 mm.), which presumably represented 2,4-dimethylbenzyl acetate, reported[15] b.p. 157° (50 mm.). The main product was polymer.

**Anisole.**—The polymer which was the most important product did not solidify, but remained a viscous liquid, in both experiments. From 0.15 mole of anisole, the fraction calculated as *p*-methoxybenzyl acetate was 0.9–1.0 g., b.p. 110–117° (3.5 mm.), $n^{20}_{\rm D}$ 1.4650, reported[16] b.p. 137–139° (12 mm.).

**Diphenyl Ether.**—No reasonably pure fraction corresponding to the monomeric ester was isolated, although 1.0 mole of diphenyl ether yielded about 3 g. of material boiling approximately in the expected range. The polymer, obtained in large amount, solidified to a white waxy material on cooling.

**Pentamethylbenzene.**—The reaction was carried out as for mesitylene, but at 85° for 4 hours. White crystalline material precipitated. The mixture was cooled to 25° and filtered and the residue was washed with methanol. This left 8.0 g. (52%) of crystals, m.p. 213–215°. Reported[17] m.p. for bis-(pentamethylphenyl)-methane is 217–218°. The filtrate, worked up as usual, yielded white crystals, m.p. about 75°, from which no material of b.p. corresponding to that of pentamethylbenzene could be isolated. Recrystallization from aqueous ethanol gave 4.4 g. (20%) of pentamethylbenzyl acetate, m.p. 83–85°. Reported[18] m.p. is 85°. From the saponification equivalent, this product might still have contained a little pentamethylbenzene.

*Anal.* Calcd. for $C_{12}H_{17}OCOCH_3$: sapn. equiv., 220. Found: sapn. equiv., 226, 226.

The pentamethylbenzyl alcohol from the saponification, after recrystallization from 95% ethanol, had m.p. 155–158°. Reported values are 160.5°[18] and 136–137°.[19]

*Anal.* Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.96; H, 10.06.

The experiment was repeated, but at 30° for 26 hours. Yield of bis-(pentamethylphenyl)-methane was 8.3 g. (54%). The product from the filtrate apparently contained in this case more unreacted pentamethylbenzene, and did not solidify at room temperature. After freezing in an ice-bath, it melted at about 30°. The saponification equivalent would indicate the presence of about 5% of unreacted pentamethylbenzene, plus 29% of pentamethylbenzyl acetate.

*Anal.* Found: sapn. equiv., 245, 243.

**Reaction of Mesitylene with "Aged" Solution of Chloromethyl Methyl Ether.**—Chloromethyl methyl ether, freshly distilled, b.p. 58–59°, 24.2 g. (0.30 mole) was dissolved in 150 ml. of A.R. acetic acid, and the mixture was allowed to stand in a reaction flask, protected by a drying tube, for 48 hours at 25–30°. It was then heated at 65° for 0.5 hour (hydrogen chloride was evolved). To this "aged"[4b] solution there was now added 36.1 g. (0.30 mole) of mesitylene, and the mixture was stirred at 60–70° for 1 hour. (This time should represent about 30% reaction[4b]; the purpose was to interrupt the reaction when it had not proceeded very far, in order to detect 2,4,6-trimethylbenzyl acetate if present.) Distillation through the Wheeler concentric-tube column gave 17.9 g. of mesitylene, 10.0 g. of 2,4,6-trimethylbenzyl chloride (b.p. steady at 69.2° at 1.0 mm.), and 1.3 g. of crystalline residue, apparently bis-(chloromethyl)-mesitylene. No fraction corresponding to 2,4,6-trimethylbenzyl acetate (b.p. 97–98° at 1.5 mm.) was present.

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[13] W. Th. Nauta and J. W. Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).

[14] P. Carré, *Compt. rend.*, **151**, 149 (1910); *Bull. soc. chim.*, [4] **7**, 843 (1910).

[15] M. Sommelet, *Compt. rend.*, **157**, 1443 (1913).

[16] M. Tiffeneau and K. Führer, *Bull. soc. chim.*, [4] **15**, 162 (1914).

[17] I. I. Lapkin, *Zhur. Obshchei Khim.*, **16**, 729 (1946).

[18] O. Jacobsen, *Ber.*, **22**, 1215 (1889).

[19] H. Clement, *Ann. chim.*, **13**, 243 (1940); *Compt. rend.*, **207**, 864 (1932).