[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Reduction and Benzylation by Means of Benzyl Alcohol. V. A New Synthesis of α,β-Diarylpropionic Acids and the Corresponding Nitriles[1]

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α,β-Diphenylacrylonitrile is converted to α,β-diphenylpropionic acid on heating with benzyl alcoholic potassium hydroxide. The reaction involves reduction of the ethylenic bond (eq. 2), followed by hydrolysis of the cyano group (eq. 3). With other β-aryl substituents, the corresponding propionic acids are formed, accompanied by α,β-diphenylpropionic acid. The presence of the latter can be accounted for by a reverse aldol condensation of the acrylonitrile (eq. 6). This side reaction is avoided by performing the reduction under anhydrous conditions. The procedure makes possible the isolation of the intermediate propionitrile in good yield. The corresponding acid can be obtained directly by adding water to the reduction mixture and refluxing to effect hydrolysis.

A method frequently used for the preparation of α,β-diphenylpropionitrile consists in treating benzyl chloride with phenylacetonitrile under anhydrous conditions[2] in the presence of a strong base such as sodium amide or a metal alkoxide (eq. 1).

$$\mathrm{PhCH_2Cl + PhCH_2CN \xrightarrow{NaNH_2} PhCH_2CHPhCN} \qquad (1)$$

Yields are usually low[3] or else the purity of the product leaves much to be desired.[4] Few other α,β-diarylpropionitriles have been prepared by this method.[5] Several α-phenyl-β-arylpropionitriles have been obtained, in unspecified yields, by reduction of the corresponding acrylonitriles, readily prepared from aromatic aldehydes and phenylacetonitrile, with sodium amalgam.[6] Catalytic hydrogenation also has been used, but the product seems to be of a low purity.[7]

Hydrolysis of α,β-diarylpropionitriles proceeds with difficulty and requires high reaction temperatures.[8] An alternative route to α,β-diarylpropionic acids consists in reducing the appropriate acrylic acids, prepared by the Perkin condensation of arylacetic acids and aromatic aldehydes, with sodium amalgam.[6,9] High yields of the saturated acids have been obtained by hydrogenating the acrylic acids in the presence of Raney nickel.[10]

It has been shown in previous parts of this series[11] that certain types of compounds containing an activated ethylenic bond are capable of being reduced by benzyl alcoholic potassium hydroxide. It was consequently thought likely that α,β-diarylacrylonitriles would exhibit the same property owing to the presence of the cyano group. In fact, when α-phenylcinnamonitrile was heated with the above reagent, α,β-diphenylpropionic acid was obtained in 70% yield. The reaction may be represented by the equations

$$\mathrm{PhCH{=}CPhCN + PhCH_2OH \xrightarrow{KOH} PhCH_2CHPhCN + PhCHO} \qquad (2)$$

$$\mathrm{(2PhCHO + KOH \longrightarrow PhCH_2OH + PhCO_2K)}$$

$$\mathrm{PhCH_2CHPhCN + PhCH_2OH + 2KOH \longrightarrow PhCH_2CHPhCO_2K + PhCH_2OK + NH_3} \qquad (3)$$

A similar result was obtained when α-phenylcinnamonitrile was replaced by an equimolecular mixture of benzaldehyde and phenylacetonitrile. Under alkaline conditions these compounds condense readily (eq. 4) to form the unsaturated nitrile. Moreover, the benzaldehyde can be omitted. In this case reaction is initiated by a small amount of aldehyde formed by dehydrogenation of benzyl alcohol[11a] and possibly also by its oxidation by the cyano group.[12] The quantity of benzaldehyde required for transforming the bulk of phenylacetonitrile into the intermediate unsaturated nitrile (eq. 4) is then gradually generated in the subsequent reduction of the latter (eq. 2). However, under these conditions the yield of diphenylpropionic acid is appreciably lower (45%), possibly because of the self-condensation of phenylacetonitrile.[13]

$$\mathrm{PhCHO + PhCH_2CN \xrightarrow{KOH} PhCH{=}CPhCN + H_2O} \qquad (4)$$

The assumption that reduction of the double bond precedes hydrolysis of the cyano group is borne out by the isolation of the saturated nitrile in good yield (see below). That only a negligible amount of the saturated acid could be produced by an alternative sequence as shown in equation 5 is confirmed by the observation that little α,β-di-

$$\mathrm{PhCH{=}CPhCN \longrightarrow PhCH{=}CPhCO_2H \longrightarrow PhCH_2CHPhCO_2H} \qquad (5)$$

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[1] Part IV, M. Avramoff and Y. Sprinzak, *J. Org. Chem.*, **22**, 571 (1957).

[2] Recently the remarkable observation was made that α,β-diphenylpropionitrile could be obtained in a 50% yield by interaction of benzyl chloride and phenylacetonitrile in the presence of aqueous sodium hydroxide and triethylamine [J. Jarrousse, *Compt. rend.*, **232**, 1424 (1951)].

[3] (a) H. Janssen, *Ann.*, **250**, 125 (1889); (b) D. Shapiro, *J. Org. Chem.*, **14**, 839 (1949); (c) C. R. Hauser and W. R. Brasen, THIS JOURNAL, **78**, 494 (1956).

[4] (a) M. Protiva, J. O. Jílek and J. Pliml, *Chem. Listy*, **46**, 640 (1951); *C. A.*, **47**, 8069 (1953); (b) N. Campbell and E. Ciganek, *J. Chem. Soc.*, 3834 (1956).

[5] (a) Ng. Ph. Buu-Hoi and P. Cagniant, *Rec. trav. chim.*, **64**, 355 (1945); (b) H. Lettré, W. Haede and L. Schafer, Hoppe-Seyler's *Z. physiol. Chem.*, **289**, 298 (1952).

[6] P. C. Jocelyn, *J. Chem. Soc.*, 1640 (1954).

[7] A. Dobrowsky, *Monatsh.*, **82**, 140 (1951).

[8] D. Libermann and L. Hengl, *Bull. soc. chim. France*, 974 (1951); S. Rovira, *Ann. chim. (Paris)*, [11] **20**, 660 (1945); ref. 4b, *cf.* also ref. 5a.

[9] B. B. Day and V. S. Ramanathan, *Proc. Natl. Inst. Sci. India*, **9**, 193 (1943); *C. A.*, **43**, 5025 (1949).

[10] (a) D. Papa, H. Breiger and V. Peterson, *J. Org. Chem.*, **14**, 362 (1949); (b) W. D. McPhee and E. S. Erickson, Jr., THIS JOURNAL, **68**, 624 (1946).

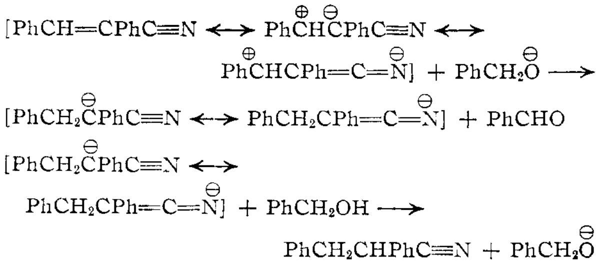
[11] (a) Y. Sprinzak, *ibid.*, **78**, 466 (1956); (b) M. Avramoff and Y. Sprinzak, *ibid.*, **78**, 4090 (1956); *cf.* also P. Mastagli, *Ann. chim. (Paris)*, [11] **10**, 281 (1938).

[12] Reduction products, including benzylamine, dibenzylamine and lophine, have been obtained in experiments with benzonitrile (unpublished results).

[13] E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1906 (1906).

phenylpropionic acid was formed when α-phenylcinnamic acid was used as the starting material.

Applying Doering's hydride ion mechanism for the reduction of carbonyl compounds by metal alkoxides[14] to the reduction of the ethylenic bond in the unsaturated nitrile, the following scheme may be written

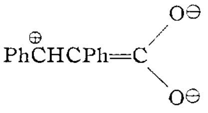


$$[\mathrm{PhCH{=}CPhC{\equiv}N} \longleftrightarrow \mathrm{Ph\overset{\oplus}{C}H\overset{\ominus}{C}PhC{\equiv}N} \longleftrightarrow \mathrm{Ph\overset{\oplus}{C}HCPh{=}C{=}\overset{\ominus}{N}}] + \mathrm{PhCH_2\overset{\ominus}{O}} \longrightarrow$$

$$[\mathrm{PhCH_2\overset{\ominus}{C}PhC{\equiv}N} \longleftrightarrow \mathrm{PhCH_2CPh{=}C{=}\overset{\ominus}{N}}] + \mathrm{PhCHO}$$

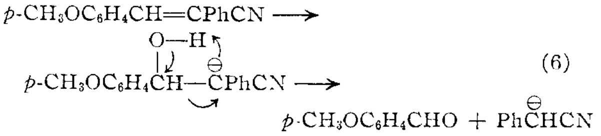
$$[\mathrm{PhCH_2\overset{\ominus}{C}PhC{\equiv}N} \longleftrightarrow \mathrm{PhCH_2CPh{=}C{=}\overset{\ominus}{N}}] + \mathrm{PhCH_2OH} \longrightarrow \mathrm{PhCH_2CHPhC{\equiv}N} + \mathrm{PhCH_2\overset{\ominus}{O}}$$

Resonance forms in which a carbon atom is doubly linked to carbon and nitrogen have previously been postulated for the anion of phenylacetonitrile.[15] Zwitterionic structures for the anion of α-phenylcinnamic acid, such as



are apparently much less likely.

When α-phenyl-*p*-methoxycinnamonitrile was submitted to the same reaction, the expected α-phenyl-β-(*p*-methoxyphenyl)-propionic acid was formed; it was, however, accompanied by a considerable amount of α,β-diphenylpropionic acid. The latter presumably results from the liberation of phenylacetonitrile from the starting compound by a reverse aldol condensation, induced by competition of the hydroxide ions with the (reducing) benzylate ions (eq. 6). The liberated phenylacetonitrile would then condense with some of the benzaldehyde produced in the reduction to form α-phenylcinnamonitrile. A similar side reaction was observed with other β-aryl-α-phenylacrylonitriles.[16]

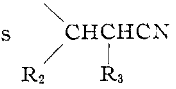


(6)

As a consequence of the above consideration of the role of hydroxide ions, the reduction was attempted with a solution from which water had been removed by distillation to secure complete conversion of potassium hydroxide to potassium benzylate. Evidently this expedient, designed to exclude the side reaction discussed above, should also serve to prevent hydrolysis of the saturated nitrile formed in the reduction. Actually both ends were achieved. The procedure thus constitutes a convenient method for the preparation of both α,β-diarylpropionitriles (Table I) and the corresponding acids (Table II). When the latter are desired, the requisite amount of water is added to the reaction mixture after termination of the reduction, and refluxing is continued until the evolution of ammonia is complete. Obviously, when the starting compound is a β-phenyl-α-arylacrylonitrile and the acid alone is required, a separate reduction step is not necessary, and the reaction is carried out in one step as in the case of α,β-diphenylpropionic acid (see Special Procedure in the Experimental).

TABLE I

PREPARATION OF PROPIONITRILES

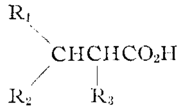


R_1	R_2	R_3	Reflux time, min.	Yield pure prod., %
C_6H_5	H	C_6H_5[a]	40	62[h]
o-ClC_6H_4	H	C_6H_5	90	33[h]
p-ClC_6H_4	H	C_6H_5	60	58
p-$CH_3OC_6H_4$	H	C_6H_5[b]	60	75
p-$CH_3C_6H_4$	H	C_6H_5	30	55[h]
3,4-$(CH_2O_2)C_6H_3$	H	C_6H_5[c]	30[f]	48
O—CH=CH—CH=C—	H	C_6H_5	30[g]	57[h]
1-$C_{10}H_7$	H	C_6H_5	60	56
C_6H_5	H	1-$C_{10}H_7$[d]	60	64[h]
C_6H_5	H	3,4$(CH_3O)_2C_6H_3$	15	43[h]
C_6H_5	C_6H_5	C_6H_5[e]	30	52[h]

[a] Ref. 3b. [b] Ref. 5b. [c] M.p. 75–76° (from 80% alcohol) as compared with 57° for a crude product, given by Dobrowsky.[7] [d] Ref. 5a. [e] E. P. Kohler, *Am. Chem. J.*, **35**, 386 (1905); *Chem. Zentr.*, **77**, **II**, 46 (1906). [f] Heated at 160–170°. [g] Heated at 185–195°. [h] Distilled *in vacuo* before recrystallization.

TABLE II

PREPARATION OF PROPIONIC ACIDS



R_1	R_2	R_3	Reflux time, min.	Yield pure prod., %
C_6H_5	H	C_6H_5[a,d]	60	70
o-ClC_6H_4	H	C_6H_5	30	53
p-ClC_6H_4	H	C_6H_5	30	53
p-$CH_3OC_6H_4$	H	C_6H_5[e]	30	67
p-$CH_3C_6H_4$	H	C_6H_5	30	71
3,4-$(CH_2O_2)C_6H_3$	H	C_6H_5[f]	30	41
O—CH=CH—CH=C—	H	C_6H_5[g]	30	44
1-$C_{10}H_7$	H	C_5H_5	45	47
C_6H_5	H	1-$C_{10}H_7$[a,h]	60	45
C_6H_5	H	3,4$(CH_3O)_2C_6H_3$[b,i]	60	70
C_6H_5	C_6H_5	C_6H_5[c,j]	150	54

[a] Prepared by the special procedure. [b] Prepared by the special procedure, but using 100 ml. of benzyl alcohol. [c] See Experimental. [d] W. v. Miller and G. Rhode, *Ber.*, **25**, 2017 (1892). [e] E. Schwenk, D. Papa, B. Whitman and H. F. Ginsberg, *J. Org. Chem.*, 9, 175 (1944). [f] Ref. 10b. [g] M.p. 105° as compared with 95.5°, given by P. Lambert and P. Mastagli [*Compt. rend.*, **235**, 626 (1952)]. [h] M.p. 93–95° as compared with 136–137°, given by Papa and co-workers (ref. 10a). Following their instructions we obtained however an acid with a m.p. 93–95°, which did not depress the m.p. of our product. [i] Ref. 6. [j] J. F. Eijkman, *Chem. Weekblad*, 5, 655 (1908); *Chem. Zentr.*, **79**, II, 1100 (1908).

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(14) W. von E. Doering and T. C. Ashner, THIS JOURNAL, **75**, 393 (1953).

(15) T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 315.

(16) An analogous replacement of an alkyl group by the benzyl group has been observed in this Laboratory in the dibenzofulvene series. While benzalfluorene was quantitatively reduced to 9-benzylfluorene on treatment with benzyl alcoholic potassium hydroxide,[11a] ethylidenefluorene furnished, in addition to the expected 9-ethylfluorene, a considerable quantity of 9-benzylfluorene (unpublished results).

The method also has been tested in one case of a fully substituted acrylonitrile, *viz.*, triphenylacrylonitrile; both α,β,β-triphenylpropionic acid and the corresponding nitrile have been obtained in good yield.

Experimental

Commercial potassium hydroxide, containing 15% of water, was used. Melting points are corrected. Unless otherwise indicated, the melting points of known compounds agreed satisfactorily with the literature values. The identity of these compounds was also checked by elementary analysis.

Preparation of Acrylonitriles.—α-Phenylcinnamonitrile,[17] α-phenyl-*p*-chlorocinnamonitrile,[18] α-phenyl-*o*-chlorocinnamonitrile,[19] α-phenyl-*p*-methoxycinnamonitrile,[20] α-phenyl-*p*-methylcinnamonitrile,[21] α-phenyl-3,4-methylenedioxycinnamonitrile,[22] α-(3,4-dimethoxyphenyl)-cinnamonitrile,[23] α-(1-naphthyl)-cinnamonitrile[24] and α-phenyl-β-(1-naphthyl)-acrylonitrile were prepared by the method of v. Walther[25]: several ml. of aqueous 30% sodium hydroxide solution were added to a concentrated alcoholic solution of the acetonitrile and the aldehyde in equimolecular proportions, and the mixture was heated to boiling. The products crystallized on cooling and were filtered and washed with alcohol. The yields varied between 88 and 100%.

In the case of α-(1-naphthyl)-cinnamonitrile[24] the reaction mixture was refluxed for 2 hr. The product crystallized on dilution with alcohol; m.p. 77.5°. *Anal.* Calcd. for $C_{19}H_{13}N$: C, 89.38; H, 5.13. Found: C, 89.40; H, 5.02.

In the case of α-phenyl-*p*-methylcinnamonitrile the crude product was extracted with ether and distilled (b.p. 195–205° at 6 mm.) before recrystallization from petroleum ether.

α-Phenyl-β-(1-naphthyl)-acrylonitrile appears to be new; m.p. 113–114° (from alcohol). *Anal.* Calcd. for $C_{19}H_{13}N$: C, 89.38; H, 5.13. Found: C, 89.26; H, 5.12.

Literature procedures have been used for the preparation of α-phenyl-β-(2-furyl)-acrylonitrile[20] and α,β,β-triphenylacrylonitrile.[26]

Preparation of Propionitriles.—Water was distilled from a mixture of 4.0 g. of potassium hydroxide and 110 ml. of benzyl alcohol. The operation was terminated by the distillation of 10 ml. of benzyl alcohol. The acrylonitrile (0.025 mole) was added and the mixture refluxed. In two cases (see Table I) the reaction was conducted at a lower temperature to avoid decomposition of the starting material. After cooling, the mixture was treated with water and ether and the ethereal layer washed several times with water, dried over sodium sulfate, the ether evaporated and the benzyl alcohol removed *in vacuo*. The residue was either recrystallized directly or distilled *in vacuo* before recrystallization.

The amounts of potassium hydroxide and benzyl alcohol could probably be reduced considerably without affecting the yields. This was indicated by supplementary experiments in which α-phenylcinnamonitrile, α-phenyl-*p*-methoxycinnamonitrile and α-phenyl-*p*-chlorocinnamonitrile, in 0.025 molar quantities, were treated with a mixture prepared from 1.65 g. of potassium hydroxide and 30 ml. of benzyl alcohol and freed of water by distilling off 5 ml. of liquid.

The following compounds appear to be new[27]: **α-Phenyl-β-(*o*-chlorophenyl)-propionitrile**, b.p. 164–172° (5 mm.), m.p. 65° (from petroleum ether and then from 80% alcohol). *Anal.* Calcd. for $C_{15}H_{12}ClN$: C, 74.55; H, 5.01. Found: C, 74.61; H, 4.86.

α-Phenyl-β-(*p*-chlorophenyl)-propionitrile, m.p. 113–114° (from alcohol). *Anal.* Calcd. for $C_{15}H_{12}ClN$: C, 74.55; H, 5.01. Found: C, 74.73; H, 5.01.

α-Phenyl-β-(*p*-tolyl)-propionitrile, b.p. 200–220° (25 mm.), m.p. 58° (from petroleum ether). *Anal.* Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83. Found: C, 87.41; H, 6.57.

β-Phenyl-β-(2-furyl)-propionitrile, b.p. 185–189° (30 mm.), $n^{25}D$ 1.5480. *Anal.* Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 79.20; H, 5.42.

α-Phenyl-β-(1-naphthyl)-propionitrile, m.p. 85° (from alcohol). *Anal.* Calcd. for $C_{19}H_{15}N$: C, 88.69; H, 5.88. Found: C, 88.69; H, 6.14.

α-(3,4-Dimethoxyphenyl)-β-phenylpropionitrile, b.p. 190–210° (3 mm.), m.p. 74° (from 80% alcohol). *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.10; H, 6.24.

Preparation of Propionic Acids. General Procedure.—The acrylonitrile was reduced to the propionitrile as described above. The reaction mixture was left to cool to about 100°, 1 ml. of water was added and the mixture refluxed again. After cooling there was added to the mixture 20 ml. of water, 10 ml. of concentrated hydrochloric acid and 250 ml. of ether. The organic layer was washed with water, dried over sodium sulfate, the ether evaporated and the benzyl alcohol removed *in vacuo*. The residue was dissolved in 100 ml. of 10% sodium carbonate, the solution was extracted with ether, acidified with an excess of concentrated hydrochloric acid and steam distilled to remove the benzoic acid present.[28] The residue of the steam distillation was recrystallized from 50% alcohol to remove traces of α,β-diphenylpropionic acid and then recrystallized from the appropriate solvent.

When reduced amounts of potassium hydroxide and benzyl alcohol were used in the reduction (see above), only 0.6 ml. of water, together with an additional 2.4 g. of potassium hydroxide, were added to effect hydrolysis.

Special Procedure.—A mixture of 0.025 mole of the acrylonitrile, 4.0 g. of potassium hydroxide and 25 ml. of benzyl alcohol was refluxed for 1 hr. The reaction mixture was worked up as in the general procedure, except that the crude product was recrystallized from the appropriate solvent without previous recrystallization from 50% alcohol.

The following compounds appear to be new: **α-Phenyl-β-(*o*-chlorophenyl)-propionic acid**, m.p. 122° (from heptane). *Anal.* Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.14; H, 5.10.

α-Phenyl-β-(*p*-chlorophenyl)-propionic acid, m.p. 144° (from benzene). *Anal.* Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.30; H, 5.07.

α-Phenyl-β-(1-naphthyl)-propionic acid, m.p. 98° (from petroleum ether). *Anal.* Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.58; H, 6.29.

α-Phenyl-β-(*p*-tolyl)-propionic acid,[29] m.p. 115–116° (from heptane). *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.26; H, 6.61.

α,β-Diphenylpropionic Acid from Phenylacetonitrile.—To an anhydrous solution of 13.0 g. of potassium hydroxide in 300 ml. of benzyl alcohol, prepared as described in the preparation of propionitriles, was added 11.8 g. of phenylacetonitrile, and the mixture was refluxed for 3 hr. After cooling to about 100°, 2 ml. of water was added and refluxing was continued for 45 min. The mixture was worked up as described in the general procedure to yield 10.3 g. (45%), m.p. 97–97.5°.

α,β,β-Triphenylpropionic Acid.—The acid was prepared as described in the general procedure. The residue left after the evaporation of benzyl alcohol was dissolved in 100 ml. of 10% sodium hydroxide by heating on a water-bath. The solution was filtered hot and acidified, and the precipitated acid was filtered, washed several times with hot water

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[17] S. Wawzonek and E. M. Smolin, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 715.

[18] R. v. Walther and W. Raetze, *J. prakt. Chem.*, [2] **65**, 258 (1902); *Chem. Zentr.*, **73**, I, 1213 (1902).

[19] A. McRae and A. S. Townshed, *Can. J. Research*, **11**, 628 (1934); *C. A.*, **29**, 1077 (1935).

[20] H. V. Frost, *Ann.*, **250**, 156 (1889).

[21] A. Bistrzycki and E. Stelling, *Ber.*, **34**, 3081 (1901).

[22] R. v. Walther and A. Wetzlich, *J. prakt. Chem.*, [2] **61**, 169 (1900); *Chem. Zentr.*, **71**, I, 909 (1900).

[23] J. B. Niederl and A. Ziering, THIS JOURNAL, **64**, 885 (1942).

[24] This nitrile is described by I. Hechenbleikner [U. S. Patent 2,286,363; *C. A.*, **36**, 7224 (1942)] as an oil, b.p. 240° (less than 1 mm.).

[25] R. v. Walther, *J. prakt. Chem.*, [2] **53**, 454 (1896).

[26] S. Wawzonek and E. M. Smolin, *Org. Syntheses*, **31**, 52 (1951).

[27] The boiling points are those of the crude nitriles.

[28] The amount of benzoic acid formed usually exceeds the quantity calculated on the basis of the reduction reaction, owing to the formation of some benzaldehyde by dehydrogenation of the benzyl alcohol under the reaction conditions [M. Guerbet, *Bull. soc. chim. France*, [4] **3**, 500 (1908)].

[29] A. Spasov and S. Robev [*Doklady Akad. Nauk, S.S.S.R.*, **95**, 559 (1954)] attribute this formula to a compound of m.p. 161°. Considering the range of melting points of closely related acids, this value appears to be unduly high.

and dried to afford 4.4 g., m.p. 205–215°. Recrystallization from benzene afforded 3.7 g., m.p. 222–224°. From the benzene solution an additional 0.4 g. was recovered.

Formation of α,β-Diphenylpropionic Acid in the Reduction of α-Phenyl-*p*-methoxycinnamonitrile.—A mixture of 11.8 g. of α-phenyl-*p*-methoxycinnamonitrile, 8.0 g. of potassium hydroxide and 200 ml. of benzyl alcohol was refluxed for 90 minutes. The reaction mixture was worked up as described in the general procedure. The residue left after the steam distillation was dissolved in 50 ml. of hot 50% alcohol, and the semi-solid deposited was filtered by suction after several days. It was fractionated to yield 4.0 g., b.p. 190–198° (0.8 mm.), which after several recrystallizations from 50% alcohol afforded 0.65 g. of α-phenyl-β-(*p*-methoxyphenyl)-propionic acid, m.p. and mixed m.p. 121–123.3°. The mother liquor from the filtration of the crude acid, which contained an oily portion, was evaporated and fractionated to yield 1.5 g., b.p. 170–180° (0.8 mm.), which after several recrystallizations from petroleum ether afforded 0.6 g. of α,β-diphenylpropionic acid, m.p. 92–95°, mixed m.p. 94–96°.

REHOVOTH, ISRAEL

COMMUNICATIONS TO THE EDITOR

MOLECULAR WEIGHTS FROM STUDIES OF SEDIMENTATION AND DIFFUSION IN THREE-COMPONENT SYSTEMS

Sir:

One of the chief methods used to find molecular weights of proteins is by combining the results of sedimentation and diffusion experiments performed with systems of at least three components (protein, salt, water). Yet the study of interacting flows in liquid diffusion[1-7] has shown that Svedberg's equation[8] is not applicable to finding the molecular weight of a solute in a three-component system. This may be seen readily from the fact that four diffusion coefficients are required to describe the flows of the two solutes in a three-component system. Moreover, recent studies by Dunlop[5,7] have shown that the cross-term diffusion coefficients D_{12} and D_{21} are not in general negligible in comparison with the main diffusion coefficients D_{11} and D_{22}. The purpose of this communication is to derive an equation analogous to Svedberg's equation for use with three-component, non-electrolyte systems.

As a starting point, equation 22 of Hooyman[9] will be used (with somewhat different notation) to describe the flow of a solute in a centrifugal field. This equation was derived[9] by the methods of thermodynamics of irreversible processes.[10,11]

$$J_i = \sum_{j=1}^{2} L_{ij}\left[\omega^2 r(1 - \bar{v}_j\rho) - \sum_{k=1}^{2}\left(\frac{\partial\mu_j}{\partial c_k}\right)_{\substack{T,P,c_m\\(m\neq 0)}}\left(\frac{\partial c_k}{\partial r}\right)_t\right] \qquad (i = 1,2) \quad (1)$$

J = flow relative to the cell, ω = angular velocity of the rotor, r = distance from the center of rotation, $\bar{v}$ = partial specific volume (assumed constant), ρ = density of solution, μ = chemical potential per gram, c = concentration in g./ml., T = absolute temperature, P = pressure, t = time; for brevity $(\partial\mu_j/\partial c_k)$ will be written μ_{jk}. The phenomenological coefficients L_{ij}, which enter into both the term for sedimentation and the terms for diffusion, relate the flow of solute i to the "forces" causing the flow. This is apparent when equation 1 is written in the more compact form

$$J_i = -\sum_{j=1}^{2} L_{ij}\left(\frac{\partial\bar{\mu}_j}{\partial r}\right)_t \qquad (i = 1,2) \quad (2)$$

where $\bar{\mu}_j$ is the total potential, per gram, of j. Comparison of (1) with the practical flow equation used to measure sedimentation and diffusion coefficients

$$J_i = c_i s_i \omega^2 r - \sum_{k=1}^{2} D_{ik}\left(\frac{\partial c_k}{\partial r}\right)_t \qquad (i = 1,2) \quad (3)$$

shows that

$$s_1 = \frac{1}{c_1}\left[L_{11}(1 - \bar{v}_1\rho) + L_{12}(1 - \bar{v}_2\rho)\right] \quad (4)$$

$$D_{11} = L_{11}\mu_{11} + L_{12}\mu_{21} \quad (5a)$$

$$D_{12} = L_{11}\mu_{12} + L_{12}\mu_{22} \quad (5b)$$

An expression for the molecular weight of solute 1 (M_1) is obtained by solving (5a) and (5b) for L_{11} and L_{12} and then by substituting the results into equation (4)

$$s_1 = \left\{\frac{(1 - \bar{v}_1\rho)}{(c_1\mu_{11})}\left[\frac{D_{11} - D_{12}\mu_{21}/\mu_{22}}{(1 - \gamma)}\right] + \frac{c_2(1 - \bar{v}_2\rho)}{(c_2\mu_{22})} \times \left[\frac{(D_{12}/c_1) - D_{11}\mu_{12}/(c_1\mu_{11})}{(1 - \gamma)}\right]\right\} \quad (6)$$

$$\gamma = (\mu_{12}\mu_{21}/\mu_{11}\mu_{22}) \quad (6a)$$

$$c_i\mu_{ii} = \frac{RT}{M_i}\left[1 + c_i\left(\frac{\partial \ln y_i}{\partial c_i}\right)_{\substack{T,P,c_j\\(j\neq 0)}}\right] \quad (6b)$$

When c_2 is held fixed and the sedimentation and diffusion coefficients are extrapolated to zero c_1, this relation becomes (since[5,6] $D_{12} \rightarrow 0$ as $c_1 \rightarrow 0$ and, by L'Hopital's rule, $\lim_{c_1 \rightarrow 0} (D_{12}/c_1) = (\partial D_{12}/$

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