TABLE I

DISPROPORTIONATION OF ETHYLBENZENE IN THE PRESENCE OF XYLENE AND 150 VOLUME % HF

Feed composition, mole %									
o-Xylene	0	0	0	20	20	75	75	75	0
m-Xylene	67	33	75	40	40	0	0	0	0
p-Xylene	0	34	0	20	20	0	0	0	50
Ethylbenzene	33	33	25	20	20	25	25	25	50
Temp., °C.	24	24	63	25	50	0	20	65	20
Reaction time, min.	30	30	30	4160	240	90	60	60	90
Moles BF_3 per mole aromatic	1.5	1.1	1.0	1.6	2.0	1.1	1.1	1.1	1.1
Product distribution, mole %									
Benzene	15	15.5	22	20	19	12.5	18	24	21
C_8 Fraction	70	69	56	60	62	74	63	52	58
C_{10} Fraction	15	15.5	22	20	19	13.5	19	24	21
Composition of C_8 fraction, %									
o-Xylene	0	0	4	0	1	69	16	1	0
m-Xylene	77	71	83	98	95	15	73	95	64
p-Xylene	2	18	7	1	3	0	0	0	17
Ethylbenzene	10	11	6	Trace	1	16	11	4	19
Composition of C_{10} fraction, %									
1,3-Diethylbenzene	85	90	0	0	0	10	Trace	0	93
1,3-Dimethyl-5-ethylbenzene	15	10	100	100	100	Trace	20	100	7
1,2-Dimethyl-4-ethylbenzene	0	0	0	0	0	90	80	0	0
1,4-Dimethyl-4-ethylbenzene	0	0	0	0	0	0	0	0	0
1,3-Dimethyl-4-ethylbenzene	0	0	0	0	0	0	0	0	0
Ethylbenzene converted, %	85	90	88	99+	97	60	75	96	75

higher boiling *o*-xylene, then the lower-boiling fraction—ethylbenzene, *m*- and *p*-xylene—can be transformed under mild conditions into benzene, *m*- and *p*-xylene and 1,3-diethylbenzene. Also, under mild conditions, the *o*-xylene can be converted by transalkylation with ethylbenzene into 1,2-dimethyl-4-ethylbenzene, another pure ten-carbon alkylbenzene not readily obtained by direct alkylation.

WHITING, INDIANA

[CONTRIBUTION FROM THE WALKER LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE]

The Metalation and Addition Reactions of Allylbenzene and Propenylbenzene with Butyllithium and Lithium Amide

BY HARRY F. HERBRANDSON AND DAVID S. MOONEY

RECEIVED MARCH 1, 1957

1-Phenylallyllithium has been prepared in liquid ammonia and in ether. Its reactions with proton donors and with carbon dioxide are very similar to those of 1-phenylallylsodium and cinnamylsodium leading to the conclusion that the compound is probably ionic in both solvents, albeit existing as ion pairs or higher aggregates in ether. A possible explanation is offered for the formation of propenylbenzene from the quenching of 1-phenylallyllithium in a kinetically controlled reaction. Propenylbenzene undergoes addition reactions with butyllithium and is quite unreactive to lithium amide.

Although a number of examples have appeared of allylic rearrangements of organolithium compounds,[1] those which have been reported do not afford a good basis for comparison with allylic rearrangements of other organometallic compounds. The most extensive studies of allylic rearrangements of organometallic compounds have been concerned with the cinnamyl and butenyl Grignard reagents[2] and cinnamylsodium[3a,b] as well as 1-phenylallylsodium.[3a,c] Other reactions of allylic derivatives of sodium,[3b,c,4] potassium[5] and cesium[6] also have been reported.

That the inorganic alkali metal cation can have an effect on the behavior of the organic anion has been emphasized.[7] In view of the marked differ-

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[1] H. Gilman and F. Breuer, THIS JOURNAL, **56**, 1127 (1934); H. Gilman and C. W. Bradley, *ibid.*, **60**, 2333 (1938); K. Ziegler, N. Eimers, W. Hechelhammer and H. Wilms, *Ann.*, **567**, 43 (1950).

[2] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 1133 ff.

[3] (a) T. W. Campbell and W. G. Young, THIS JOURNAL, **69**, 688 (1947); (b) A. A. Morton and E. Grovenstein, Jr., *ibid.*, **74**, 5437 (1952); (c) R. Y. Mixer and W. G. Young, *ibid.*, **78**, 3379 (1956).

[4] A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little and R. L. Letsinger, *ibid.*, **72**, 3785 (1950).

[5] A. A. Morton, M. L. Brown, M. E. T. Holden, R. L. Letsinger and E. E. Magat, *ibid.*, **67**, 2224 (1945).

[6] J. de Postis, *Compt. rend.*, **224**, 579 (1947).

[7] J. B. Conant and G. W. Wheland, THIS JOURNAL, **54**, 1212 (1932); C. G. Swain, *ibid.*, **69**, 2306 (1947); C. G. Swain and L. Kent, *ibid.*, **72**, 518 (1950); O. L. Brady and J. Jakobovits, *J. Chem. Soc.*, 767 (1950); A. A. Morton and C. E. Claff, Jr., THIS JOURNAL, **76**, 4935 (1954); H. Gilman and J. W. Morton, Jr., in "Organic Reactions," R. Adams, editor, Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 258; A. A. Morton and E. J. Lanpher, Abstracts of the 129th Meeting of the American Chemical Society, April 1956, p. 12-N.

ences in behavior of cinnamylmagnesium chloride and cinnamylsodium and the marked difference in ionic character between organosodium and organolithium compounds,[8] the behavior of the lithium derivative of allylbenzene toward a number of electrophilic reagents was investigated. Some comparisons between the behavior of allylbenzene and propenylbenzene toward butyllithium and lithium amide were also made.

Results

The quenching of 1-phenylallyllithium with a proton donor gave a mixture of allylbenzene and propenylbenzene whose composition depended on the solvent. The complete reaction of allylbenzene with lithium amide in liquid ammonia required 45 minutes after which quenching with ammonium chloride gave 80% propenylbenzene and 20% allylbenzene. If the mixture was quenched after only 30 minutes a greater proportion of allylbenzene was found in the product: 40–50% allylbenzene and only 50–60% propenylbenzene. In ether the reaction of butyllithium with allylbenzene was also slow. As estimated from the carbonation experiments, less than 5% reaction was accomplished after 2 hr. at −15°, whereas the reaction was better than 90% complete after 2 hr. of refluxing. Added to a large excess of methanol, 1-phenylallyllithium in ether gave approximately 54% allylbenzene and 46% propenylbenzene. Correction of these figures for unreacted allylbenzene (about 7%) gives for the product of quenching a 50:50 ratio of propenylbenzene:allylbenzene.

Lithium amide in liquid ammonia did not react to any appreciable extent with propenylbenzene during a period of 2.25 hr. The reaction of butyllithium in ether with propenylbenzene was more rapid than with allylbenzene; however, quenching after 15 minutes reflux gave only a 4% recovery of propenylbenzene. Of the original hydrocarbon, 22% was accounted for as 2-methyl-1-phenylhexane, 44% (25% purified) was presumed to be 2,4-dimethyl-1,3-diphenyloctane, and the remainder appeared as higher molecular weight products.

The carbonation of 1-phenylallyllithium in ether gave a 48–57% yield of acid which was refluxed for 2 hr. with 10% sodium hydroxide to isomerize the 2-phenyl-3-butenoic acid to 2-phenyl-2-butenoic acid.[9] That little of this acid was lost in the 2-hr. reflux is indicated by Fittig's isolation of 80–90% of unchanged 4-phenyl-3-butenoic acid after 20–80 hr. reflux with 10% sodium hydroxide,[10] although Linstead recovered only 50% of the acid from a more drastic 100–110 hour reflux with 20% alkali.[11]

Quantitative estimations of the relative amounts of 2-phenyl-2-butenoic acid and 4-phenyl-3-butenoic acid in the resulting product were made by fractional vacuum sublimation and comparison of the m.p. of each fraction with a m.p.–composition curve[12] determined from mixtures of authentic 2-phenyl-2-butenoic acid[13] and 4-phenyl-3-butenoic acid[14] and in two instances by quantitative comparison of the ultraviolet spectra of the mixtures with those of authentic samples of the acids. In four preparations 4-phenyl-3-butenoic acid constituted 59–69% and 2-phenyl-2-butenoic acid 31–41% of the total acid.[15]

Carbonation of the product of reaction of butyllithium and propenylbenzene after 1 hr. at 0° gave an 80% recovery of propenylbenzene, 5% of 3-methyl-2-phenylheptanoic acid and 15% of hydrocarbon, mainly 2-methyl-1-phenylhexane. Refluxing of the reactants in ether for 15 minutes before carbonation gave 5% of 3-methyl-2-phenylheptanoic acid, about 8–10% of acid presumed to be 3,5-dimethyl-2,4-diphenylnonanoic acid, about 55% of higher molecular weight acids and 30% of neutral material composed mainly of 2-methyl-1-phenylhexane and 2,4-dimethyl-1,3-diphenyloctane.

The carbonation of the products of competition between equivalent amounts of allylbenzene and propenylbenzene for butyllithium resulted in the formation of 2-phenyl-3-butenoic acid (isolated as 2-phenyl-2-butenoic acid) and 4-phenyl-3-butenoic acid as the only acids. The refluxing in ether for 15 minutes of equimolar quantities of allylbenzene, propenylbenzene and butyllithium gave after carbonation 40% of acid, 59–69% 4-phenyl-3-butenoic acid and 31–41% 2-phenyl-3-butenoic acid and 11% of recovered allylbenzene and propenylbenzene. That these were the only acids was demonstrated by the determination of the neutralization equivalent of the total acid recovered, the ultraviolet spectrum and the m.p. range of the acid. The remainder consisted largely of about equal amounts of 2-methyl-1-phenylhexane and 2,4-dimethyl-1,3-diphenyloctane and lesser amounts of higher molecular weight hydrocarbons. A similar reaction effected with 2 hr. of reflux gave only 27% of acid, 63–64% 4-phenyl-3-butenoic acid and 36–37% 2-phenyl-3-butenoic acid and a greater amount of 2-methyl-1-phenylhexane and higher molecular weight hydrocarbons.

The reaction of 1-phenylallyllithium with benzophenone gave 41% crude, or 25% pure, 1,1,4-triphenyl-3-butene-1-ol. The alcohol was identified through dehydration by vacuum distillation over a trace of iodine to give 1,1,4-triphenyl-1,3-butadiene.[17] None of the isomeric alcohol, 1,1,2-triphenyl-3-butene-1-ol, could be isolated.

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[8] (a) G. E. Coates, "Organo-Metallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 6, 12; (b) M. T. Rogers and A. Young, THIS JOURNAL, **68**, 2748 (1946); (c) L. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., p. 74.

[9] H. Gilman and S. A. Harris, THIS JOURNAL, **49**, 1825 (1927); **53**, 3541 (1931).

[10] R. Fittig and A. Luib, *Ann.*, **283**, 297 (1894).

[11] R. P. Linstead and L. T. D. Williams, *J. Chem. Soc.*, 2735 (1926).

[12] This m.p.–composition curve has been deposited as Document number 5199 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm payable to: Chief, Photoduplication Service, Library of Congress.

[13] H. Rupe and E. Busolt, *Ann.*, **369**, 332 (1909).

[14] R. Fittig and W. Jayne, *ibid.*, **216**, 98 (1883).

[15] It is possible that a small amount of *o*-propenylbenzoic acid may have been present[5b] as the ultraviolet spectra probably would not distinguish this acid from 4-phenyl-3-butenoic acid (compare the spectra of sodium 4-phenyl-3-butenoate and *trans*-propenylbenzene[16]; but from the sublimations it must be concluded that this amounted to less than 10% of the total acid.

[16] R. Y. Mixer, R. F. Heck, S. Winstein and W. G. Young, THIS JOURNAL, **75**, 4094 (1953).

[17] H. Staudinger, *Ber.*, **42**, 4249 (1909).

2-Methyl-1-phenylhexane, prepared from α-methylcaprophenone[18] by Wolff–Kishner reduction, proved to be identical with the product from the quenching of the butyllithium–propenylbenzene reaction mixtures. The structure of the 3-methyl-2-phenylheptanoic acid follows from its manner of preparation, analysis, and neutralization equivalent and the assignments of structures to the 2,4-dimethyl-1,3-diphenyloctane and the 3,5-dimethyl-2,4-diphenylnonanoic acid follow from their analyses and by analogy.

Discussion

1-Phenylallyllithium in liquid ammonia behaves on quenching just as do 1-phenylallylsodium[3a,c] and cinnamylsodium,[3a] giving about the same ratio of propenylbenzene to allylbenzene (Table I). It appears that each of these three compounds is essentially ionic and the reactive species in liquid ammonia, which can effectively solvate the cation and anion, is the free carbanion.

TABLE I

PRODUCTS OF REACTION OF PROTON DONORS WITH METALLIC DERIVATIVES OF ALLYLBENZENE AND PROPENYLBENZENE

Organometallic compound	Solvent	Proton donor	Propenylbenzene in the propenylbenzene–allylbenzene mixture, %
1-Phenylallyllithium	NH_3(l.)	NH_4Cl	81[a]
1-Phenylallylsodium[b]	NH_3(l.)	CH_3OH[c]	93
1-Phenylallylsodium[d]	NH_3(l.)	CH_3OH, NH_4Cl, or phenylacetylene	85
Cinnamylsodium[d]	NH_3(l.)	CH_3OH, NH_4Cl, or phenylacetylene	85
1-Phenylallyllithium	Ether	CH_3OH	50[a]
1-Phenylallylsodium[b]	Pentane[e]	CH_3OH[c]	26
Cinnamylmagnesium chloride[d,f]	Ether	Dil. H_2SO_4	25

[a] If the propenylbenzene contained as much as 20% of the *cis* isomer,[16] the amount of allylbenzene in the mixture would be from 5–8% more than that reported here. [b] Ref. 3c. [c] Reverse addition. [d] Ref. 3a. [e] Heterogeneous. [f] Ref. 21.

The major product of quenching from liquid ammonia is the thermodynamically more stable propenylbenzene, yet it is formed in a kinetically controlled reaction. The best evidence for this is the slow reaction of lithium amide with allylbenzene, which would seem to preclude rapid equilibration during the actual quenching and the recovery of a greater proportion of allylbenzene from reactions in which some unreacted allylbenzene remained at the time of quenching. This result is in contrast to the formation of the less stable isomer, 1,4-dihydronaphthalene rather than 1,2-dihydronaphthalene, from the anion of 1,4-dihydronaphthalene in liquid ammonia at temperatures of −70 to −75°.[19] At higher temperatures the sodium salt in liquid ammonia gives the more stable 1,2-dihydronaphthalene, yet the lithium derivative in ether at 0° gives 1,4-dihydronaphthalene.[20] In this respect it is similar to the lithium derivative of allylbenzene in ether which gives a greater proportion of the less stable allylbenzene on quenching as do also the sodium derivative in pentane[3c] and the cinnamyl Grignard reagent in ether[21] (Table I).

One explanation is the possible existence in the organic solvents of the organometallic derivatives as ion-pairs or partially covalently bonded species which, with proton donors, would give the less stable olefin through a coördinated allylic displacement.[3a,22] That a similarly bonded sodium salt of the dihydronaphthalene may exist in liquid ammonia at −70° but not to as great an extent at higher temperatures could result from the fact that the sodium would be bonded to a more nucleophilic secondary carbon than would be the case with the corresponding allylbenzene anion which appears to exist as the free ion in liquid ammonia even at Dry Ice temperature.

Alternatively, Hammond[23] has considered the sodium salt of the dihydronaphthalene to exist as free ions even at low temperatures and has interpreted the formation of 1,4-dihydronaphthalene as being the result of electrostatic control of the position of attack by the proton donor. Birch[24] has applied this concept to other anions as well. The distribution of charge in the allylbenzene anion[25] is such that if it existed as the free anion and if interaction in the transition state were largely electrostatic, the preponderant product would be the thermodynamically less stable allylbenzene. It would appear, if both exist as free anions in liquid ammonia, that covalent bond formation in the transition state must contribute more in the case of the allylbenzene anion than in the case of the dihydrophthalene anion. That the recombination of ions from a pseudo-acid need not have a negligible energy of activation has been shown by Pearson.[26] From quenching in the less polar solvents one would anticipate, if the organometallic compounds are ionic, a looser transition state than in liquid ammonia and thus a greater influence of the charge distribution in the anion on the position which is attacked by the proton donor with formation of a greater proportion of the less stable allylbenzene as is found to be the case. It is obvious that from these observations alone on 1-phenylallyllithium it is impossible to conclude whether, in ether, the lithium is covalently bonded or not. The intense red color of the ether solution indicates easy delocalization of the bonding electrons in any case.

The diminished reactivity of the allylic hydrogen of the more stable propenylbenzene is emphasized by the fact that, in liquid ammonia, propenylbenzene is quite unreactive to lithium amide and, in

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(18) A. D. Campbell, C. L. Carter and S. N. Slater, *J. Chem. Soc.*, 1741 (1948).

(19) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).

(20) W. Schlenk, E. Bergmann and J. Appenrodt, *ibid.*, **463**, 90 (1928).

(21) W. G. Young, G. Ballou and K. Nozaki, THIS JOURNAL, **61**, 12 (1939).

(22) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 200.

(23) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

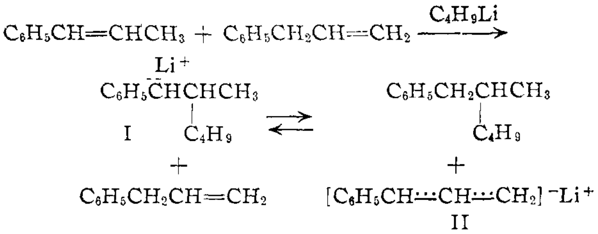
(24) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950); A. J. Birch, *Disc. Faraday Soc.*, **2**, 246 (1947); *cf.* also M. J. S. Dewar, "Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p. 103; M. J. S. Dewar, *Disc. Faraday Soc.*, **2**, 261 (1947).

(25) H. C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 265 (1950); M. J. S. Dewar, THIS JOURNAL, **74**, 3345 (1952).

(26) R. G. Pearson and R. L. Dillon, *ibid.*, **72**, 3574 (1950); R. G. Pearson and J. M. Miller, *ibid.*, **72**, 1692 (1950); R. G. Pearson, *ibid.*, **70**, 204 (1948); *cf.* also A. R. Hawdon, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2499 (1952).

ether, propenylbenzene undergoes addition of butyllithium at the double bond. Quenching of the adduct gave 2-methyl-1-phenylhexane and higher molecular weight hydrocarbons; carbonation gave 3-methyl-2-phenylheptanoic and higher molecular weight acids.

Competition between allylbenzene and propenylbenzene for butyllithium confirmed the fact that the addition to the propenylbenzene was more rapid than the abstraction of a proton from the allylbenzene. Nonetheless, of the two possible products, 2-methyl-1-phenylhexyllithium (I) and 1-phenylallyllithium (II), the unsaturated 1-phenylallyllithium is the more stable since from the carbonation only 4-phenyl-3-butenoic acid and 2-phenyl-3-butenoic acids were obtained.



$$C_6H_5CH{=}CHCH_3 + C_6H_5CH_2CH{=}CH_2 \xrightarrow{C_4H_9Li}$$

$$\underset{\text{I}}{C_6H_5\overset{Li^+}{\bar{C}}H\underset{C_4H_9}{\underset{|}{C}}HCH_3} + C_6H_5CH_2CH{=}CH_2 \rightleftarrows C_6H_5CH_2\underset{C_4H_9}{\underset{|}{C}}HCH_3 + \underset{\text{II}}{[C_6H_5CH\cdots CH\cdots CH_2]^-Li^+}$$

Only 11% of unreacted allylbenzene and propenylbenzene was recovered together with 2-methyl-1-phenylhexane and higher molecular weight hydrocarbons.

The addition of carbanions to aryl-substituted olefins is not unusual; for example,[27] a very similar case is the addition of 2-phenyl-2-propylpotassium to propenylbenzene. A number of instances of like additions to non-activated olefins have been reported.[28]

The results of carbonation of 1-phenylallyllithium in ether are presented in Table II together with data on the carbonation of other metallic derivatives of allyl- and propenylbenzene. In every case the alkali metal derivatives in ether give a preponderance of 4-phenyl-3-butenoic acid which may indicate that even in ether solution 1-phenylallyllithium is essentially ionic, presumably existing as ion-pairs, or higher aggregates. In contrast, cinnamylmagnesium chloride gives exclusively 2-phenyl-3-butenoic acid.[9]

TABLE II

PRODUCTS OF CARBONATION OF METALLIC DERIVATIVES OF ALLYLBENZENE AND PROPENYLBENZENE

Organometallic compound	Solvent	Total yield of acid, %	2-Phenyl-3-butenoic acid, %	4-Phenyl-3-butenoic acid, %
1-Phenylallyllithium	Ether	48–57	31–41[a]	59–69
1-Phenylallylsodium[b]	NH_3(l.)	2	90[a]	10
1-Phenylallylcesium[c]	Ether[d]	. . .	. . .	Chiefly
Cinnamylsodium[b]	NH_3(l.)	2	90[a]	10
Cinnamylsodium[e]	Pentane[d,f]	50	26–27	39–41
Cinnamylmagnesium chloride[b,g]	Ether	11–27	100[a]	0

[a] Isolated as 2-phenyl-2-butenoic acid. [b] Ref. 29. [c] Ref. 6. [d] Heterogeneous. [e] Ref. 3b. [f] Contained sodium isopropoxide. [g] Ref. 9.

The reaction of 1-phenylallyllithium in ether with benzophenone to give solely 1,1,4-triphenyl-3-butene-1-ol appears to be comparable to the similar reaction of 1-phenylallylsodium.[29]

Experimental[30]

Quenching of 1-Phenylallyllithium in Liquid Ammonia.—Allylbenzene[31] (37 g., 0.31 mole), b.p. 157°, n^{20}D 1.5120 [lit.[3a] b.p. 156–157° (uncor.), n^{25}D 1.5132], prepared from phenylmagnesium bromide and allyl chloride, was added over a period of 10 minutes to a solution of lithium amide prepared from 2.18 g. (0.314 mole) of lithium in 300 ml. of liquid ammonia with 0.3 g. of hydrated ferric nitrate. The color of the solution appeared to reach a maximum intensity after 20–30 minutes. Stirring was maintained for a total of 45 minutes after mixing after which the red-orange solution was quenched at Dry Ice temperature by the rapid (1.5 minutes) addition of powdered ammonium chloride. The hydrocarbon was recovered in 66% yield and consisted of 82% propenylbenzene and 18% allylbenzene. The column used in the separation, a 40-cm., glass helices-packed, heated column, was not capable of separating the *cis*- and *trans*-propenylbenzenes. The product presumably contained some of the *cis* isomer, but the characteristic infrared bands for this isomer[16] were extremely weak. The composition was determined after fractionation by a comparison of the refractive indices of the fractions with a refractive index *vs.* composition curve using propenylbenzene of n^{20}D 1.5510 and allylbenzene of n^{20}D 1.5120 as reference.

A reaction, similar in all respects except that no cooling bath was used during the quenching, which was effected over a period of 18 minutes gave a 64% recovery which consisted of 80% propenylbenzene and 20% allylbenzene.

From two reactions carried out for a period of 30 minutes after mixing and quenched in 10–15 minutes, the hydrocarbon recovered consisted of 63 and 49% propenylbenzene and 37 and 51% allylbenzene.

Quenching of 1-Phenylallyllithium in Ether.—1-Phenylallyllithium from the refluxing for 2 hr. of 59 g. (0.50 mole) of allylbenzene, b.p. 157.5°, n^{20}D 1.5120, and 0.51 mole of butyllithium[32] was forced with nitrogen into 300 ml. of methanol. Fractional distillation of the organic phase after extraction with water and drying gave 49.5 g. (84%) of a mixture composed of 54% allylbenzene and 46% propenylbenzene.

Quenching of the Product of Reaction of Propenylbenzene with Lithium Amide.—Propenylbenzene was prepared from allylbenzene by isomerization with potassium hydroxide in butyl alcohol.[3a] The propenylbenzene used throughout this investigation had boiling points of 176–177.6° and n^{20}D 1.5490–1.5510 (lit.[33] b.p. 176–177°; n^{25}D 1.5473 for *trans*-propenylbenzene[16]). To prevent the oxidation to which propenylbenzene is susceptible, it was stored in the dark under nitrogen and used within a few days of preparation.

Propenylbenzene (19.5 g., 0.165 mole) added to lithium amide from 1.14 g. (0.165 mole) of lithium in 300 ml. of liquid ammonia had turned only an orange-brown after 2.25 hr. when it was quenched by adding an excess of ammonium chloride. The hydrocarbon recovered, 16.4 g., was practically pure propenylbenzene, b.p. 174–188°, six fractions of n^{20}D 1.5480–1.5490.

Quenching of the Product of Reaction of Propenylbenzene with Butyllithium.—The product of reaction by 15 minutes of reflux of 14.9 g. (0.126 mole) of propenylbenzene and butyllithium prepared from 2.1 g. (0.302 mole) of lithium and 18.2 g. (0.133 mole) of butyl bromide in 100 ml. of dry ether was forced by nitrogen into 150 ml. of stirred methanol. The crude product (17.4 g.) obtained, after washing, drying

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(27) K. Ziegler, F. Crössmann, H. Kleiner and O. Schäfer, *Ann.*, **473**, 1 (1929); ref. 8a, p. 8.

(28) K. Ziegler and H. G. Gellert, *ibid.*, **567**, 195 (1950); P. D. Bartlett, S. Friedman and M. Stiles, THIS JOURNAL, **75**, 1771 (1953); H. Hart, *ibid.*, **78**, 2619 (1956); H. Pines and V. Mark, *ibid.*, **78**, 4316 (1956)

(29) T. W. Campbell and W. G. Young, *ibid.*, **69**, 3066 (1947).

(30) Except as noted, melting and boiling points are uncorrected. Microanalyses by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(31) E. B. Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).

(32) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(33) G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publ. Corp., New York, N. Y., 1946, p. 191.

and removal of the ether, was fractionally distilled to yield 0.6 g. of propenylbenzene, 4.8 g., b.p. 77–95° (10 mm.), n^{20}_{D} 1.4913, an intermediate fraction, and then 8.1 g., b.p. 170–190° (10 mm.), n^{20}_{D} 1.5350. The 4.8-g. fraction on redistillation gave **2-methyl-1-phenylhexane** of b.p. 227–230°, n^{20}_{D} 1.4864.

Anal. Calcd. for $C_{12}H_{20}$: C, 88.64; H, 11.36. Found: C, 88.59; H, 11.39.

The 8.1-g. fraction was redistilled to give 4.6 g. of a rather viscous liquid presumed to be **2,4-dimethyl-1,3-diphenyloctane**, b.p. 200–202° (10 mm.), n^{20}_{D} 1.5349, which gave a negative test for unsaturation with potassium permanganate.

Anal. Calcd. for $C_{22}H_{30}$: C, 89.80: H, 10.20. Found: C, 89.38: H, 10.23.

1-Phenylallyllithium with Carbon Dioxide.—Allylbenzene (22.4 g., 0.19 mole) was added at room temperature over a period of 20 minutes to a solution of butyllithium prepared from 3.2 g. (0.455 mole) of lithium and 27.4 g. (0.2 mole) of *n*-butyl bromide in a total of 150 ml. of dry ether. During 2 hr. of subsequent reflux the color of the solution changed from green to red-orange. After the solution had been forced by nitrogen into a slurry of freshly crushed Dry Ice in ether, the acids were extracted with dilute alkali. Acidification of the alkaline solution after two hours of reflux gave 11.3 g. (0.070 mole, 48% based on allylbenzene consumed) of acid. The hydrocarbon recovered from the ether solution weighed 5.3 g.

In another experiment, carbonation of the 1-phenylallyllithium by forcing the solution onto crushed Dry Ice gave 13.1 g. (57% based on allylbenzene consumed) of acid and 5.6 g. of recovered hydrocarbon.

Reaction of butyllithium with allylbenzene at −15° for 2 hr. and then carbonation gave no solid acid and only 5% of liquid acid after steam distillation to remove valeric acid.

A portion of the acid from the second experiment above was recrystallized from aqueous methanol. 4-Phenyl-3-butenoic acid of m.p. 86–87° (cor.), which gave a mixed m.p. of 86–87° (cor.) with authentic acid[14] of m.p. 86.3–86.6° (cor.), was obtained together with 2-phenyl-2-butenoic acid of m.p. 136.8–137.4° (cor.), which gave a mixed m.p. of 136.5–137.2° (cor.) with authentic acid[13] of m.p. 136.8–137.4° (cor.).

A quantitative measure of the composition of the acid obtained on carbonation was achieved by fractionally subliming the acid to weighed aluminum foil cups and ascertaining the composition of the sublimed acid by comparing its m.p. range, after one fusion and resolidification in a capillary m.p. tube with the m.p.–composition curve obtained by fusing mixtures of known composition using a calibrated thermometer corrected for the emergent stem.

The sublimations were carried out at pressures of 1–60 μ and temperatures of 38–90°. From the sublimation residues and the good agreement of the sublimed fractions with the m.p.–composition curve, it would appear that greater than 90% of the acid material obtained was 4-phenyl-3-butenoic acid and 2-phenyl-3-butenoic acid. The ratios of 4-phenyl-3-butenoic acid to 2-phenyl-3-butenoic acid (determined as 2-phenyl-2-butenoic acid) in the two runs were 68:32 and 66:34.

Competition between Allylbenzene and Propenylbenzene for Butyllithium.—A mixture of 15 g. (0.127 mole) of allylbenzene and 15 g. (0.127 mole) of propenylbenzene was added to a solution of 0.134 mole of butyllithium in 100 ml. of dry ether. A red color developed immediately as was the case when propenylbenzene was used alone. Maximum color intensity was achieved after about 10 minutes of reflux, so after 15 minutes the solution was forced under nitrogen pressure into a slurry of freshly crushed Dry Ice in dry ether. Worked up in the usual manner, 22.8 g. of neutral material and, after alkaline isomerization, 8.3 g. (0.051 mole, 40%) of solid acid was recovered. From the m.p.–composition curve this was found to consist of about 69% 4-phenyl-3-butenoic acid and 31% 2-phenyl-2-butenoic acid. The ultraviolet spectrum corresponded closely to a mixture of 59% 4-phenyl-3-butenoic acid and 41% 2-phenyl-2-butenoic acid. These spectra were determined in 0.1 *N* sodium hydroxide solution with a Beckman DU spectrophotometer. In this solution the spectra of the salts of the pure acids were as listed in Table III. There was no structure to the spectrum of the 2-phenyl-2-butenoate in the region covered.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF SODIUM 4-PHENYL-3-BUTENOATE AND SODIUM 2-PHENYL-2-BUTENOATE IN 0.1 *N* SODIUM HYDROXIDE

λ_{max}[a]	λ_{min}[a]	4-Phenyl-3-butenoate	2-Phenyl-2-butenoate[b]
293		930	21
	290	720	27
283		1,600	70
	281	1,500	93
252		19,000	2,800

[a] For 4-phenyl-3-butenoate. [b] Molecular extinction coefficients of 2-phenyl-2-butenoate at λ_{max} and λ_{min} for 2-phenyl-3-butenoate.

The neutralization equivalent was determined on the total acid recovered: neut. equiv. calcd. for $C_{10}H_{10}O_2$, 162; found, 163.

The neutral material was fractionally distilled to yield 3.2 g. of a mixture, mainly allylbenzene; 5.3 g., mainly 2-methyl-1-phenylhexane; 5.0 g., 2,4-dimethyl-1,3-diphenyloctane; and 2.8 g. of higher molecular weight material.

A similar reaction carried out by refluxing the reactants for 2 hr. yielded 27% of acid composed of 64% 4-phenyl-3-butenoic acid and 36% 2-phenyl-2-butenoic acid as determined from the m.p.–composition curve and 63% 4-phenyl-3-butenoic acid and 37% 2-phenyl-2-butenoic acid as determined from the spectrum. The neutralization equivalent of this mixture was 163. In this instance 3.8 g. of a mixture of allylbenzene and propenylbenzene was recovered together with 6.4 g. of 2-methyl-1-phenylhexane and 9 g. of higher molecular weight hydrocarbon.

Carbonation of the Product of Reaction of Propenylbenzene with Butyllithium.—Propenylbenzene (14.9 g., 0.126 mole) was added at room temperature to a solution of butyllithium prepared from 2.1 g. (0.30 mole) of lithium and 18.2 g. (0.133 mole) of butyl bromide in 100 ml. of dry ether. The solution which was maroon in color on completion of the addition turned even deeper red after 15 minutes of reflux. It was forced with nitrogen into a slurry of Dry Ice and ether. Extraction with dilute alkali led to the separation of two aqueous phases which were separated and worked up individually. After a 2-hr. reflux of the alkaline solutions, acidification and vacuum steam distillation to remove valeric acid, there were obtained 1.4 g. of acid and 9.9 g. of acid from the two phases. The neutral fraction recovered from ether weighed 5.9 g. Four recrystallizations from aqueous methanol of the acid obtained in lesser amount resulted in a product of m.p. 81–87.5°. One recrystallization from Skellysolve E (petroleum solvent, b.p. 100–140°) of the acid obtained in greater amount yielded 1.6 g. of acid, m.p. 155–169°, and 7.9 g. of viscous acid which could not be crystallized. Two additional recrystallizations from Skellysolve E and eight from methanol raised the m.p. of the presumed **3,5-dimethyl-2,4-diphenylnonanoic** acid to 178–184.5°.

Anal. Calcd. for $C_{23}H_{30}O_2$: C, 81.66; H, 8.88; neut. equiv., 338. Found: C, 81.89; H, 9.25; neut. equiv., 338.

The neutral material was found on distillation to consist mainly of 2-methyl-1-phenylhexane and 2,4-dimethyl-1,3-diphenyloctane with less than 0.7 g. of propenylbenzene.

From a similar reaction between propenylbenzene and butyllithium at 0° for 1 hr., only about 5% of the lower melting acid was obtained together with 80% propenylbenzene and a small amount of higher molecular weight hydrocarbon. Recrystallization of this acid from aqueous methanol gave **3-methyl-2-phenylheptanoic acid** of m.p. 92.8–93.2°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09; neut. equiv., 220. Found: C, 76.26· H, 9.23; neut. equiv., 219.

1-Phenylallyllithium with Benzophenone.—1-Phenylallyllithium from the refluxing for 1 hr. of 12.0 g. (0.102 mole) of allylbenzene and 0.102 mole of butyllithium in 75 ml. of dry ether was forced under nitrogen pressure into a solution of 18.5 g. (0.102 mole) of benzophenone in 150 ml. of dry ether. The color of the organolithium compound was instantly discharged. The ether was removed under a vacuum after it had been washed well with water and dried, and finally 0.8 g. of hydrocarbon, n^{20}_{D} 1.5130, which was presumably unreacted allylbenzene, was removed under a high vacuum. The residual viscous liquid, 28.4 g., was crystallized by the use of a small amount of Skellysolve E and recrystallized twice from methanol to yield 6.8 g. of white needles, m.p. 94.0–94.5° (lit.[29] m.p. of 1,1,4-triphenyl-3-butene-1-ol 94.0–94.5°). Vacuum distillation of 3.1 g. of the product with a trace of iodine gave, after one recrystallization from ethanol, 1.5 g. of white needles, m.p. 100.5–101.5° (lit.[17] m.p. of 1,1,4-triphenyl-1,3-butadiene 101.5–102.0°).

The liquid product, 16.7 g., from the filtrates of the recrystallization of the alcohol was not crystallizable, so it was dehydrated to the diene which, recrystallized three times from ethanol, had a m.p. of 101.0–101.5°. Based on combined alcohol and diene, the yield of crude 1,1,4-triphenyl-3-butene-1-ol was 41% and of pure product 25%.

2-Methyl-1-phenylhexane.—α-Methylcaprophenone[18] was reduced by the Huang-Minlon modification of the Wolff-Kishner reduction[34] in 43% yield. Redistillation gave the hydrocarbon, b.p. 228–230°, n^{20}_D 1.4868.

The sulfonamides[35] from the authentic 2-methyl-1-phenylhexane and from the material obtained by quenching the products of reaction of propenylbenzene and butyllithium both had m.p. and mixed m.p. of 93–94° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{21}O_2NS$: C, 61.15; H, 8.23; N, 5.5; S, 12.55. Found: C, 61.32; H, 8.03; N, 5.6; S, 12.59.

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[34] D. Todd in "Organic Reactions," R. Adams, editor, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 378.

[35] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 197.

TROY, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NOVOCOL CHEMICAL MFG. CO., INC.]

Alkyl and Diethylaminoethyl Esters of N-Substituted Aminoacylaminobenzoic Acids

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RECEIVED MAY 6, 1957

Several alkyl esters of *o*- and *p*-N-substituted aminoacetyl- and propionylaminobenzoic acids as well as diethylaminoethyl esters of *p*-N-substituted aminoacetylaminobenzoic acids were prepared. They were tested as salts for anesthetic potency, toxicity and for irritation. The anesthetic efficiencies (ratio of potency to toxicity) of some of these compounds were sufficiently high to warrant further study.

At the turn of the century and prior to his discovery of procaine, Einhorn and his associates synthesized a group of alkylaminoacetylaminobenzoates.[1,2] The clinical use of one of these, methyl 5-diethylaminoacetylaminosalicylate (Nirvanine), was discontinued because of its irritating properties. Since then several investigators[3–8] have prepared substituted anilide anesthetics and found them too irritating for clinical use.

In 1946, Lofgren[9] prepared ω-diethylamino-2,6-dimethylacetanilide (lidocaine), which had a high anesthetic potency and was sufficiently non-irritating for clinical use. His success in finding this relatively non-irritating anilide anesthetic encouraged other investigators to prepare many other anilide derivatives.

Since Lofgren[10] has shown that relatively small changes in the molecular structure of his group of anilides can produce substantial changes in their toxicity, potency and irritating properties, it was of interest to us to reinvestigate the alkylaminoacylaminobenzoates of Einhorn. We extended the series to other alkyl and diethylaminoethyl esters of alkyl- and heterocyclic aminoacylaminobenzoic acids in order to determine the effect of molecular structure on the anesthetic potency, toxicity and irritating properties of this group of compounds.

Three series of N-substituted aminoacylamino benzoates were prepared: alkyl esters of *o*- and *p*-N-substituted aminoacetylaminobenzoic acids, alkyl esters of *o*- and *p*-N-substituted aminopropionylaminobenzoic acids and diethylaminoethyl esters of *p*-N-substituted aminoacetylaminobenzoic acids.

The method of preparation consisted of treating a chloroacyl chloride with an ester of aminobenzoic acid and subsequent condensation of the resulting chloroanilide with a primary or secondary amine to yield the anesthetic base. The hydrochloride salts of the anesthetic bases were purified by recrystallization from isopropyl alcohol or isopropyl alcohol–water mixtures. Table I lists the chloroacylamino benzoates with their melting points and analyses. Table II lists the melting points of the free bases together with the melting points, analyses and molecular weight determination of the hydrochlorides.

Pharmacology

A preliminary pharmacological investigation of these compounds as local anesthetics on experimental animals was conducted. The toxicities were determined intraperitoneally and subcutaneously on white mice. The irritation was determined by topical application on the rabbit cornea and by intradermal injection in the rabbit skin. The topical anesthetic potency was determined by noting the length and depth of anesthesia on the rabbit cornea produced by varying concentrations of the compound. The method of blocking the sciatic nerve of

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[1] A. Einhorn, German Patent 106,502 (1898).

[2] A. Einhorn and M. Oppenheimer, *Ann.*, **311**, 155 (1900).

[3] E. Puxeddu and G. Sanna, *Gazz. chim. ital.*, **60**, 126 (1930) (*C. A.*, **24**, 3770 (1930)).

[4] G. Sanna and M. Grannata, *Rend. seminar facolta sci. univ. Cagliari*, **5**, 88 (1935) (*C. A.*, **33**, 5827 (1939)).

[5] G. Sanna, *Ann. chim. applicata*, **25**, 638 (1936) (*C. A.*, **30**, 5722 (1936)).

[6] H. Erdtman and N. Lofgren, *Svensk Kem. Tid.*, **49**, 163 (1937).

[7] K. Gaind, J. Ray and J. Yajnik, *J. Indian Chem. Soc.*, **17**, 400 (1940).

[8] K. Gaind, J. Ray and B. Sarin, *ibid.*, **17**, 619 (1940).

[9] N. Lofgren, *Arkiv Kemi, Mineral. Geol.*, **A22**, No. 18 (1946).

[10] N. Lofgren, "Studies on Local Anesthetics, Xylocaine, A New Synthetic Drug," Ivar Haeggstroms, Stockholm, 1948.