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DIBORANE AS A REDUCING AGENT—I

THE REDUCTION OF ELECTRON-RICH AROMATIC ALDEHYDES AND KETONES

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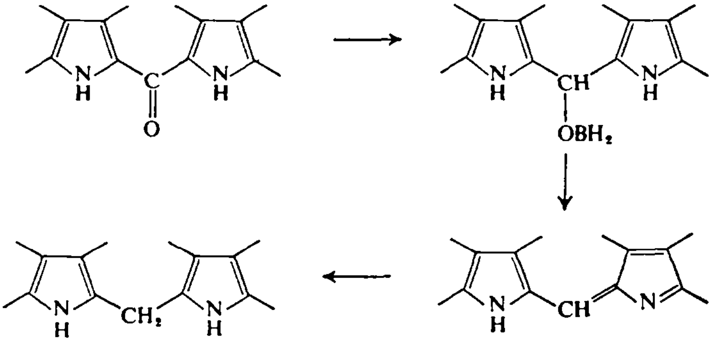
Abstract—Aromatic aldehydes and ketones bearing electron-releasing substituents are usually reduced to the corresponding substituted hydrocarbons by diborane generated "externally" or in the reaction mixture. It is suggested that the greater potency of borontrifluoride–borohydride mixtures in effecting the "internal" reductions is due to the presence of both electrophilic and nucleophilic species in the reaction medium. Anisaldehyde gives complex mixtures on reduction by "internally" generated diborane.

MOST aldehydes and ketones are reduced by diborane to the corresponding alcohols, and hydrogenolysis of the oxygen function does not occur.[1] However our recent studies of pyrroketones have shown that they are rapidly reduced to pyrromethanes by diborane, and that certain pyrrole-2-aldehydes and pyrrole-2-carboxylic acids are likewise reduced to the corresponding 2-methylpyrroles.[2] The reduction of the pyrroketones was shown to proceed through the stages outlined below, and similar mechanisms presumably operate in the cases of the pyrrole-2-aldehydes and -2-carboxylic acids, as the intermediate pyrryl carbinols may be isolated if limited amounts of diborane are used with short reaction times.[2]



The ease of reduction and complete hydrogenation of the carbonyl function in these pyrrole derivatives was attributed to the highly polar character of the carbonyl groups engendered by electron release from the pyrrole nuclei. Indeed the recognition of this polar character (as revealed by spectroscopic and other chemical properties) originally led to the prediction[2] that diborane (as an electrophilic species) would be a

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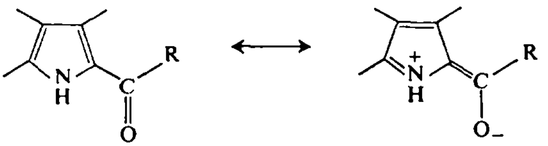
[1] H. C. Brown, *Hydroboration*. Benjamin, New York (1962).

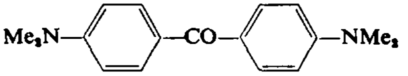
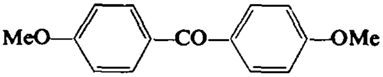
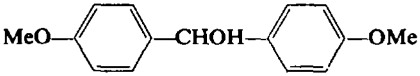
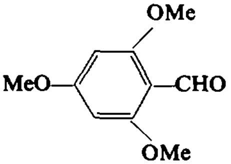
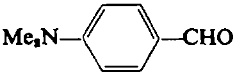
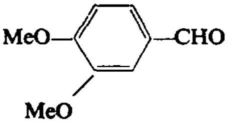
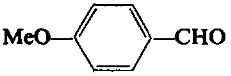
[2] J. A. Ballantine, A. H. Jackson, G. W. Kenner and G. McGillivray, *Tetrahedron* **22**, Suppl. I, 241 (1966).

particularly suitable reducing agent for such carbonyl groups,[cf. 1] whereas borohydride (an essentially nucleophilic species) and catalytic hydrogenation had proved ineffective.



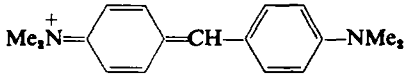
It was therefore of interest to investigate the generality of this phenomenon, i.e. the complete hydrogenation of highly polarized carbonyl groups by diborane. In this paper we describe the results (Table 1) of our experiments with "electron-rich" carbonyl compounds in the benzenoid series. Two different methods of reduction were used; in the first diborane was generated *in situ* from borohydride and boron trifluoride in the reaction medium ("internal reduction"), and in the second the diborane was generated externally ("external reduction").[cf. 1]

TABLE 1. PRODUCTS FROM THE REDUCTION OF AROMATIC CARBONYL COMPOUNDS WITH DIBORANE

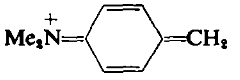
		"Internal" reduction		"External" reduction	
No.	Compound	Product	Yield (%)	Product	Yield (%)
I		H	78	H	90
II		H	65	H	85
III		—		H	82
IV		—		H	95
V		H	72	a A b* H	95 95
VI		H	95	a A b† A	87 89
VII		Complex products —see text		A	92

H = the corresponding hydrocarbon
A = the corresponding alcohol
* with added sodium borohydride
† with added boron-trifluoride etherate

As can be seen from the Table the nature of the product depends both on the nature and number of electron releasing substituents in the aromatic nuclei, and on the mode of reduction. With the more electron-rich compounds e.g. Michler's ketone (I) the corresponding diphenyl methane is the sole product whether the reduction is carried out externally or internally, whereas anisaldehyde (VII) is reduced externally to the alcohol, and internally gives a complex mixture of products derived essentially from the alcohol (see below). *p*-Dimethylaminobenzaldehyde and veratraldehyde fall between these two extremes in that they are completely reduced by the more powerful internal reagent (to the corresponding methyl compounds), but externally reduction proceeds only as far as the alcohol stage. Reduction to the methane or methyl compound almost certainly proceeds via "methene-like" intermediates (as in the pyrrolic examples described in the preceding paper), e.g. VIII and IX, since a faint blue colour due to VIII persists throughout the reduction of Michler's ketone (I), and the corresponding carbinol (III) is also readily reduced to the methane.

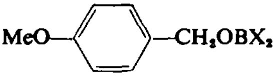


VIII

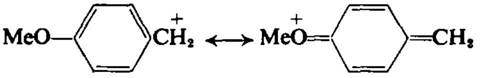


IX

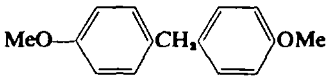
At least five products have been encountered in the internal reduction of anisaldehyde (VII); two of these were fully characterized as 4,4'-dimethoxydiphenylmethane (XI), and 2,4'-dimethoxy-5-methyldiphenylmethane (XII), and the other three were assigned structures of types XIII, XIV and XV on the basis of NMR and mass spectral studies, (see below). The first three of these products were isolated and



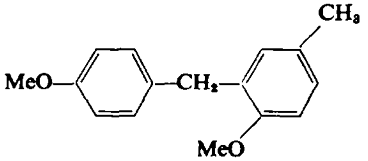
Xa



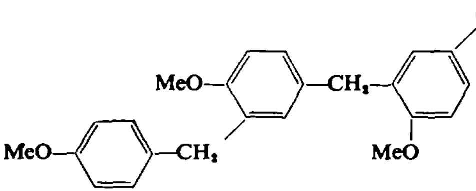
Xb



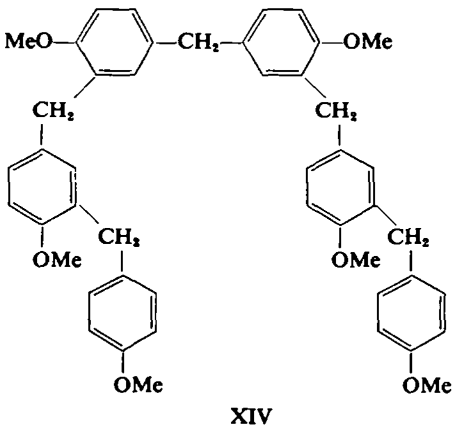
XI



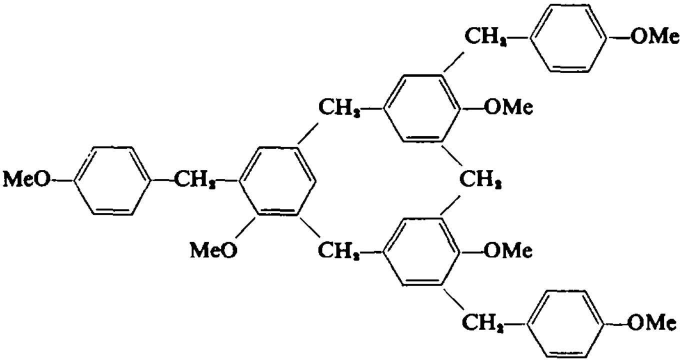
XII



XIII



XIV



XV

separated from each other by TLC in one experiment, and the last two products were isolated in another experiment, conducted as far as possible under the same conditions. It was clear at this point that the precise nature of the products was critically dependent on the reaction conditions, but their general type (diphenylmethanes) was not in doubt. The formation of these products may be attributed to the attack of electrophilic species such as Xb upon their progenitors (Xa) followed by reduction of the oxygen functions. The mode of formation of dianisylmethane (XI) is slightly different from the formation of the other products as it must involve elimination of a one-carbon fragment, but there are many analogies in the pyrrole field (i.e. the formation of pyrromethanes by self condensation of 2-oxymethylpyrroles[3]) and at least three examples are known in the benzenoid series.[4] That products of the same type as XI–XV are not formed in the other internal reductions is presumably due to the fact that reduction takes place much more rapidly in the latter.

The different results obtained with the external and internal reductions are of considerable interest with regard to the mechanism of diborane reductions. Our experiments bear out previous workers' experience that the internally generated species is a more powerful reducing agent than diborane in ethereal solvents.[cf.1] The use of LAH–$AlCl_3$ mixtures in the reduction of a variety of aromatic carbonyl compounds closely parallels our own results with diborane reductions, e.g. electron-releasing groups increase both the yield of products and the extent of reduction.[5] It has been suggested that these LAH–$AlCl_3$ mixtures, which have a greater tendency to bring about hydrogenolysis than LAH alone (e.g. benzophenone is reduced to diphenylmethane by the mixed reagent, but to benzhydrol by lithium aluminium hydride) owe their potency to the formation of species such as $AlHCl_2$ or AlH_2Cl (rather than AlH_3) which are more powerful electrophiles than AlH_3.[6] However when veratraldehyde (VI) was reduced externally with diborane in presence of added BF_3-etherate (which would be expected to give rise to mixed reagents such as BHF_2 and BH_2F) the only product was the alcohol (isolated in 89% yield). A more satisfactory explanation for

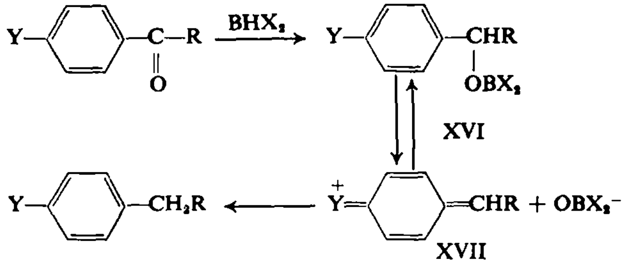
[3] H. Fischer and H. Orth, *Die Chemie des Pyrrols* Vol. I. Akademische Verlag, Leipzig (1934).

[4] A. H. Jackson and J. Harley-Mason, *J. Chem. Soc.* 1168 (1954); T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *Ibid.* 912 (1958); J. A. Martin, Ph.D. Thesis, Liverpool (1965).

[5] B. R. Brown and A. M. S. White, *J. Chem. Soc.* 3755 (1957); R. F. Nystom and C. R. A. Berger, *J. Amer. Chem. Soc.* **80**, 2896 (1958).

[6] cf. E. L. Eliel, *Records of Chem. Progr.* **22**, 129 (1961).

the potency of the mixed reagents is that it is due to the combined presence of both electrophilic and nucleophilic species in the same medium. An electrophilic species (BHX_2; $X = H$ or F) would be the effective reagent for the reduction of the carbonyl groups in the electron-rich compounds to the corresponding borate esters (XVI):

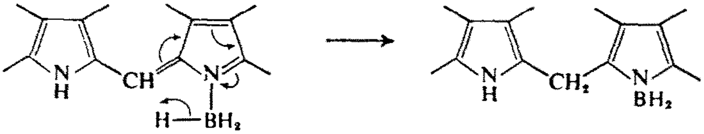


Whether or not further reduction occurs (with hydrogenolysis of the oxygen function) would then depend on the importance of two further factors, (i) the tendency of an elimination reaction to occur to give a positively charged methene-like species, e.g. XVII and (ii) the ability of the reducing agent to transfer a hydride ion to the "methene". The first process would clearly be favoured by strongly electron releasing groups (e.g. a dimethylamino group or two or more methoxy groups) which can readily stabilize a methene-like species (XVII). In the second process borohydride will clearly be more effective in transferring hydride ion than borane-etherates, BHX_2–OR_2. Thus with Ehrlich's reagent (V) external reduction yields only the corresponding alcohol, and this may be accounted for on the assumption that the intermediate borate ester (XVI; $Y = NMe_2$, $R = H$) shows little tendency to dissociate into the corresponding methene-like species (IX). (Such a dissociation would in any event be at least partially inhibited by complex formation of the amino-group with excess diborane). On the other hand in the internal reductions any "methene" present would be rapidly reduced by the powerful hydride ion donor, borohydride anion, thus displacing the equilibrium and leading eventually to complete hydrogenolysis, with formation of the *p*-dimethylaminotoluene. Evidence for these suggestions is provided by the fact that external reduction of Ehrlich's reagent (V) in presence of added borohydride gives the toluene and not the alcohol, whereas either diborane or borohydride alone gives only the alcohol (see Table). An analogy for the second step is provided by Brown and Bell's demonstration that stabilized carbonium ions can be reduced by borohydride.[7]

In the cases of the carbonyl compounds (I–IV) which possess a larger number of electron releasing groups, one must assume that dissociation of the intermediate borate esters (corresponding to XVI) to methenes is more pronounced, and that accordingly the borane-etherate complex is a sufficiently powerful hydride donor to effect complete reduction externally. (The ease with which the carbinol derived from Michler's ketone (I), and mesohydroxypyrromethanes, eliminate the hydroxyl group in the presence of electrophilic species to give stable coloured methene salts is well known.) The complex mixture of products isolated in the internal reduction of anisaldehyde can be accounted for by the assumption that the rate of electrophilic attack of the rather unstable methene-like species (Xb) on other intermediates in the reactions must be faster than its reduction.

[7] H. C. Brown and H. M. Bell, *J. Org. Chem.* 27, 1928 (1962).

Dipyrroketones can in fact be reduced to pyrromethanes by borohydride alone (but forcing conditions are required, and the reaction is slow), and some pyrromethenes are reduced by borohydride to the corresponding pyrromethanes.[2] However, Dr. G. S. Sach has shown that pyrromethenes bearing electron withdrawing carbonyl groups in both α-positions are unaffected by borohydride, as nucleophilic addition of hydroxide or alkoxide ion (present in the aqueous alcoholic media used for borohydride reductions) supervenes addition of hydride ion, and on acidification of the reaction mixture the methene salt is regenerated.[8] Pyrromethenes are all however very rapidly reduced by diborane,[2,8] and this is presumably facilitated by formation of the borane complex, which can then undergo internal hydride ion transfer as indicated in the following sequence (whereas the hydride transfer in the benzenoid examples described in the present paper must of necessity be external). Thus the importance of both electrophilic and nucleophilic reducing species in the "internal" reductions can readily be appreciated.



During the course of our work Wechter[9] in a preliminary communication reported that xanthones, thioxanthones and acridones are reduced to the corresponding xanthanes, thioxanthanes and acridanes by diborane, and these results accord with ours since these heterocyclic carbonyl compounds may be regarded as electron rich by virtue of the electron donating capacities of their hetero-atoms. Wechter also reported that benzophenone, fluorenone and 4,4′-dimethoxybenzophenone (II) are only reduced to the corresponding alcohols. His results with the last compound thus differ from ours, and may perhaps be accounted for by a shorter reaction time or by the use of insufficient diborane. We have repeated our experiment several times, but the result was always the same, and moreover the carbinol (III) is also hydrogenolysed to the diphenyl methane by external reduction with diborane.

Characterization of the anisaldehyde reduction products

(A) $C_{16}H_{18}O_2$, m.p. 73–74°. The NMR spectrum showed the following resonances†, Aromatic-H, ca. 3·1, m (7); Ar—CH_2—Ar, 6·10, s (2); —OCH_3, 6·24, s (6); Ar—CH_3, 7·78, s (3). These are consistent with a diphenylmethane substituted with two methoxy and one methyl groups. The structure was assigned as shown in formula XII, the *p*-methoxybenzyl residue being placed *ortho* to the methoxyl in the other ring since this would be the predominant position for electrophilic attack. This was confirmed by the m.p. (74°) given in the literature for XII.

The mass spectrum showed prominent ions at m/e 242, (100%), M^+; 227, (32%), M—CH_3; 211, (36%), M—OCH_3 [metastable ion (m*) at 184; calc. for 242 → 211,

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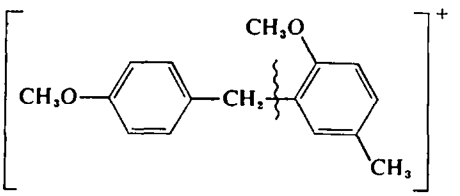
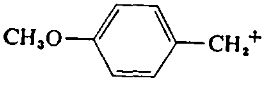
† The positions of the peaks are given on the τ-scale, *m* and *s* indicate multiplet and singlet respectively, and the numbers in brackets indicate the numbers of protons giving rise to each of the observed signals.

[8] G. S. Sach, Ph.D. thesis, Liverpool (1964).

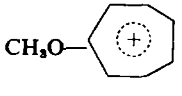
[9] W. J. Wechter, *J. Org. Chem.* **28**, 2935 (1963).

184·1]; 121, (38%), M-121 (m*, 60·5; calc. 60·5); 91, (15%), $C_7H_7^+$. The ion *m/e* 121 can be assigned structure *a* or *b*; the isomeric ion *c* which would be formed if the positive charge was retained by the other ring would be expected to rearrange to give ion *a*, or the troponoid structure *b*.[cf. 10]

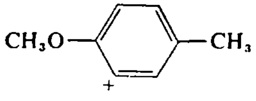




a

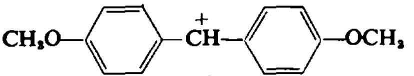


b



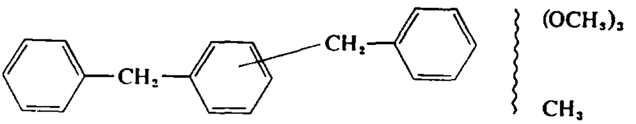
c

(B) $C_{15}H_{16}O_2$, m.p. 51–52°. The NMR spectrum showed the following resonances; Aromatic-*H*, ca. 3·1, *m*, (8); Ar—CH_2—Ar, 6·14, *s*, (2); —OCH_3, 6·24, *s*, (6). This was consistent with its formulation as 4,4′-dimethoxydiphenylmethane (XI) and was confirmed by comparisons with authentic material. The mass spectrum showed prominent peaks at *m/e* 228, (100%), M^+; 227, (34%), M—H; 197, (50%), M—OCH_3; 121, (27%). The ion *m/e* 227 may be formulated as *d* (or an isomeric troponoid structure), and its relatively high intensity is probably due to the symmetrical structure of the parent compound. The ion *m/e* 121 is clearly identical with the ion *a* (or *b*) produced from compound *A*.



d

(C) m.p. 110–113°. The mass spectrum (see below) showed that the mol. wt. was 362, and on this basis the NMR spectrum was analysed as follows: Aromatic-*H*, ca. 3·1, *m*, (10); Ar—CH_2—Ar, 6·15 *s* (2) and 6·21 *s* (2); —OCH_3, 6·25, *s* (6) and 6·30, *s* (3); Ar—CH_3, 7·80, *s* (3). These values are consistent with partial structure XVIII, and the presence of two distinct methylene resonances at 6·15 and 6·21 excludes symmetrical structures. By analogy with the formation of compound *B* (assigned structure XI) the most likely structure for *C* would appear to be XIII, although alternative isomeric structures cannot be excluded.



XVIII

The mass spectrum supports this assignment for it shows ions at *m/e* 362 (100%),

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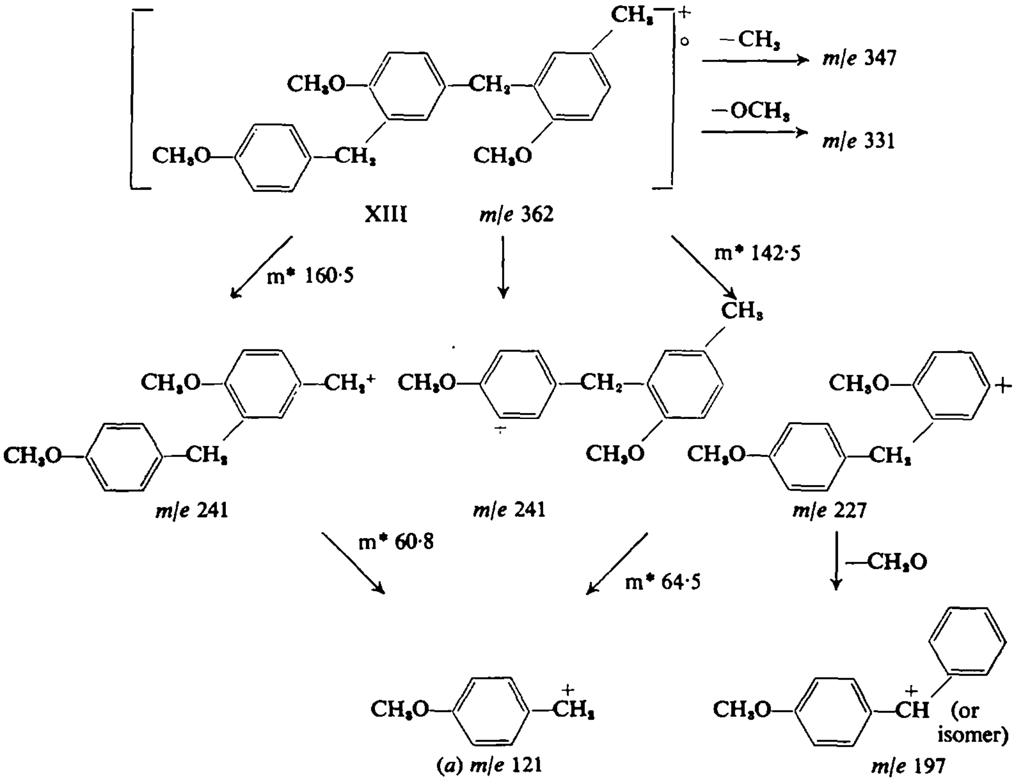
[10] cf. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds* pp. 175–176, Holden-Day, San Francisco (1964).

M+; 347, (7%), 331, (13%); 241, (53%); 227 (33%); 197, (13%) 135, (20%); and 121, (80%), which may be accounted for by the following scheme:



Troponoid structures may also be written for most of the fragment ions given in the above scheme: the formation of ion *m/e* 227 shows that the ring bearing both methoxy and methyl groups must be one of the two end rings and not the central ring.

(D) The NMR spectrum, like those of A, B and C, showed peaks in the 3·0–3·4 (aromatic-H) and 6·1–6·3 (Ar—CH_2—Ar and OCH_3) regions but, unlike A and C, did not exhibit any resonances in the 7·8 τ region corresponding to aromatic-CH_3. The mass spectrum showed molecular ions at *m/e* 720 (3%) and 708 (6%), and prominent ions (>10%) at *m/e* 469 (32%), 348 (25%), 256 (10%), 242 (25%), 228 (30%) and 121 (100%). Several structures isomeric with XIV derived from six *p*-methoxybenzyl residues may be written for the species mol. wt. 708, a one-carbon fragment having been eliminated as in the formation of the related 4,4′-dimethoxydiphenylmethane (B). The other component mol. wt. 720 must still contain this one-carbon fragment and the difference in mol. wt. (12) indicates that it must have a cyclic structure probably based on a branched isomer of XIV containing an extra methylene bridge (as in XV).

The formation of fragments containing 1, 2 or 3 *p*-methoxybenzyl residues in the mass spectrum is in agreement with the structures proposed, and the ratio of the integrals of the aromatic proton to the methoxyl and methylene proton resonances in the NMR spectrum is in accord with these structures (observed ratio 0·70; Calc. for XIV, 0·71; Calc. for XV, 0·60).

Further work on these "internal" reduction products was discontinued owing to their complexity, and the difficulty of separating them, and since their general structural type was clearly evident.

EXPERIMENTAL

NMR spectra were determined in $CDCl_3$ solution with a Varian A-60 spectrometer, and mass spectra were determined with an A.E.I. MS9 spectrometer using a direct inlet.

The reductions of the various aromatic carbonyl compounds were carried out by the two procedures described below, and the results are given in Table 1. The reduction products were characterized by comparison with authentic samples, or with physical data from the literature (m.p. or b.p.), and by means of spectral determinations. In addition the homogeneity of the products was confirmed by TLC or gas chromatography. Anisaldehyde gave a mixture of products when reduced "internally", and further details are given below.

External reductions

Diborane, generated externally from $NaBH_4$ (0·76 g, 0·02 mole) in diglyme (20 ml) by the dropwise addition of BF_3-etherate (6·3 ml) in diglyme (13·7 ml) over 30 min, was passed into a solution of the aromatic carbonyl compound (0·002 mol) in dry tetrahydrofuran (100–150 ml). The apparatus was flushed with N_2 before beginning the addition, and after completion of the addition the $NaBH_4$–BF_3 mixture was heated briefly at 60–70° and residual diborane was swept out in a slow stream of N_2 into the reaction mixture. The latter was then allowed to stand for a further 3 hr at room temp, and the tetrahydrofuran removed by distillation under red press. The residue was taken up in MeOH (100 ml) and boiled under reflux for 30–60 min to decompose any boron complexes. The solvent was then distilled off, and the reduction product crystallized, or distilled and characterized.

Internal reductions

BF_3-etherate (12·6 ml) in diglyme (27·4 ml) was added dropwise with stirring to the aromatic carbonyl compound (0·004 mole) and $NaBH_4$ (1·52 g, 0·04 mole) in diglyme (40 ml). The reaction mixture was stirred for a further 1½ hr at room temp, and then most of the diglyme was removed by evaporation under red press at 60°. MeOH (100 ml) was added and the mixture boiled under reflux for 1 hr to decompose excess borohydride, boron complexes etc. The MeOH was then distilled off under red press and the residue taken up in ether and water. The ethereal layer was separated, washed with $NaHCO_3$aq, then with water, dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized, or distilled and characterized.

Internal reduction of anisaldehyde

Anisaldehyde (680 mg, 0·005 mole) was reduced by the method described above except that the solvent was tetrahydrofuran. The crude product (503 mg) was a light brown oil which did not exhibit any peaks in the hydroxyl or carbonyl regions of its IR spectrum. The NMR spectrum indicated the presence of aromatic hydrogen, methoxyl and aromatic methyl groups. The material could not be purified satisfactorily by chromatography on alumina, but TLC on Kieselgel G (Merck) in benzene–light petroleum (1/1: v/v) showed the presence of three components R_f 0·80 (A), 0·68 (B), and 0·54 (C). These were separated by thick-layer chromatography on Kieselgel G (20 × 20 cm plates, 1 mm thick), using benzene-light petroleum (b.p. 60–80°) (1/1: v/v) as eluent. The mixture (180 mg) was applied in $CHCl_3$ solution to the bottom of four plates as a thin line using an automatic applicator, and was eluted with 3 successive passes of solvent (allowing the plates to dry between each pass). The positions of the 3 components were determined by observation under UV light, and each band was scraped off the plates and extracted with MeOH. The MeOH extracts were evaporated to dryness, and the residue taken up in ether, washed with a little water, dried over $MgSO_4$ and evaporated to dryness.

(A) Yield, 57 mg, needles m.p. 73–74° from EtOH. (Found: C, 79·3; H, 7·5. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%.) The literature[11] gives m.p. 74° for 6,4′-dimethoxy-3-methyldiphenylmethane.

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[11] R. Pummerer, H. Puttfarken and P. Schopflocher, *Ber. Dtsch. Chem. Ges.* **58**, 1820 (1925).

(B) Yield, 28 mg, needles m.p. 51–52° (from light petroleum b.p. 60–80°). Mixed m.p. with 4,4′-dimethoxydiphenylmethane, 52°.

(C) Yield, 17 mg of an almost colourless oil, which crystallized slowly on standing to give needles m.p. 110–113°. Insufficient material was available for analysis after determination of spectra etc.

The structures of these three products are discussed in the theoretical section on the basis of their NMR and mass spectra. An attempt to repeat this experiment under the same conditions gave more complex products, only one apparently homogeneous component of which (D), m.p. 85–90°, was isolated in low yield by thick-layer chromatography. The mass spectrum showed that D contained two components, and possible structures for these based on mass spectral and NMR interpretations are given in the theoretical section.

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