Hyflo Super-Cel. The solution was filtered and the solid on the filter washed with 500 ml. of water. The combined filtrates were run into a freshly prepared and filtered solution of 48 g. of ammonium reineckate[9] in 2000 ml. of water. The precipitate was filtered with suction, washed on the filter thoroughly with water, methanol and finally with ether and dried over calcium chloride *in vacuo* to constant weight. The yield of crude reineckate was 60.8 g. (93%). For further purification it was dissolved in 1000 ml. of dry acetone and the solution filtered through a precoated filter (Hyflo Super-Cel). The clear filtrate[10] was diluted with 3000 ml. of distilled water, of which the first 1000 ml. was added very slowly. The reineckate was filtered with suction, washed with water, methanol and ether, and dried *in vacuo*. The yield of pure diphenylphosphorylcholine reineckate was 53.5 g. (81.7%); m. p. 162–164°. *Anal.* Calcd. for $C_{21}H_{31}O_4N_7PS_4Cr$ (654.5): N, 14.95; P, 4.75. Found: N, 15.01, 15.05; P, 4.62, 4.75, 4.68.

Diphenylphosphorylcholine Sulfate.—A solution of 12.7 g. of silver sulfate in 1700 ml. of warm (50°) water was added, together with a small amount of Hyflo Super-Cel, to the clear solution of 53.5 g. of diphenylphosphorylcholine reineckate in 1300 ml. of acetone. The mixture was filtered with suction through a pre-coated filter, the residue washed with water and the combined filtrates concentrated under diminished pressure (bath 45–50°) to a volume of 150 ml. Traces of diphenylphosphorylcholine reineckate, if present, were decomposed by the dropwise addition of a dilute solution of silver sulfate, avoiding an excess of silver sulfate. The silver reineckate

was removed, the aqueous solution taken to dryness under reduced pressure and the residue triturated with 250–300 ml. of dry acetone. After standing for several hours on ice, the crystals were filtered with suction, washed on the filter several times with small quantities of ice-cold acetone and dried for twenty-four hours at 0.05 mm. over calcium chloride at room temperature. The diphenylphosphorylcholine sulfate was obtained in almost quantitative yield (31.2 g.). For analytical purposes the sulfate was purified by dissolving it, at room temperature, in a mixture of 96 parts (by volume) of dry acetone and 4 parts of methanol and removing the insoluble material. The filtrate was evaporated to dryness under reduced pressure and the residue triturated with dry acetone. The sulfate was filtered with suction and dried *in vacuo* at room temperature over calcium chloride.

Anal. Calcd. for $(C_{17}H_{23}O_4NP)_2SO_4 + 2H_2O$ (804.5): N, 3.48; P, 7.70; SO_4, 11.92. Found: N, 3.53; P, 7.68; SO_4, 12.19.

The sulfate, when being kept for several days at room temperature over phosphorus pentoxide at a pressure of 0.001 mm., loses its water of crystallization and forms a viscous mass (P, 7.96%). On exposing the anhydrous sulfate to moist air, it regains its water of crystallization and solidifies (P, 7.58).

The diphenylphosphorylcholine sulfate (hydrate) is readily soluble in water, methanol, glacial acetic acid, tetrachloroethane and insoluble in dry acetone, ethyl acetate and benzene.

Summary

A convenient procedure for the preparation of phosphorylcholine is reported.

(9) The commercial ammonium reineckate is often not sufficiently pure. It was found more economical to prepare the ammonium salt as described in "Organic Syntheses," Coll. Vol. II, p. 555.

(10) The acetone solution can be used directly for the preparation of the diphenylphosphorylcholine sulfate.

Studies on the Reduction of Aromatic Ketones by the Clemmensen Method

By H. Leon Bradlow[1] and Calvin A. VanderWerf

The fact that reduction of p,p'-difluorobenzophenone by a modification of the Clemmensen procedure has been found to yield almost 80% of the theoretical amount of the pinacolone 1,2,2,2-tetra-p-fluorophenylethanone,[2] prompted this study of the applicability of the Clemmensen method to the reduction of aromatic ketones. Although a few examples of the successful reduction of aromatic ketones by the Clemmensen method have been reported, the reduction of benzophenone and many related compounds is generally considered to be unsatisfactory because of the formation of resinous products.[3]

Experimental[4]

Materials.—Amalgamated zinc was prepared according to Martin[5] with two modifications: (1) the zinc was first washed with dilute hydrochloric acid to remove any oxide coating, and (2) the amalgamated zinc was washed with

distilled water. Of the ketones submitted to reduction, numbers I, VII, VIII, XIV and XV were obtained from commercial sources, whereas the remainder were prepared according to standard procedures.

General Procedures.—Three somewhat varied procedures were used for the reduction of ketones, as follows:

Procedure A.—About 0.05 mole of the ketone was refluxed vigorously for forty-eight hours with 12 g. of amalgamated zinc, 18 cc. of water, 8 cc. of concentrated hydrochloric acid and 15 cc. of toluene. Concentrated hydrochloric acid (5 cc.) was added every eight hours.

Procedure B.—Same as A, excepting that 20 g. of amalgamated zinc, 40 cc. of concentrated hydrochloric acid, 15 cc. of water and 20 cc. of toluene were used, and that 10 cc. of concentrated hydrochloric acid was added every eight hours.

Procedure C.—About 0.05 mole of the ketone was refluxed for from twenty-four to thirty-six hours with 20 g. of amalgamated zinc, 20 cc. of ethanol and 50 cc. of concentrated hydrochloric acid. Additional acid (5 cc.) was added after eight and after sixteen hours.

Isolation of the reduction products was effected in two general ways. Where the formation of dimeric products[6] was indicated by the appearance of crystalline deposits on the zinc, the reaction mixtures were exhaustively steam distilled in order to remove any monomeric reduction prod-

(1) H. P. Cady Fellow, 1946.

(2) Bradlow and VanderWerf, This Journal, **69**, 662 (1947).

(3) See Martin, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 159.

(4) All melting points corrected; boiling points uncorrected.

(5) Martin, This Journal, **58**, 1438 (1936).

(6) The exact nature of these varied; in some cases pinacols were formed, in others pinacolones, and occasionally mixtures of both.

Table I

Reduction of Aromatic Ketones

No.	Ketone	Dimeric reduction product (D)	Monomeric reduction product (M)	Procedure A Yield D, %	Procedure A Yield M, %	Procedure B Yield D, %	Procedure B Yield M, %	Procedure C Yield D, %	Procedure C Yield M, %
I	p,p'-Dichlorobenzophenone	p,p',p'',p'''-Tetrachlorobenzopinacol[a]	p,p'-Dichlorodiphenylmethane	80	0	55–65	Trace[b]		
II	p-Chlorobenzophenone	sym-p,p'-Dichlorobenzopinacol[c]		65	0				
III	p-Fluorobenzophenone	sym-p,p'-Difluorobenzopinacol[d]		75–80	0				
IV	p,p'-Difluorobenzophenone	p,p',p'',p'''-Tetrafluorobenzopinacolone[e]		80	0				
V	p,p'-Diphenylbenzophenone	Tetraxenylethylene[f]	Dixenylmethane			None[b] 65%[g]	0 Trace		
VI	Anthrone	Anthrapinacol[h]	9,10-Dihydroanthracene	80–82	Trace	10–20	15–18[b]		
VII	o,p'-Dichlorobenzophenone	o,p',o'',p'''-Tetrachlorobenzopinacol[i]	o,p'-Dichlorodiphenylmethane[j]	50–55	5–15	5–8	46–48		
VIII	Benzophenone	Mixture of benzopinacol and/or α-benzopinacolone with β-benzopinacolone[k]	Diphenylmethane	72–75	Trace	10–15	63–65	95	Trace
IX	Fluorenone	9-Diphenylenephenanthrone[l]	Fluorene	40[m]	30[n]	30–35[m]	65–70	45[m]	48
X	p,p'-Dimethylbenzophenone		p,p'-Dimethyldiphenylmethane[o]	0	20–25[b,p]	0	20–25[b,p]		
XI	α-Benzoylnaphthalene		α-Benzylnaphthalene[q]	0	70–75	0	63[r]	0	51[s]
XII	p,p'-Dihydroxybenzophenone		p,p'-Dihydroxydiphenylmethane[t]			0	25[p]		
XIII	o-Benzoylbenzoic acid		o-Benzylbenzoic acid[u]	0	70–75		High[r]		
XIV	Anthraquinone		9,10-Dihydroanthracene	0	8–10[b,v]	0	7[b,v]	0	5[b,v]
XV	p-Hydroxybenzophenone		p-Hydroxydiphenylmethane	0	40–50[p,w]		40–50[p,w]		40–50[p,w]
XVI	Chalcone[x]			0[p]	0				
XVII	Dibenzalacetone[x]			0[b,p]	0			0[b,p]	0

[a] Recrystallized from dioxane–water; m. p. 175.1–176.0°, in agreement with value reported by Montagne, *Rec. trav. chim.*, **24**, 105 (1904). Converted to p,p',p'',p'''-tetrachlorobenzopinacolone, m. p. 194.4–195.5°, by treatment with acetic acid and iodine. [b] Considerable amounts of ketone recovered. [c] Recrystallized from dilute acetic acid; m. p. 172–178°, as reported by Gomberg and Bachmann, This Journal, **49**, 236 (1927). [d] Recrystallized from propyl alcohol; m. p. 174.8–175.8°, as reported by Koopal, *Rec. trav. chim.*, **34**, 152 (1915). [e] M. p. 170.8–171.4°, from alcohol or Skellysolve B; did not depress m. p. of sample prepared from known pinacol[2] by treatment with acetic acid and iodine. [f] Recrystallized from chlorobenzene; m. p. 328.0–329.0°, as reported by Schlenk and Racky, *Ber.*, **44**, 1180 (1911). [g] Chlorobenzene (25 cc.) added to reaction mixture in place of toluene, and 3/2 usual amount of zinc and hydrochloric acid used. [h] M. p., from benzene, 185.2–186.0°, in agreement with value of Gomberg and Bachmann, ref. cited under [c]. [i] M. p., from dioxane–water, 174.5–175.1°. *Anal.* Calcd. for $C_{26}H_{18}O_2Cl_4$: C, 62.0; H, 3.5. Found: C, 62.0, 62.3; H, 3.4, 3.6. [j] Characterized by oxidation to VII with chromic anhydride in acetic acid. *Anal.* Calcd. for $C_{13}H_{10}Cl_2$: Cl, 29.9; Found: Cl, 30.1, 29.7. [k] Converted, by treatment with acetic acid and iodine, to β-benzopinacolone, m. p., from benzene–Skellysolve B, 181.1–182.1°, showing no depression when mixed with authentic sample prepared according to Gomberg and Bachmann (ref. cited under [c]). The pure pinacolone was also obtained by method A if the reduction was continued for over fifty hours. High yields (70–75%) of benzopinacol were obtained when no organic solvent was used or when an ethyl alcohol solution of VIII and concentrated hydrochloric acid were added gradually and a ternately to refluxing hydrochloric acid in the presence of amalgamated zinc (general method of Miller and Bachman, This Journal, **57**, 2447 (1935). [l] M. p. from benzene, 245.2–246.2°, somewhat lower than value reported by Gomberg and Bachmann. [m] Crude yield. [n] Higher yields (75–80%) of fluorene were obtained when reduction was run according to method of Miller and Bachman. [o] B. p. 132–135° at 5 mm. *Anal.* Calcd. for $C_{15}H_{16}$: C, 91.8; H, 8.2. Found: C, 91.7; H, 8.3. [p] Considerable high-boiling resinous material formed. [q] B. p. 185–192 at 8 mm. Identified as the picrate, m. p. 100.5–101.4°, in agreement with value of Elbs, *J. prakt. Chem.*, **35**, 465 (1887). [r] Reported by Martin.[5] [s] Unamalgamated zinc used, according to directions of Elbs, ref. cited under [q]. [t] Long needles from water, m. p. 155.0–157.0°, in agreement with value reported by Staedel and Beck, *Ann.*, **194**, 318 (1878). [u] Long needles from dilute ethyl alcohol, m. p. 113.3–114.2°, in agreement with value of Rotering and Zincke, *Ber.*, **9**, 631 (1876). [v] Poor yields probably due to low solubility of XIV in reaction medium. [w] Result obtained only when very pure XV was used. [x] Not a true aromatic ketone, but a vinylog.

ucts.[7] The residue from the steam distillation was then extracted with chloroform, the extract washed and dried, and the solvent evaporated, leaving the dimeric product, which was purified by recrystallization or by other suitable methods. The distillate was extracted with di-i-propyl ether or benzene and the extract treated in the same manner. Where necessary to free it from impurities, the monomeric reduction product thus obtained was distilled, or recrystallized from a suitable solvent.

(7) Those resulting from complete reduction of the carbonyl group. Such products were, in almost every case, volatile with steam.

Results

The experimental results are indicated in Table I. In several cases where the total yield of all products reported is considerably below 100%, appreciable amounts of resinous materials were formed. Excepting where otherwise noted, percentages refer to yields of product isolated in pure form.

Discussion

Inspection of Table I reveals that reduction by the general Clemmensen procedure of the following ketones resulted largely in the formation of dimeric reduction products: p,p'-dichlorobenzophenone, p-chlorobenzophenone, p-fluorobenzophenone, p,p'-difluorobenzophenone, p,p'-diphenylbenzophenone and anthrone, and if the reaction was carried out using dilute acid in the Martin procedure, o,p'-dichlorobenzophenone and benzophenone. When more concentrated acid was used, the major products from the reduction of the last mentioned compounds were those resulting from the complete reduction of the carbonyl groups, as was the case, under all conditions tried, for the following ketones: p,p'-dimethylbenzophenone, α-benzoylnaphthalene, p,p'-dihydroxybenzophenone, o-benzoylbenzoic acid, anthraquinone and p-hydroxybenzophenone. Attempted reduction of chalcone and dibenzalacetone led very largely to the production of resinous materials, probably polymeric in nature, from which no pure compounds could be isolated.

In general, it appears that, with certain exceptions discussed below, the presence of substituent groups whose predominant static effect is one of electron withdrawal from the benzene ring, favors the formation of the dimeric product. Groups which exhibit a predominant I_s or M effect, on the other hand, appear to inhibit the formation of dimeric products, thereby increasing the yield of the monomeric product. Lowered concentration of the ketone in the reacting phase likewise tends to favor monomeric reduction. Thus, the use of an immiscible solvent such as toluene or chlorobenzene aids in maintaining a constant low concentration of ketone in the aqueous layer and increases the yield of the monomeric product. The use of a miscible solvent such as alcohol, which makes possible an increased concentration of the ketone in the reacting medium, increases the yield of the dimeric product at the expense of the monomeric product.

If it may be assumed that the reduction is initiated in all cases by the addition of a hydrogen atom to the carbonyl oxygen, then it is likely that the course of the reaction may be determined by the stability of the resulting radical. An increase in the stability of the latter, or in its concentration in the reacting medium, would be expected to favor dimerization. The experimental results support this hypothesis. It would be predicted from the electronic theory that the stability of the radical would be increased by the presence of groups which tend to withdraw electrons from the benzene ring, and decreased by those which release electrons toward the benzene ring.

The difference in the results reported for fluorenone and anthrone may be accounted for by the fact that stabilization through resonance of the radical obtained from fluorenone can occur only to a much lesser extent than in the case of the corresponding anthrone radical, because the structure of the former is not planar.[8,9]

The unexpected formation of monomeric reduction products of o,p'-dichlorobenzophenone, as contrasted with its p,p'-isomer, and of o-benzoylbenzoic acid, is best explained on the basis of steric hindrance. The formation of tetraxenylethylene from p,p'-diphenylbenzophenone is not altogether anomalous, in light of the isolation by Gomberg and Bachmann,[10] of a small amount of that compound as a by-product in the rearrangement of tetraxenylpinacol to the pinacolone.

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Summary

1. The reduction of a number of aromatic ketones by variations of the generalized Clemmensen procedure has been studied.

2. Ketones bearing substituents whose predominant electronic effect is one of electron withdrawal from the benzene ring are reduced largely to dimeric products.

3. Ketones bearing substituents whose predominant electronic effect is one of electron release toward the benzene ring are reduced largely to monomeric products.

4. *ortho*-Substitution appears to favor the formation of monomeric reduction products.

5. An explanation for the effects of the various substituent groups is offered.

(8) This fact may be demonstrated by means of Fisher–Hirschfelder models.

(9) Coplanarity is demanded of valence bonds which enter into conjugative resonance. See Remick, "Electronic Interpretations of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 187.

(10) Reference cited under ^{c}, Table I.