were used as a source of scandium, approximately 40 g. having been recovered to date by a modification of the procedure of Fischer and Bock.[8] The ionium was then recycled to the dibutoxytetraethylene glycol step.

The losses of ionium incurred in the re-extraction and precipitation steps are less than 0.02 and 0.04%, respectively. The loss at the dissolution step is zero.

Consequently, the over-all loss in ionium, making use of simple recycle procedures, is limited essentially to the loss incurred in the initial extraction from the Mallinckrodt waste. The resultant yield is, therefore, 95% or more, depending upon the efficiency of the initial extraction.

In practice, the ionium was not recovered from the aqueous wastes resulting from the fluoride precipitation step by simple recycle of these wastes to the next feed. Instead, these aqueous wastes, which were found to have an average Pa^{231} content of 0.3 mg. per liter were set aside for recovery of Pa^{231}.[9] Following recovery of the Pa^{231}, the ionium was recovered by recycle of the aqueous waste to the initial extraction step.

Acknowledgment.—The authors wish to thank W. M. Manning and S. Lawroski of the Argonne National Laboratory for making the combined facilities of the Chemistry and Chemical Engineering Divisions available and the Mallinckrodt Chemical Works, St. Louis, Missouri, and the St. Louis Area Office of the United States Atomic Energy Commission for supplying the feed material.

(8) W. Fischer and R. Bock, *Z. anorg. allgem. Chem.*, **249**, 146 (1942).

(9) R. Elson, G. W. Mason, D. F. Peppard, P. A. Sellers and M. H. Studier, THIS JOURNAL, **73**, 4974 (1951).

LEMONT, ILLINOIS

NOTES

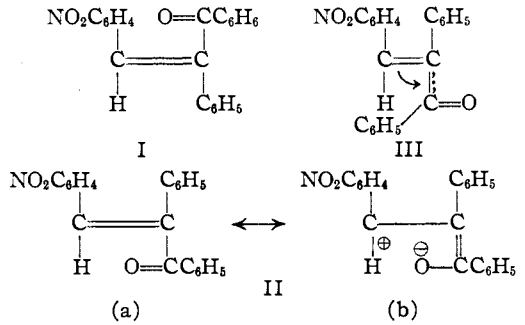
The Non-existence of the "Third Isomer" of *p*-Nitrobenzaldesoxybenzoin

BY W. BRUCE BLACK[1] AND ROBERT E. LUTZ

RECEIVED MAY 16, 1953

This work stemmed from studies in progress on stereoisomeric (*cis–trans*) pairs of chalcones (benzalacetophenones) substituted in the α- or β-positions, studies dealing with differences in the ultraviolet absorption spectra and their correlation with differences in chemical reactivities of the conjugated systems involved.

Stobbe[2] in an extensive series of researches has claimed the existence of three isomers in each of two α-phenylchalcone series (*cf.* I, II). He assumes two of these in each series to be *cis–trans* isomers, but he has not explained the nature of the supposed "third isomer" in any instance. Only *cis* and *trans* forms can be accounted for in terms of classical formulations. We thought at first that conjugation and resonance between the styryl system and the carbonyl group in one stereoisomer [presumably the *trans*-chalcone form (II)] might conceivably impart sufficient double bond character to the bond between these two systems so that *cis–trans* isomerism based on planarity of this area of the molecule might prevail, with the carbonyl oxygen pointing inward toward the β-position (II) or outward from it (III).[3] It was later shown[4] that significant resonance between the styryl and carbonyl systems existed only in the *trans*-α-phenylchalcone system,[4] as might have been predicted. Thus the "third isomer" could conceivably be represented (by III) as an example of the kind of isomerism spoken of by Pauling[5] as possible when the double bond character between two conjugated double bonds becomes sufficiently large to maintain planarity of the system. Under the stimulus of this idea (unsound though it was here) careful and extensive attempts were made, unsuccessfully, to reproduce Stobbe's experiments in the *p*-nitrobenzaldesoxybenzoin series. However, the results of these attempts led us to conclude that in this series the "third isomer" does not exist as a compound and that Stobbe's product was in reality a mixture of the normal *cis* and *trans* isomers (I and II).



Experimental

Each of Stobbe's isomerization reactions on the high-melting isomer where he obtained high yields of the "third isomer," was repeated and the products were fractionally recrystallized with exceeding care (*e.g.*, more than 40 recorded fractionations were made on a single reaction product). In no case was a sample obtained that could not be resolved into one and the other of the same pair of isomers. The best recrystallization solvent was a benzene–isoöctane mixture. Stobbe had used benzene–petroleum ether mixtures, but we found that substitution of isoöctane for petroleum ether diminished creeping of the solvent and advantageously low-

(1) Holder of Philip Francis du Pont Research Fellowship, 1952-1953.

(2) H. Stobbe and F. Wilson, *Ann.*, **374**, 237 (1910).

(3) *Cf.* a consideration of the conformation of the bromochalcones, R. E. Lutz, D. F. Hinkley and R. H. Jordan, THIS JOURNAL, **73**, 4647 (1951).

(4) W. B. Black and R. E. Lutz, *ibid.*, paper in press.

(5) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 218.

ered the rate of evaporation and rate of crystal growth. Although we found no definitely formed crystals which corresponded to Stobbe's description of the "third isomer," we many times encountered mixtures of somewhat similar but wider melting range [131–135° (he gave 133–135°)] which untold times raised false hopes. We have been unsuccessful in every one of our many experiments in obtaining any evidence whatsoever for the existence of a "third isomer." It is therefore clear that of the three products reported by Stobbe[2] (m.p. 133–135°, 148–149° and 164–165°) only the latter two are individual compounds.

The following data in Stobbe's paper[2] are themselves bases for question as to the existence of a third isomer.

(a) For the two higher-melting isomers, melting ranges of 1° were reported, whereas the lowest-melting product (the supposed third isomer) had a wider melting range of 2°.

(b) Melting points obtained from mixtures of this "isomer" with equal amounts of the two higher-melting isomers showed no depressions in either case.

(c) All three products decolorized potassium permanganate solution, with an intermediate rate in the case of the "third isomer."

(d) On dissolution of the isomers in concd. sulfuric or trichloroacetic acid the color from the "third isomer" was intermediate between those from the other two.

(e) The "third isomer" of the three reacted with desoxybenzoin in absolute ethanolic sodium ethoxide at an intermediate rate and gave an intermediate yield of benzameron, $C_6H_5CH[CH(C_6H_5)COC_6H_5]_2$. (We find that the 149° and 165° compounds are not isomerized in any degree whatsoever under the conditions involved.)

All these observations can best be explained on the assumption that the lowest-melting product was a mixture of the other two. (However, it must be mentioned that in the case of bromination Stobbe reported that of the three products, the supposed "third isomer" reacted at a rate other than intermediate).

Still further data were obtained by us which added considerably to the weight of evidence against the existence of Stobbe's "third isomer" and indicated it to be a mixture of the *cis* and *trans* isomers. Stobbe claimed to have obtained a 70% yield of this 133–135° "isomer" and a 5% yield of the 148–149° isomer upon four months exposure to sunlight of a benzene–iodine solution of the 164–165° isomer. In repeating this experiment we used a 10^{-3} molar solution and at the end of one month exposure (which had been shown to be ample to affect photoequilibrium) upon fractionally crystallizing the products we obtained 30% yield of the 149° isomer and approximately 70% of unchanged 165° isomer. These differences in yields were far too great to be accounted for by different experimental conditions.

p-Nitrobenzaldesoxybenzoin (a *cis*-*p*-nitrobenzalacetophenone) (I), prepared according to Stobbe[2] (m.p. 164–165°), was found upon purification to melt at 169–169.5°.

The stereoisomer (a *trans*-*p*-nitrobenzalacetophenone) (II) was prepared[2] by sunlight inversion of the isomer (I) and melted at 153–153.5° (Stobbe, m.p. 148–149°[2]).

Sunlight Isomerizations of the 169° Isomer (I).—The first two of the experiments below are repetitions of Stobbe's experiments. The products were isolated by fractional crystallizations from benzene–isoöctane mixtures,

(a) A 1.6% benzene solution containing a trace of iodine was refluxed for 11.5 hours under exposure to diffuse sunlight: yield 13% of II; the rest of the material was nearly pure I. In another experiment with refluxing time 10 hours, the yields were 24% of II and 76% of I. (Stobbe reported smaller yields with 35% yield of the supposed 135° isomer).

(b) In a similar experiment using a 0.16% solution in benzene at room temperature for one month with intermittent additions of iodine to maintain color, the yields were 30% of II and 70% of I (Stobbe reported 70% of the 135° compound).

(c) A 0.6% benzene solution without catalyst was exposed to direct sunlight for two months, with similar results: yields 25% of II and 75% of I.

(d) **Photoequilibrium** was reached within several minutes upon exposure of 10^{-5} molar alcohol solutions of both I and II to direct sunlight, and within 30 seconds under a G.E. sunlamp. A similar solution of I but containing a trace of iodine also came to equilibrium within several minutes in sunlight. Ultraviolet absorption spectra were used to determine these equilibria.

Acid-catalyzed isomerization according to Stobbe's directions of a 1.7% benzene solution of the 169° isomer (I) saturated with dry hydrogen chloride, allowed to stand for one week in darkness at room temperature, gave 2–3% of II, and the rest of the product was I (Stobbe reported 33% of the 133–135° product).

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Some Reactions in the 1,3,5-Triazine Series

BY ALFRED BURGER AND EDWIN D. HORNBAKER[1]

RECEIVED MAY 11, 1953

The purpose of this study was the preparation of 2-chloro-1,3,5-triazine as an intermediate in the synthesis of other monosubstituted triazine derivatives. The catalytic hydrogenolysis of halogen substituted triazine derivatives has been studied for monoaminodichlorotriazines[2] and for diaminochlorotriazines,[3] but the stepwise or complete removal of chlorine atoms from cyanuric chloride has not been reported. Hydrogenation experiments using nickel or palladium catalysts with cyanuric chloride under various conditions, even by the Rosenmund method, have remained inconclusive in our hands, and similar failures have been attributed to a poisoning of the catalyst by the reaction products in another laboratory.[4]

The reduction of cyanuric chloride with lithium aluminum hydride in ether solution took an unexpected course. The only reaction product was 2-dimethylamino-4,6-dichloro-1,3,5-triazine. The path of this reaction may be visualized as a hydrogenolysis of the triazine ring with the formation of dimethylamine which then reacts with as yet unchanged cyanuric chloride.

The only monosubstituted derivatives of 1,3,5-triazine containing functionally reactive groups reported in the literature are 2-phenoxytriazine,[2] 2-aminotriazine[5,6] and four simple alkylaminotriazines.[2] In the hope of utilizing 2-aminotriazine as a synthetic intermediate, we subjected this compound to several typical simple reactions of α-aminoazines but observed only formation of inorganic ammonium salts, or recovery of starting material. This behavior suggests the absence of a primary amino group, and this conclusion is borne out by the ultraviolet absorption spectrum which shows no peak at about 236 mμ as it is found for melamine.[7] Cyanuric chloride shows a similar peak at 238 mμ which is attributed to a typical triazine ring.[7]

We are grateful to Parke, Davis and Co. for support of this work, and to American Cyanamid Co. for the cyanuric chloride used in this study.

Experimental

Reduction of Cyanuric Chloride.—To a stirred solution of 8.0 g. of lithium aluminum hydride in 500 ml. of dry

(1) Parke, Davis & Co. Fellow.

(2) R. Hirt, H. Nidecker and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950).

(3) J. R. Geigy A.G., Swiss Patent 252,530 (1949), 261, 811(1949).

(4) C. Grundmann, H. Ulrich and A. Kreutzberger, *Chem. Ber.*, **86**, 181 (1953).

(5) O. Diels, *Ber.*, **32**, 691 (1899).

(6) J. P. English and J. H. Paden, British Patent 566,933 (1942)

(7) I. M. Klotz and T. Askounis, THIS JOURNAL, **69**, 801 (1947).

ether was added 20.0 g. of pure cyanuric chloride in several portions. The solution was stirred for another 15 minutes, excess hydride was decomposed with water, 200 ml. of 10% sulfuric acid was added and the mixture was extracted with ether. The ether extract yielded 1.5 g. of colorless needles which after recrystallization from petroleum ether melted at 124–124.5° (cor.).

Anal. Calcd. for $C_5H_6Cl_2N_4$: C, 31.11; H, 3.13; N, 29.02. Found: C, 31.52; H, 3.10; N, 29.13.

A mixture melting point with an authentic sample of 2-dimethylamino-4,6-dichloro-1,3,5-triazine[8] showed no depression.

Ultraviolet Spectrum.—The ultraviolet absorption spectrum of 2-amino-1,3,5-triazine in a 10^{-5} molar aqueous solution was measured with a Beckman model DU spectrophotometer at 26°. A continuously decreasing absorption was observed from 225 to 240 mμ.

(8) W. M. Pearlman and C. K. Banks, THIS JOURNAL, **70**, 3726 (1948).

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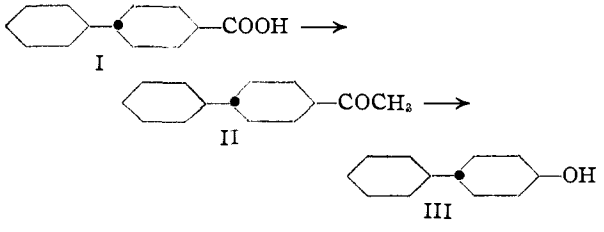
Determination of the Configuration of 4-Cyclohexylcyclohexanols

BY WILLIAM G. DAUBEN, VICTOR M. ALHADEFF AND MASATO TANABE

RECEIVED MAY 11, 1953

In the course of a study of the hydrogenation of 4-hydroxybiphenyl-4′-carboxylic acid,[1] it became of interest to determine, with certainty, the stereochemistry of the 4-phenyl- and the 4-cyclohexylcyclohexanols. In 1948, Ungnade[2] prepared the pure *cis* and *trans*-isomers of this series and assigned the configurations on the basis of method of preparation and on thermodynamic stability. Recently, Dauben and Hoerger[3] showed that by converting a carboxylic acid to a methyl ketone and cleaving the resulting ketone with perbenzoic acid,[4] an acid could be related, stereospecifically with retention, to an alcohol. Since Fieser, *et al.*,[5] have related *trans*-4-cyclohexylcyclohexylcarboxylic acid (I) to *trans*-hexahydroterephthalic acid, a compound whose stereochemistry has been rigorously established by Mills and Keats,[6] application of the methyl ketone–perbenzoic acid sequence above to *trans*-acid I would determine the stereochemistry of the 4-substituted cyclohexanols in an unequivocal manner.



Such a sequence of reactions was performed and it was found that *trans*-acid I was, indeed, related to the *trans*-alcohol III. Thus, the stereochemical configurations of the 4-phenyl- and 4-cyclohexylcyclohexanols assigned by Ungnade[2] are correct. It is of passing interest to note that in this series, the thermodynamically stable isomer is the one which has both of its substituents in equatorial conformations.[7]

(1) W. G. Dauben and M. Tanabe, in press.
(2) H. E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).
(3) W. G. Dauben and E. Hoerger, THIS JOURNAL, **73**, 1504 (1951).
(4) R. B. Turner, *ibid.*, **72**, 878 (1950); T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).
(5) L. F. Fieser, *et al.*, *ibid.*, **70**, 3186 (1948).
(6) W. H. Mills and G. H. Keats, *J. Chem. Soc.*, 1373 (1935).

Experimental

***trans*-4-Cyclohexylcyclohexylcarboxylic Acid** (I).—The acid was prepared following the procedure of Fieser, *et al.*,[5] m.p. 160.5–161.9° (lit. 161–162°).

***trans*-4-Cyclohexylcyclohexanol** (III).—A solution of 0.9 g. (4.28 millimoles) of *trans*-acid I in 15 ml. of dry ether was added dropwise with stirring to 18 ml. of a 0.6 *M* solution of methyllithium in ether. Following the addition, the mixture was stirred for 12 hours and then poured onto ice. The ethereal layer was removed, washed neutral with water, dried and the solvent removed through a small column. The residue weighs 0.8 g. (89.7%) and was used directly in the oxidation.

Perbenzoic acid (0.638 g.) in 8.8 ml. of chloroform was added to the crude ketone which had been dissolved in 5 ml. of chloroform. The solution was allowed to stand for 8 days at room temperature in the dark. At the end of this time the reaction was diluted with ether and washed thoroughly with dilute sodium hydroxide. The residue remaining after removal of the solvents was heated for 7 hours with 50 ml. of 1 *N* sodium hydroxide in 30 ml. of methanol and the methanol removed under reduced pressure. The aqueous residue was extracted with ether, the ether distilled and the 4-cyclohexylcyclohexanol recrystallized from hexane, yield 0.28 g. (40%), m.p. 99.6–102.4° (lit.[2] 103–104°). The phenylurethan was prepared and melts 154.9–156.6° (lit.[2] 156–156.8°).

(7) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

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The Structure of the Solid Product from the Condensation of Methyl γ-Bromocrotonate with Sodium Methoxide[1]

BY ANDRE S. DREIDING AND RICHARD J. PRATT

RECEIVED MAY 6, 1953

Owen and Sultanbawa[2] reported the isolation of a small amount of a solid from the reaction of methyl γ-bromocrotonate with dry sodium methoxide in benzene. The product was characterized by its analysis (empirical formula of $C_5H_6O_2$), melting point (168–169°) and ultraviolet absorption spectrum (λ_{max}^{alc} 303 mμ, $E_{1cm}^{1\%}$ 2600). The authors considered that it was possibly methyl cyclopropenecarboxylate.

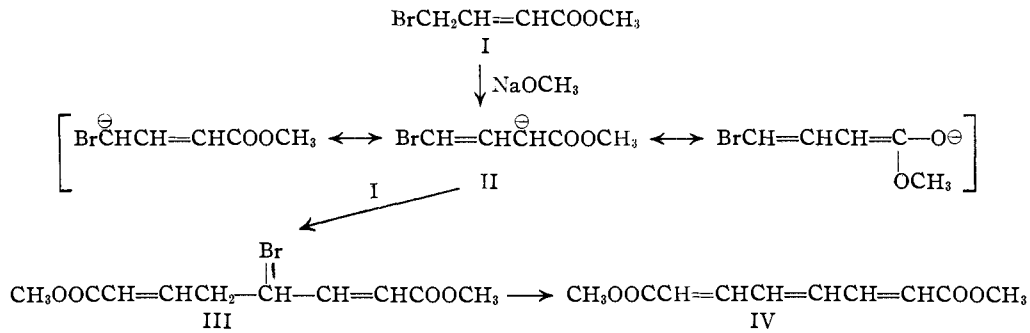
A re-examination of the reaction confirmed the observations of Owen and Sultanbawa, the solid product being formed in 1.3% yield. However, its high melting point and its spectrum, which appeared uncharacteristic of either of the double bond isomers of methyl cyclopropenecarboxylate, suggested a reconsideration of its structure.

α-Haloesters are known to be attacked by bases with the formation of enolates.[3] The vinylogous reaction with methyl γ-bromocrotonate (I) is the abstraction of a proton from the γ-position with the

(1) Supported in part by grants to the Detroit Institute of Cancer Research from the American Cancer Society, Inc., the Michigan Cancer Foundation and The Kresge Foundation.

(2) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3098 (1949).

(3) M. S. Newman and B. J. Magerlein, "The Glycidic Ester Condensation" in R. Adams, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., p. 413.



formation of the anion II. The cyclopropene ring would have to be formed by an intramolecular nucleophilic displacement of a vinyl type bromine atom, An alternative (and perhaps more likely) reaction is the displacement by II of an allyl type bromine atom in another molecule of methyl γ-bromocrotonate with the formation of III. Further elimination of the elements of hydrobromic acid gives dimethyl 2,4,6-octatrienedioate (IV) with an empirical formula of $C_5H_6O_2$. This type of reaction with a base has been described for 9-fluorenyl bromide,[4] for diethyl bromo- and chloromalonate,[5] and for allyl chloride.[6]

The properties of Owen and Sultanbawa's product coincided closely with those reported for dimethyl 2,4,6-octatrienedioate (IV, m.p. 172°,[7a] $\lambda_{max}^{methanol}$ 303 mμ[7b]). That this is indeed its structure has now been shown by hydrogenation and saponification which afforded an 83% yield of suberic acid.

Several attempts to improve the yield of IV in the self-condensation of I by the use of inverse addition, different bases and different solvents were without success. The consistently low yield may be due to the large number of structural and geometrical isomers which could conceivably be formed in this reaction.

Experimental[8]

Dimethyl 2,4,6-Octatrienedioate (IV).—To a stirred and cooled suspension of dry sodium methoxide (prepared from 1.4 g. (0.06 mole) of sodium and 20 cc. of dry methanol followed by distillation of the methanol) in 80 cc. of dry benzene was added slowly 10 g. (0.056 mole) of methyl γ-bromocrotonate. The ice-bath was allowed to warm to room temperature and the dark mixture was stirred for a total of 45 hours. After the addition of 80 cc. of water, the benzene layer was separated and the aqueous layer was extracted with ether. The organic solution was washed with 10% hydrochloric acid and water, dried (magnesium sulfate) and concentrated. A solution of the dark residue in 10 cc. of carbon tetrachloride deposited on chilling 0.072 g. (1.3%) of dimethyl 2,4,6-octatrienedioate (IV), m.p. 164–167°. Recrystallization from methanol afforded colorless needles, m.p. 169.5–170° (reported[7a] 172°); λ_{max}^{alc} 301 mμ (ε 51,000), $\lambda_{inflection}^{alc}$ 290 and 314 mμ (ε 37,400 and 43,100), λ_{min}^{alc} 238 mμ (ε 1,170) (reported[7b] $\lambda_{max}^{methanol}$ 303 mμ).

The mother liquor was concentrated to a dark brown heavy oil, which weighed 3.1 g., λ_{max}^{alc} 248 and 303 mμ (ε 2,290 and 1,270). While no further crystalline material was obtained from this oil, the spectrum suggests the possible presence of IV or a compound with a similar chromophore (possibly a geometrical isomer of IV) to an approximate extent of 2.5%.

The yield in this reaction was not improved when the sodium methoxide was added to a benzene solution of methyl γ-bromocrotonate, when sodium hydride, sodamide or potassium *t*-butoxide was used instead of sodium methoxide or when the benzene was replaced with ether or with collidine.

Suberic Acid.—A solution of 30 mg. (0.153 mmole) of dimethyl 2,4,6-octatrienedioate (IV, prepared as described in the preceding experiment) in 5 cc. of ethanol was shaken under an atmosphere of hydrogen with 5 mg. of prereduced Adams catalyst. Ten and five-tenths milliliters (0.470 mmole) of hydrogen was absorbed. The residue after filtration and concentration was heated with 3 cc. of 35% aqueous potassium hydroxide to give, after acidification and crystallization from ether–petroleum ether, 22 mg. (83%) of suberic acid, m.p. 139–141°. There was no depression in m.p. when mixed with an authentic sample.

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(4) J. Thiele and A. Wanschedt, *Ann.*, **376**, 278 (1910).

(5) For reference see A. H. Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 275.

(6) M. S. Kharasch and E. Sternfeld, THIS JOURNAL, **61**, 2318 (1939).

(7) (a) R. Kuhn and Ch. Grundmann, *Ber.*, **69**, 1757 (1936); (b) *ibid.*, **69**, 1979 (1936).

(8) The melting points are uncorrected. We are indebted to Dr. J. M. Vandenbelt of Parke, Davis and Co. for the ultraviolet absorption spectrum of IV.

The Preparation of 4-Bromo- and 4-Iodo-ω-nitrostyrene

BY XORGE ALEJANDRO DOMINGUEZ, JORGE SLIM S. AND ARTURO ELIZONDO

RECEIVED MARCH 30, 1953

In the course of our research work it was necessary to prepare 4-bromo- and 4-iodo-ω-nitrostyrene. It has recently been reported by Schales and Graefe[1] that several substituted ω-nitrostyrenes showed antibacterial activity and it seemed of interest to test 4-bromo-ω-nitrostyrene and 4-iodo-ω-nitrostyrene against *Staphylococcus aureus* and report their syntheses. The former was prepared but not characterized by Worrall.[2] Their antibacterial activity was determined according to the procedure of Schales and Graefe.[1] The concentrations of the test compounds needed to inhibit bacterial growth by 50% after an incubation time of 18 hours were: 0.73 mg./100 ml. for the 4-bromo-ω-nitrostyrene and 1.06 mg./100 ml. for the 4-iodo-ω-nitrostyrene.

The necessary 4-bromo- and 4-iodobenzaldehydes were prepared from the corresponding nitriles employing Stephen's reaction[3] as modified by Sah[4] in yields of 65 and 68%, respectively. The 4-halo-arylnitroalkenes were easily obtained by condensation of the corresponding 4-halobenzaldehydes with nitromethane using ammonium

(1) O. Schales and H. A. Graefe, THIS JOURNAL, **74**, 4486 (1952).

(2) D. E. Worrall, *ibid.*, **56**, 1556 (1934).

(3) H. Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

(4) P. P. T. Sah, THIS JOURNAL, **64**, 1487 (1942).

acetate in acetic acid as condensing agent[5]; none of the condensation procedures catalyzed by alcoholic potassium hydroxide[6] and alcoholic methylamine,[7] were found suitable.

Experimental

4-Bromo-ω-nitrostyrene.—A mixture of 1 g. of 4-bromobenzaldehyde (m.p. 56°), 2 ml. of nitromethane and 0.2 g. of ammonium acetate in 20 ml. of glacial acetic acid was refluxed for 2 hours. The hot dark mixture was poured into 200 ml. of ice-cold water and allowed to stand 4 hours. The crude yellow product was collected, rinsed thoroughly with water and recrystallized from hot ethanol. Yellow small prisms, melting at 156–158°, were obtained, yield 700 mg. (56%).

Anal. Calcd. for $C_8H_6O_2NBr$ (228.04): N, 6.13. Found: N, 6.01.

4-Iodo-ω-nitrostyrene.—Using the same procedure as described above, 1 g. of 4-iodobenzaldehyde gave 916 mg. (75%) of small yellow needles of 4-iodo-ω-nitrostyrene, melting at 183–184°.

Anal. Calcd. for $C_8H_6O_2NI$ (275.04): N, 5.09. Found: N, 5.14.

Acknowledgment.—The authors express their thanks to Miss Beatriz Gomez for the microanalytical data, to Ing. Carlos Duhne for his encouragement and to Avelino Guerra for preparing the 4-iodobenzonitrile.

(5) (a) M. G. S. Rao, C. Strikantia and M. S. Iyengar, *Helv. Chim. Acta*, **12**, 581 (1924); (b) L. C. Raiford and D. E. Fox, *J. Org. Chem.* **9**, 170 (1944); (c) F. A. Ramirez and A. Burger, THIS JOURNAL, **72**, 2781 (1950); (d) C. B. Gairaud and G. R. Lapping, *J. Org. Chem.*, **18**, 1 (1953); (e) J. H. Mason, *J. Chem. Soc.*, 200 (1953).

(6) J. Thiele, *Ber.*, **32**, 1293 (1899); (b) D. E. Worrall, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 413.

(7) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

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The Anhydrous Chlorination of Thioesters and Related Compounds[1,2]

BY IRWIN B. DOUGLASS AND CHARLES E. OSBORNE

RECEIVED APRIL 27, 1953

In continuing the study of the action of anhydrous chlorine on different types of organic sulfur compounds,[3] various thioesters and closely related compounds have been treated with anhydrous chlorine in liquid butane near the temperature of solid carbon dioxide. Compounds containing the thiol group are split between the acyl group and sulfur with the formation of an alkylsulfur trichloride from the thiol portion and an acyl chloride or some related compound from the other part of the molecule. When the compound chlorinated is a dithioester, in addition to the removal of the the thiol group as alkylsulfur trichloride, chlorine appears to add to the carbon–sulfur double bond of the thiocarbonyl portion to form a 1,1-dichloroalkanesulfenyl chloride. Alkoxy groups in xanthate esters, which may also be considered as being dithioesters, are not disturbed by the chlorination reaction under the conditions employed,

The following equations illustrate reaction types which have been found to occur and at least one example of each is described in the Experimental part.

$$RCOSR' + 2Cl_2 \longrightarrow RCOCl + R'SCl_3 \quad (1)$$

$$RC(=S)SR' + 3Cl_2 \longrightarrow RCCl_2SCl + R'SCl_3 \quad (2)$$

$$ROC(=S)SR' + 3Cl_2 \longrightarrow ROCCl_2SCl + R'SCl_3 \quad (3)$$

$$ROCS{-}SCOR + XCl_2 \longrightarrow$$

$$2ROCCl_2SCl + \text{unknown compound contg. S and Cl} \quad (4)$$

$$RSO_2SR' + 2Cl_2 \longrightarrow RSO_2Cl + R'SCl_3 \quad (5)$$

In equation 1 shown above, the immediate formation of solid $R'SCl_3$ after beginning the passage of chlorine indicates that reaction 1 takes place rapidly. If chlorination is interrupted, however, the solid alkylsulfur trichloride gradually disappears, presumably because a slower reaction takes place between the solid sulfur trichloride and the original thiol ester.

$$RCOSR' + R'SCl_3 \longrightarrow RCOCl + 2R'SCl \quad (6)$$

An effort was made to study the action of chlorine on methyl thionpropionate, $C_2H_5CSOCH_3$. Reaction occurred and a white solid product with a chlorine content corresponding to $(C_2H_5CSOCH_3)$-Cl_2 was formed, but the solid decomposed at 8° and the evolved gas appeared to consist more of chlorine than hydrogen chloride. One does not seem justified in concluding that the chlorination reaction produced 1-chloro-1-methoxypropane-1-sulfenyl chloride, $C_2H_5\underset{\displaystyle OCH_3}{\overset{\displaystyle Cl}{\overset{|}{\underset{|}{C}}}}SCl$, since the properties of analogous compounds described in this paper lead one to believe that such a compound would be a yellow liquid rather than the white solid obtained.

The formation of an alkylsulfur trichloride precipitate in a chlorination reaction affords a ready means for separating this product of the reaction provided the other product is soluble in liquid butane at the temperature employed.

Experimental Part

Preparation of Intermediates.—The thiol, xanthate and dithio esters, methyl methanethiolsulfonate and the bis-[alkoxythiocarbonyl] disulfides were prepared by standard methods.

Methyl thionpropionate was prepared by a modification of the method of Sakurada.[4] Absolute methyl alcohol, propionitrile and dry hydrogen chloride reacted to form methyl propionimidate hydrochloride. Dry pyridine was added to neutralize the hydrochloride, and hydrogen sulfide was passed into an ether solution of the free imino ether to form the thion ester. Difficulty was encountered in this preparation due to the tendency of the ester to hydrolyze and oxidize. In numerous attempts only a 10% yield was obtained.

Chlorination Procedure.—Ten grams of the ester was dissolved in approximately 50 ml. of liquid C.P. butane in a 30 × 200 mm. culture tube which was cooled in a bath containing solid carbon dioxide and acetone. A gentle stream of chlorine was led into the space above the liquid and was continued until, after alternately shaking and settling, no more solid appeared to form. The mixture was centri-

(1) This represents a portion of the work done on Project NR-356-165 under Contract N8 onr 647(00) with the Office of Naval Research, United States Navy.

(2) Taken from the master's thesis of Charles E. Osborne.

(3) See I. B. Douglass, K. R. Brower and F. T. Martin, THIS JOURNAL, **74**, 5770 (1952), and preceding papers.

(4) Sakurada, *Mem. Coll. Sci. Kyoto*, **9**, 237 (1926); **10**, 79 (1926); *C. A.*, **21**, 2458, 3609 (1927).

fuged, the liquid decanted into another cooled culture tube, and the solid was washed 2–3 times with butane and centrifuged as before. The combined centrifugates were again chlorinated to cause any ester previously trapped in the solid to react and the solid was removed. After being combined, the butane solutions were allowed to evaporate and the residue was distilled using an 18-in. Vigreux column. Evaporation of the butane tended to sweep out some of the more volatile chlorination products. It was found that this loss could be minimized by condensing the butane in a clean tube, again allowing it to evaporate and combining the residues before distillation.

Substances Chlorinated and Products Formed

1. **Methyl thiolbenzoate**, $C_6H_5COSCH_3$, yielded: (a) benzoyl chloride, b.p. 194–195°, 78–79° (15 mm.), $n^{25}D$ 1.5498, d^{25}_4 1.21 (86% yield); (b) methylsulfur trichloride, CH_3SCl_3. *Anal.* Calcd. for CH_3Cl_3S: Cl, 69.31. Found: Cl, 68.52, 70.17.

2. **Ethyl thiolacetate**, $CH_3COSC_2H_5$, yielded: (a) acetyl chloride, CH_3COCl; reacted readily with aniline to form acetanilide, m.p. 112°, mixed m.p. with an authentic sample 112°; (b) ethylsulfur trichloride, $C_2H_5SCl_3$. The white solid was hydrolyzed in cold sodium bicarbonate solution and the solution treated with benzyl chloride to form ethyl benzyl sulfone, $C_2H_5SO_2CH_2C_6H_5$, m.p. 84.5, mixed m.p. with authentic sample 84.5°.

3. **Methyl dithiopropionate**, $C_2H_5C(=S)SCH_3$, yielded: (a) 1,1-dichloropropane-1-sulfenyl chloride, $C_2H_5CCl_2SCl$, yellow liquid, b.p. 69.5° (29 mm.), 65° (27 mm.), $n^{25}D$ 1.510; d^{25}_4 1.361, d^0_4 1.391 (27% yield). *Anal.* Calcd. for $C_3H_5Cl_3S$: Cl, 59.26; MR_D 38.7; mol. wt., 179.5. Found: Cl, 59.64; MR_D 39.4; mol. wt., 175.7. (b) Methylsulfur trichloride, CH_3SCl_3, which was hydrolyzed to sodium methanesulfinate and caused to react with benzyl chloride to form benzyl methyl sulfone, m.p. 126° and unchanged when mixed with an authentic sample.

4. **Methyl dithioacetate**, $CH_3C(=S)SCH_3$, yielded: (a) yellow liquid boiling 46° (28 mm.), presumably methyldichloromethanesulfenyl chloride, CH_3CCl_2SCl, but which decomposed with the evolution of hydrogen chloride too readily to be purified; (b) methylsulfur trichloride which was identified as methyl benzyl sulfone.

5. **Methyl methylxanthate**, $CH_3OCSSCH_3$, yielded: (a) methoxydichloromethanesulfenyl chloride, CH_3OCCl_2SCl, yellow liquid, b.p. 77° (35 mm.), 82° (40 mm.), $n^{25}D$ 1.518, d^{25}_4 1.522, d^0_4 1.555 (70% yield). *Anal.* Calcd. for $C_2H_3OCl_3S$: Cl, 58.62; S, 17.61; MR_D 35.8; mol. wt., 185.1. Found: Cl, 59.06, 58.30; S, 17.4; MR_D 36.2; mol. wt., 181.5; (b) methyl sulfur trichloride, CH_3SCl_3, identified as methyl benzyl sulfone as described above.

6. **Ethyl ethylxanthate**, $C_2H_5OCSSC_2H_5$, yielded: (a) ethoxydichloromethanesulfenyl chloride, $C_2H_5OCCl_2SCl$, yellow liquid, b.p. 88° (33 mm.), $n^{25}D$ 1.507, d^{25}_4 1.422, d^0_4 1.454. *Anal.* Calcd. for $C_3H_5OCl_3S$: Cl, 54.40; MR_D 40.5; mol. wt., 195.5. Found: Cl, 54.55; MR_D 40.9; mol. wt., 195.1. (b) Ethylsulfur trichloride, $C_2H_5SCl_3$. *Anal.* Calcd. for $C_2H_5Cl_3S$: Cl, 63.5. Found: Cl, 61.7, 62.2.

7. **Methyl 1-propylxanthate**, $CH_3CH_2CH_2OCSSCH_3$, yielded: (a) 1-propoxydichloromethanesulfenyl chloride, $CH_3CH_2CH_2OCCl_2SCl$, yellow liquid, b.p. 95.5° (26 mm.), $n^{25}D$ 1.498, d^{25}_4 1.353, d^0_4 1.383. *Anal.* Calcd. for $C_4H_7OCl_3S$: Cl, 50.77; MR_D 45.1; mol. wt., 209.5. Found: Cl, 50.95; MR_D 45.4; mol. wt., 203.1. (b) Methyl sulfur trichloride, CH_3SCl_3, identified by transforming to methyl benzyl sulfone.

8. **Methyl 2-propylxanthate**, $(CH_3)_2CHOCSSCH_3$, yielded: (a) methylsulfur trichloride, CH_3SCl_3, identified by transforming to methyl benzyl sulfone; (b) a yellow liquid boiling 87° (25 mm.) and presumably 2-propoxydichloromethanesulfenyl chloride, $(CH_3)_2CHOCCl_2SCl$, but the product lost hydrogen chloride so readily that purification was impossible.

9. **Bis-[methoxythiocarbonyl] disulfide**, $CH_3OC(=S)SSC(=S)OCH_3$, yielded: (a) methoxydichloromethanesulfenyl chloride, CH_3OCCl_2SCl, yellow liquid, $n^{25}D$ 1.518 (53% yield); (b) a white solid of unknown identity melting with decomposition at 15° and hydrolyzing in water to give a sulfur-like yellow solid. The gases from the decomposition liberated iodine from potassium iodide. The original white solid was analyzed repeatedly but with inconsistent results, Found: Cl, 55.8 to 60.65; S, 20.2 to 25.1.

10. **Bis-[ethoxythiocarbonyl] disulfide**, $C_2H_5OC(=S)SSC(=S)OC_2H_5$, yielded: (a) ethoxydichloromethanesulfenyl chloride, $C_2H_5OCCl_2SCl$, yellow liquid, b.p. 83° (27 mm.), $n^{25}D$ 1.507, d^{25}_4 1.421; (b) a white solid of unknown identity, similar to that obtained from the chlorination of bis-[methoxythiocarbonyl] disulfide.

11. **Methyl methanethiosulfonate**, $CH_3SO_2SCH_3$, yielded: (a) methanesulfonyl chloride, CH_3SO_2Cl, which was allowed to react with aniline to form methanesulfonanilide, $CH_3SO_2NHC_6H_5$, m.p. 97–98° and unchanged when mixed with an authentic sample; (b) methylsulfur trichloride, CH_3SCl_3, which was identified by transformation to methyl benzyl sulfone,

12. **Methyl thionpropionate**, $C_2H_5C(=S)OCH_3$, yielded: a white solid, decomposing at 8° with evolution of a gas which fumed slightly in moist air but which also liberated iodine from potassium iodine–starch paper. *Anal.* Calcd. for $C_2H_5CSOCH_3Cl_2$: Cl, 44.57. Found: Cl, 44.2.

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The Reaction of 2,4-Dinitrobenzenesulfonic Acid with Free Amino Groups of Proteins

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In a previous communication[1] which dealt with the combination of a series of substituted 2,4-dinitrobenzenes with tissue proteins *in vivo*, it was reported that the sodium or potassium salts of 2,4-dinitrobenzene sulfonate formed a stable derivative *in vitro* with bovine gamma globulin. Because the reaction between this compound and protein may readily be carried out under conditions which cause little or no denaturation of many proteins, we have examined this reaction in greater detail.

Dinitrobenzene sulfonate reacts readily with bovine gamma globulin at *p*H 10–11 at room temperature; at *p*H 7, however, under otherwise similar conditions, protein is not derivatized after 24 hours. Since dinitrobenzene sulfonate is appreciably water soluble, the reaction may be carried out in an aqueous system, in which case the derivatized protein is soluble at *p*H 7.0 as well as at higher *p*H values.

The derivatization involves the splitting out of sulfonate and the substitution of dinitrophenyl in free NH_2 groups, yielding the same derivative as in the reaction with 2,4-dinitrofluorobenzene.[2] This conclusion is based upon evidence from three sources.

(1) Bovine gamma globulin was reacted with dinitrobenzene sulfonate and, after purification by extensive dialysis, the protein was hydrolyzed in 6 *N* HCl. After ether extraction, the hydrolysate was examined chromatographically on buffered silica gel columns.[2,3] A single yellow band was obtained with the same R_f as a sample of ϵ-dinitrophenyllysine prepared by the method of Porter and Sanger[4]; a mixed chromatogram of the latter

(1) H. N. Eisen, L. Orris and S. Belman, *J. Exp. Med.*, **95**, 473 (1952).
(2) F. Sanger, *Biochem. J.*, **39**, 507 (1945).
(3) S. Blackburn, *ibid.*, **45**, 579 (1949).
(4) R. R. Porter and F. Sanger, *ibid.*, **42**, 287 (1948).

compound and the protein hydrolysate yielded only a single band. ε-Dinitrophenyllysine is thus the predominant yellow dinitrophenylamino acid in bovine gamma globulin derivatized with dinitrobenzene sulfonate. Probably free NH_2 groups of terminal amino acids are substituted in addition to the ε-NH_2 of lysine.

(2) The ultraviolet absorption spectrum of the derivatized protein in 10 *N* HCl was corrected for the protein contribution to yield the absorption spectrum of the substituted amino acids. The latter appears not to be significantly different from that of ε-dinitrophenyllysine (Fig. 1); the close approximation of the two spectra in the region of 300 to 340 mμ suggests that little, if any, reaction with tyrosine hydroxyl groups has occurred.[5]

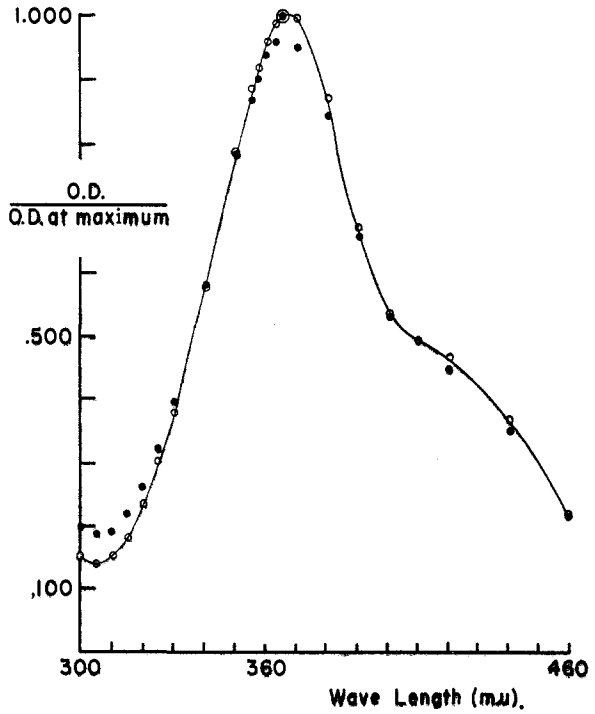

Fig. 1.—Ultraviolet absorption spectrum of ε-dinitrophenyllysine, O, and the dinitrophenylamino acids, ●, of dinitrophenyl bovine gamma globulin; the latter was obtained by correcting the spectrum of the derivatized globulin for the protein contribution. Optical densities (O.D.) are expressed as a fraction of the optical density at λ_{max} (365 mμ). The solvent was 10 *N* HCl.

(3) S^{35}-labeled dinitrobenzene sulfonate[6] (2 mc./m*M*) was diluted with non-radioactive carrier and treated with bovine gamma globulin in an aqueous system, *p*H 10–11. After 24 hours the solution was dialyzed against successive changes of 0.16 *M* NaCl, the dialysates being measured for S^{35} content. When no further S^{35} was dialyzable the dialysis bag contents were analyzed for S^{35} activity and, after dilution in 0.1 *N* NaOH, were examined spectrophotometrically at 290 and 360 mμ in order to estimate the number of dinitrophenyl groups per protein molecule.[1] The results (see Table I) indicate that an average of 22% of dinitrobenzene sulfonate reacted with the protein, while only 1.6% of S^{35} was combined. This amount of S^{35} corresponds to 5 to 10% of the dinitrophenyl groups in the derivatized protein. Inasmuch as the labeled reagent used in these experiments contained an S^{35} impurity to the extent of 10%,[6] the non-dialyzable radioactivity can probably be attributed to this impurity. The impurity has not been identified; despite its presence, it was possible to recrystallize the S^{35}-labeled dinitrobenzene sulfonate six times from water without a change in specific activity.

It is of interest that the efficiency of derivatization of protein by dinitrobenzene sulfonate was increased considerably by shaking the reactants although these were all in solution. For example, preparations A and B of Table I represent aliquots from a single solution of reactants, A having been shaken about 180 times per minute for about 20 hours, and B having been unagitated during the same time.

TABLE I

S^{35}-LABELED DINITROBENZENE SULFONATE REACTION WITH PROTEIN

Initially, labeled reagent was in 86-fold mole excess with respect to bovine gamma globulin.[6] Total S^{35} activity, 30,810 c.p.m. for A, and 53,495 c.p.m. for B.

Preparation	Dinitrophenyl groups per dinitrophenyl-bovine globulin molecule[a]	Fraction of initial dinitrophenyl groups combining with protein (= *x*), %	Fraction of total S^{35} not dialyzable (= *y*), %	Ratio *y*/*x*
A	24	28	2.4	0.086
B	14	16	0.9	.056

[a] Assuming bovine gamma globulin molecular weight to be 160,000.

Under conditions which lead to maximal substitution (*i.e.*, vigorous shaking in the presence of ethanol[2]) 2,4-dinitrofluorobenzene and the corresponding chloro and bromo reagents introduce about 60 dinitrophenyl groups per γ-globulin molecule, and the protein is rendered insoluble.[1] Dinitrobenzene sulfonate, dissolved in water, is about as effective when a large excess of reagent is employed. For example, when used in a 1000-fold mole excess with respect to protein (at *p*H 10 for 20 hours at room temperature, rocking gently about five times per minute) the sulfonate reagent substituted 50 to 55 dinitrophenyl groups per bovine γ-globulin molecule, the protein remaining soluble in water at *p*H values above 6.8. For purposes of end group analysis where denaturation is not a matter of concern, the halogen substituted reagents are probably more satisfactory. Dinitrobenzene sulfonate, however, offers a notable advantage in that it permits the preparation of soluble dinitrophenyl proteins. The latter have been found useful in immuno-chemical work,[7] and may be of interest generally in relation to the preparation of undenatured derivatized proteins.

(5) F. Sanger, *Biochem. J.*, **45**, 563 (1949).

(6) The potassium salt of S^{35}-labeled dinitrobenzene sulfonate was prepared at Technical Associates, Inc., under the direction of Mr. Allen Goldstein; it may now be obtained from Isotopes Specialties Co., Glendale, California. The manufacturer reported that radioautographs of paper chromatograms of this material revealed an impurity, containing S^{35}, to the extent of 10%; the concentration of this impurity was not reduced by numerous recrystallizations.

(7) H. N. Eisen, M. E. Carsten and S. Belman, *Federation Proc.*, **12**, 441 (1953).

In addition to bovine gamma globulin, we have reacted dinitrobenzene sulfonate with egg albumin, beef serum, sheep serum, gelatin and tuberculin with results similar to those given above.

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4-Nitro-2-thenaldehyde

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The nitration of 2-thenaldehyde diacetate has been reported to give 5-nitro-2-thenaldehyde diacetate.[1,2] Since Rinkes[3] found that nitration of methyl 2-thienyl ketone gave a mixture of methyl 5-nitro-2-thienyl ketone and methyl 4-nitro-2-thienyl ketone, it was thought that the nitration of 2-thenaldehyde diacetate should produce 4-nitro-2-thenaldehyde diacetate as well as the 5-nitro derivative. It was found that this was indeed the case. Concentration of the alcoholic filtrates from the recrystallization of the 5-nitro-2-thenaldehyde diacetate, m.p. 72–73°, yielded another nitrothenaldehyde diacetate, m.p, 54–55°. Acid hydrolysis of the latter gave the nitroaldehyde, m.p. 36–37°. Oxidation of the nitroaldehyde to the nitroacid, followed by esterification with methanol, gave a methyl ester, m.p. 99°, corresponding to the melting point of methyl 4-nitro-2-thiophenecarboxylate reported by Rinkes.[4]

Experimental

Since the conditions for the nitration of 2-thenaldehyde diacetate differ in some respects from the procedure used by Patrick and Emerson,[1] these differences are reported here.

To 143 g. of acetic anhydride at −5° was added, over a period of 17 minutes, 43.7 g. of fuming nitric acid (sp. gr. 1.5), the temperature being kept at −5 to 0°. A solution of 55 g. of 2-thenaldehyde diacetate in 102 g. of acetic anhydride was then added slowly, keeping the temperature a −5 to −10°. After addition was complete, the solution was stirred at 0° for three hours and then poured onto 1.0 kg. of ice. The mixture was allowed to stand for one hour and was then filtered. The precipitate was washed with a little cold water followed by cold alcohol and then dried, yielding 58.5 g., 88%, of the isomeric 5-nitro-2-thenaldehyde diacetates, m.p. 55–65°.[5] Three recrystallizations from alcohol gave a 64% yield of 5-nitro-2-thenaldehyde diacetate,[6] m.p. 68–69°.

4-Nitro-2-thenaldehyde Diacetate.—The combined alcoholic filtrates from the first two recrystallizations of the 5-nitro-2-thenaldehyde diacetate were evaporated to dryness. The residue was recrystallized from 18 cc. of alcohol, giving 5.2 g. of solid, m.p. about 50°. The 5.2 g. were recrystallized again from 7 cc. of alcohol, giving 4.0 g. of solid, m.p. 50–55°. A third recrystallization from 10 cc. of alcohol, gave 3.7 g., m.p. 54–55°. Crystallization of a sample from petroleum ether did not further raise the melting point. The ultraviolet absorption maximum in water occurred at 2925 Å., E_M 6,300.

Anal.[7] Calcd. for $C_9H_9NO_6S$: C, 41.70; H, 3.50; N, 5.40; S, 12.37. Found: C, 41.81; H, 3.37; N, 4.97; S, 12.31.

4-Nitro-2-thenaldehyde.—To a solution of 12.5 g. of sulfuric acid in 25 cc. of water was added 6.7 g. of 4-nitro-2-thenaldehyde diacetate. The mixture was refluxed in an atmosphere of nitrogen for 20 minutes, cooled and the resulting precipitate removed by filtration and then washed with cold water. It was recrystallized from a mixture of ether–petroleum ether to give 2.0 g., 50% of 4-nitro-2-thenaldehyde, m.p. 34–37°. Further recrystallization from petroleum ether raised the melting point to 36–37°. The ultraviolet absorption maximum in water occurred at 3025 Å., E_M 7,600.

Anal. Calcd. for $C_5H_3NO_3S$: C, 38.21; H, 1.92; N, 8.92; S, 20.40. Found: C, 37.74; H, 1.94; N, 8.95; S, 20.50.

The semicarbazone melted at 234–235°. A mixed melting point with the 5-nitro-2-thenaldehyde semicarbazone was depressed to 225–230°.

Anal. Calcd. for $C_6H_6N_4O_3S$: C, 33.64; H, 2.82; S, 14.97. Found: C, 33.87; H, 3.07; S, 14.69.

A similar hydrolytic procedure when applied to 5-nitro-2-thenaldehyde diacetate gave a 95% yield of 5-nitro-2-thenaldehyde,[8] m.p. 70–72°.

Methyl 4-Nitro-2-thiophenecarboxylate.—To a suspension of 0.5 g. of 4-nitro-2-thenaldehyde in 3 cc. of 35% sulfuric acid was added dropwise a solution of 0.8 g. of sodium dichromate in 0.5 cc. of water, keeping the temperature below 40°. The mixture was stirred for 3 hours at room temperature and then kept at 0° for 15 hours. The precipitate was removed by filtration, washed with a little cold water, and then dried. It was dissolved in 5 cc. of methanol, 0.1 g. of sulfuric acid added and the solution refluxed for 3 hours. At the end of this time the solution was poured into 15 cc. of ice-water and sufficient sodium bicarbonate solution added to neutralize any excess acid. The solid which formed was removed by filtration and recrystallized twice from petroleum ether. The melting point was 98–99° (99°[4]).

Anal. Calcd. for $C_6H_5NO_4S$: S, 17.13, Found: S, 17.44.

(1) T. Patrick and W. Emerson, THIS JOURNAL, **74**, 1356 (1952).

(2) V. M. Zubarovskii, *Doklady Akad. Nauk S.S.S.R.*, **83**, 85 (1952); *C. A.*, **47**, 2166[a] (1953).

(3) I. Rinkes, *Rec. trav. chim.*, [4] **52**, 538 (1933).

(4) I. Rinkes, *ibid.*, [4] **51**, 1134 (1932).

(5) All melting points were taken on a Fisher-Johns apparatus and are corrected.

(6) The ultraviolet absorption maximum, in water, of an analytically pure sample occurred at 3190 Å., E_M 8,300.

(7) All the analyses were carried out by Mr. Joseph Corrado of these laboratories.

(8) The ultraviolet absorption maximum, in water, of an analytically pure sample occurred at 3150 Å., E_M 11,200.

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The Resolution of *p*-Ethylphenylmethylcarbinol. Infrared Spectra of Enantiomorphs and Racemates

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RECEIVED APRIL 17, 1953

In connection with another problem we had occasion to resolve *p*-ethylphenylmethylcarbinol. The resolution was carried out by crystallization of the brucine and cinchonidine salts of the acid phthalate of the alcohol[1] and is described in detail in the experimental part. Melting point data of the active and racemic phthalates indicate that the racemic phthalate is a *dl*-compound.

Routine examination of the infrared spectra of the enantiomorphs and racemic phthalates revealed that while the (+)-, (−)- and racemic phthalates had identical spectra in chloroform solution—as was to be expected[2a] the mull spectrum of the racemate (see Fig. 1) showed significant differences

(1) A. W. Ingersoll in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 376.

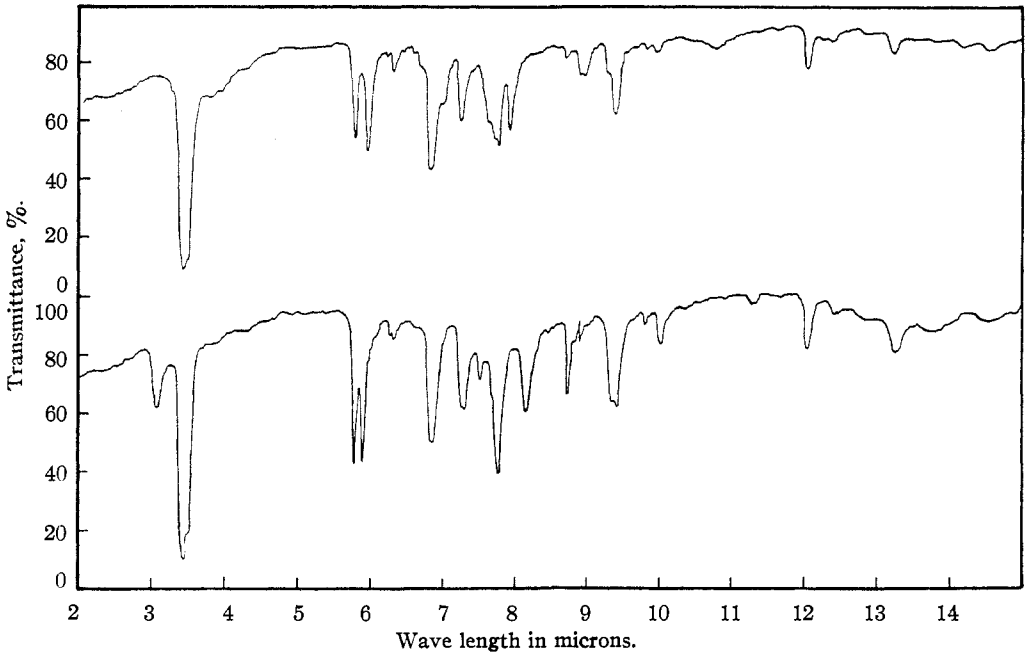

Fig. 1.—Infrared spectra of *p*-ethylphenylmethylcarbinyl hydrogen phthalate in Nujol mull: upper curve, racemate; lower curve, enantiomorph.

from that of either enantiomorph, not only in the "fingerprint region" as expected,[2] but also in the 3–7μ region of the infrared spectrum. Specifically, the enantiomorphs showed a sharp hydroxyl band at 3.05μ and an acid carbonyl band at 5.88μ in addition to the ester carbonyl band at 5.78μ. The racemate had the same ester carbonyl band, but the hydroxyl band was absent and the acid carbonyl band was shifted to 5.95μ, The precise fate of the hydroxyl band could be better observed in a hexachlorobutadiene mull (Fig. 2) where there was no interference from the 3.4–3.5μ Nujol band. In this chlorinated mulling agent, the enantiomorphic *p*-ethylphenylmethylcarbinyl phthalate showed sharp bands at 3.05μ (OH) and 3.38–3.50μ (CH) while the racemate showed a broad band at 3.4–3.6μ with satellites at 3.79–3.97μ, presumably due to combined OH- and CH-frequencies.

It is well known that both the hydroxyl band and the carbonyl band in carboxylic acids are shifted to longer wave lengths by hydrogen bonding.[3] Thus one is led to the conclusion that *inter*molecular hydrogen bonding is much more important in the crystals of the racemic compound of *p*-ethylphenylmethylcarbinyl phthalate than it is in the crystals of the enantiomorphs. One is tempted to conclude that the *dl*-compound is of the carboxylic acid dimer[4] type while the enantiomorphs do *not* form such dimers in the solid state; but even if this is true, it is not general, since α-phenethyl phthalate does not show the shifts observed in the case of the *p*-ethyl homolog.[5] It appears that in this case the

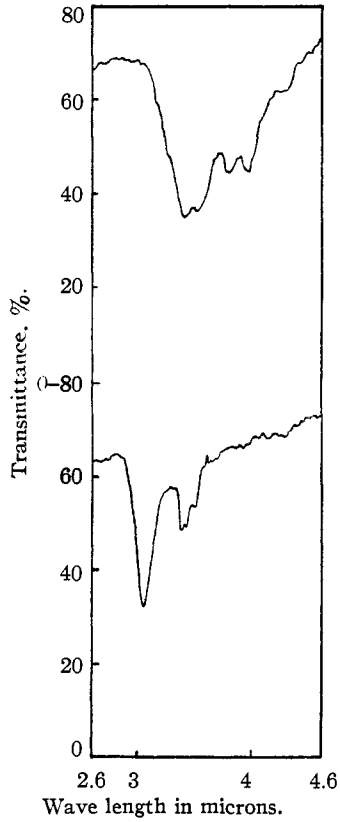

Fig. 2.—Infrared spectra of *p*-ethylphenylmethylcarbinyl hydrogen phthalate in hexachlorobutadiene mull: upper curve, racemate; lower curve, enantiomorph.

(2) (a) F. A. Miller in H. Gilman's "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 136, (b) Results somewhat similar to those described here were reported by N. Wright. *J. Biol. Chem.*, **120**, 641 (1937); **127**, 137 (1939).

(3) (a) For a summary, see L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice-Hall, Inc., New York, 1952, p. 262; (b) for recent references, see S. Searles, M. Tamres and G. M. Barrow, THIS JOURNAL, **75**, 71 (1953); P. A. Giguère and A. Weingartshofer Olmos, *Can. J. Chem.*, **30**, 821 (1952).

(4) Ref. 3a, p. 64.

(5) α-Phenethyl phthalate also forms a racemic compound. The infrared spectra (Nujol mulls) of the racemate and of the enantiomorphs resemble that of the *dl*-compound of the *p*-ethyl homolog as well as that of methyl acid phthalate in that the hydroxyl band is absent and the acid carbonyl band is found at 5.95 μ.

d- and *l*-forms can dimerize with themselves as well as with each other.[6] The apparent absence of dimerization of the enantiomorphs of the *p*-ethyl homolog must then be ascribed to steric interference of the ethyl groups. This steric interference appears to depend critically on the conformation of the molecules in the crystalline state and disappears in benzene or chloroform solution, in which both the enantiomorphs and the racemate of the *p*-ethylphenylmethylcarbinyl phthalate dimerize, as indicated by infrared spectra (absence of distinct OH-band) and molecular weight.

It would obviously be desirable to examine mull spectra of other racemates and enantiomorphs. We have had occasion to examine the infrared spectra of (+)- and *dl*-2-phenylpropanediol-1,2 and of (−) and *dl*-malic acid in hexachlorobutadiene. The OH-band for the racemic glycol[7] lies at 3.16μ while that for the enantiomorph is found at 3.08μ, indicating the possibility of enhanced hydrogen bonding in the compound. In the spectra of the malic acids[8] the principal difference appears in the resolved part of the OH-band which is a single sharp band at 2.9μ in the racemate and a doublet at 2.84 and 2,98μ in the active compound.

Experimental[9]

***dl*-*p*-Ethylphenylmethylcarbinyl Phthalate.**—A mixture of 165 g. (1.1 moles) of phthalic anhydride, 165 g. (1.1 moles) of the carbinol[10] (b.p. 111–113° (11–12 mm.),[11] n^{25}D 1.5160,[10] d^{25} 0.970[11]; phenylurethan[11] m.p. 73–74°) and 87 g. (1,1 moles) of pyridine was heated for two hours on the steam-bath and then poured into an excess of dilute hydrochloric acid. The precipitated oil was extracted with ether and the ether layer was washed successively with dilute hydrochloric acid and water and then dried over sodium sulfate and concentrated. Crystallization of the residue from benzene–petroleum ether (b.p. 30–60°) yielded 287 g. (87%) of the phthalate, m.p. 82–84°. The analytical sample melted at 85–86°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 72.47; H, 6.08; mol. wt. (dimer), 596. Found: C, 72.60; 6.37; mol. wt. (cryoscopically, in benzene), 545.

Resolution of *dl*-*p*-Ethylphenylmethylcarbinyl Phthalate.—To a solution of 135 g. (0.45 mole) of the *dl*-phthalate in 400 ml. of warm acetone was added 180 g. (0.45 mole) of brucine. On standing and chilling, a total of 170–190 g. of the crude brucine salt precipitated, This material was recrystallized three times from 300–400 ml. of acetone, care being taken to allow crystallization to take place slowly and without disturbance at room temperature, The recovered brucine salt weighed 62.5 g. (40%), melted at 113–114° (dec.) and had $[\alpha]^{25}$D −25.5° in 95% ethanol; the melting point and rotation were not changed by further recrystallization. The salt was decomposed by dissolving it in methanol, pouring the solution into dilute hydrochloric acid and extracting the precipitated phthalate with ether. The ether solution was dried over sodium sulfate and concentrated and the residue crystallized from benzene–petroleum ether (30–60°) to give 23.1 g. (86%) of active phthalate, m.p. 108–109°, $[\alpha]^{25}$D +16.1° (α 1.125°, l = 2 dm., c 35 g./l., in absolute ether) unchanged by further recrystallization.

The crude (−)-phthalate recovered from the original acetone liquor was converted into the cinchonidine salt, To a solution of 48 g. (0.16 mole) of crude (−)-phthalate in 600 ml. of warm acetone was added 48 g. (0.16 mole) of cinchonidine. The solution was allowed to stand overnight and then chilled and the precipitated salt (65 g.) collected. After two recrystallizations from methanol–methyl acetate, the salt (28.5 g.) formed asbestos-like fibers melting at 173–174° (dec.) and had $[\alpha]^{27}$D −55.2°. The rotation was not increased by further recrystallization. Decomposition of 27 g. of the cinchonidine salt (in the same way as described for the brucine salt) yielded 12,2 g. (91%) of the active phthalate, m.p, 108–109°, $[\alpha]^{25}$D −16.3° (α −1.10, l 2 dm., c 33.8 g./l.). Recrystallization from benzene–petroleum ether (b.p. 30–60°) raised the melting point to 109.5–110.5° but the rotation was not increased; mol. wt. calcd. (dimer), 596; found (cryoscopically, in benzene), 541.

A mixture of equal amounts of the (+)- and (−)-phthalate upon crystallization from benzene–petroleum ether regenerated the racemate, m.p. 84–85°. When a mixture of the racemic modification and the (−)-form was melted, and the melt allowed to solidify, the melting point of the resulting solid was 82.5–86°, Similarly, the (+)-form depressed the melting point of the racemate (m.p. 85–86°) to 84–86°; on the other hand the melting point of the racemate was not affected in any way by simple melting and resolidification, These data indicate that the racemic modification is a compound,

The infrared spectra of the (+)-phthalate, (−)-phthalate and *dl*-phthalate were identical in chloroform solution, but mull spectra of the active forms in Nujol (Fig. 1) and hexachlorobutadiene (Fig. 2) differed from corresponding spectra of the racemate.

(+)- and (−)-*p*-Ethylphenylmethylcarbinol.—Hydrolysis of 9 g. of the (+)-phthalate was effected by heating for 15 minutes at 100° with 20 g. of a 20% solution of sodium hydroxide. The heterogeneous mixture was diluted with water, extracted with pentane, and the pentane extract dried over potassium carbonate and concentrated. Distillation of the residue gave 3.5 g. (78%) of active *p*-ethylphenylcarbinol, b.p. 117–118° (13 mm.), m.p. 13–15°, n^{25}D 1,5159, d^{25} 0.970, α^{25}D −90,31° (neat, l = 2 dm.; levorotation established by observing rotation of a dilute solution in the *dl*-alcohol) whence $[\alpha]^{25}$D −46.5° (neat),

The (−)-phthalate similarly gave (+)-alcohol, b.p. 116–117° (12 mm.), m.p. 13–15°, n^{25}D 1.5158, α^{25}D +90.29° (neat, l = 2 dm.) whence $[\alpha]^{25}$D +46.5°.

When more dilute sodium hydroxide was used in the hydrolysis, the rotation of the resulting alcohol was the same indicating that alkyl-oxygen fission was apparently not taking place.[12]

Samples of (+)-, (−)- and *dl*-alcohol all had the same infrared spectrum.

Acknowledgment.—This work was supported by a Frederick Gardner Cottrell Grant of Research Corporation for which we are grateful. We are indebted to Mr. Thomas Marshall for the molecular weight determinations.

(12) *Cf.* J. Kenyon, *Bull. soc. chim. France*, 66C (1951).

DEPARTMENT OF CHEMISTRY
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(6) The possibility of strong *intra*molecular hydrogen bonding in the case of α-phenethyl phthalate would offer an alternative explanation for the similarity in the spectra of the enantiomorphs and racemate. Some support for such an explanation comes from the position of the ester carbonyl band which occurs at 5.82 μ rather than at 5.78 μ as in the *p*-ethyl homolog. The position of the OH-band in the active forms of the p-ethyl compound (at 3.05μ) suggests *intra*molecular hydrogen bonding also. The constancy of the ester C=O frequency and the marked shifts in the C—O (7.5–9μ) region (see Fig. 1) in going from the racemate to the active form suggest that this hydrogen bonding may involve the *alkyl* oxygen of the ester group.

(7) E. L. Eliel and J. P. Freeman, THIS JOURNAL, **74**, 923 (1952).

(8) We are indebted to Professor David Y. Curtin, University of Illinois (private communication) for drawing our attention to differences in the mull spectra of the malic and the tartaric acids.

(9) All melting and boiling points are uncorrected. Microanalysis by Micro-Tech Laboratories, Skokie, Ill.

(10) D. T. Mowry, M. Renoll and W. F. Huber, THIS JOURNAL, **68**, 1105 (1946). The refractive index for *p*-ethylphenylmethylcarbinol reported in this reference (1.5670 at 25°) appears to be misprinted.

(11) A. Klages, *Ber.*, **35**, 2245 (1902), reports b.p. 119.5° (14 mm.) d^{18} 0.974; phenylurethan m.p. 72–73°.

β-(*p*-Nitrobenzoyl)-acrylic Acid and *p*-Nitroacrylophenone

BY HELEN F. GINSBERG, ILSE LEDERMAN AND DOMENICK PAPA

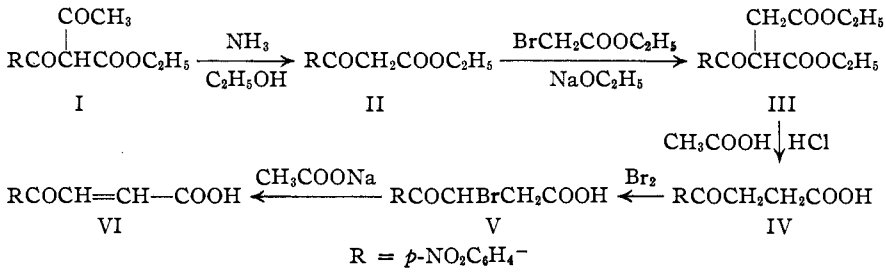
RECEIVED APRIL 27, 1953

The antibacterial and antifungal activity reported for the α,β-unsaturated ketones, acrylo-

phenones and β-aroylacrylic acids,[1] indicates that these substances are of potential clinical interest. In general, aromatic substitution by chlorine, methyl and hydroxyl groups enhanced the activity of these two types of compounds.

In the past ten years or so a diversified group of chemotherapeutic agents have been described, several of these substances having in common an "aryl" nitro group.[2] It therefore was of interest to prepare the *p*-nitro analogs of β-benzoylacrylic acid and acrylophenone in order to determine whether substantial enhancement of the antibacterial and/or antifungal activity would result by this substitution. Although β-(*m*-nitrobenzoyl)-acrylic acid, prepared in the course of a previous study,[1] was less active than the parent compound, it was reasonable to assume that the para isomer would be appreciably more active, *cf.*, sulfa drugs, chloramphenicol, etc.

The position of the substituents in the proposed compounds precluded direct nitration of the easily available intermediates. β-(*p*-Nitrobenzoyl)-acrylic acid was prepared by the sequence of reactions described by Kotake, *et al.*,[3] for the synthesis of β-(2-nitro-3-methoxy)-acrylic acid.



The reaction of freshly prepared *p*-nitrobenzoyl chloride with ethyl acetoacetate in absolute ethanol gave I in good yield. Substitution of commercial *p*-nitrobenzoyl chloride in the condensation afforded ethyl *p*-nitrobenzoylacetate (II) identical with that obtained from the ethanolic ammonia hydrolysis of I. Alkylation of II with ethyl bromoacetate followed by acid hydrolysis of the crude diester (III) gave *p*-nitrobenzoylpropionic acid (IV). Bromination of IV in chloroform[4] and subsequent dehydrohalogenation of the bromoketonic acid (V) with sodium acetate yielded the β-nitrobenzoyl)-acrylic acid (VI).[5]

Attempts to prepare *p*-nitroacrylophenone by adapting procedures applicable to the ortho and meta isomers were unsuccessful. Although both *o*- and *m*-nitroacetophenone have been reported to undergo the Mannich condensation with amines and formaldehyde[6] (VII), there is no record of the use of the *p*-nitro compound in this reaction. The desired Mannich bases were obtained from the reaction of *p*-nitroacetophenone, formaldehyde and a secondary amine hydrochloride in ethanol solution; however, the yields were consistently low and unreliable. In one run the product from piperidine hydrochloride was isolated; yet the experiment could not be successfully repeated. The only consistent results in this condensation were obtained with dimethylamine hydrochloride. Several attempts to decompose *p*-nitro-ω-dimethylaminopropiophenone hydrochloride to the acrylophenone (VIII), such as by treatment with alkali or steam distillation, resulted in either polymerization or formation of intractable oils. In view of these difficulties and the relatively low order of activity of the β-(*p*-nitrobenzoyl)-acrylic acid, these reactions were not studied further.

Experimental

Ethyl α-(*p*-nitrobenzoyl)-acetoacetate (I) from 33.4 g. of *p*-nitrobenzoic acid through the acid chloride and subsequent condensation with ethyl acetoacetate as described,[3] yield 35 g., m.p. 55–56° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.69. Found: C, 55.45; H, 5.06.

In the initial preparation of this compound, commercial *p*-nitrobenzoyl chloride gave ethyl *p*-nitrobenzoylacetate, m.p. 73–74°, identical with that obtained in the ethanolic ammonia hydrolysis of I.

Ethyl 4-nitrobenzoylacetate (II) from I (25 g.) and ethanolic ammonia, yield 17 g., m.p. 73–74° after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{11}O_5N$: N, 5.91. Found: N, 5.93.

β-(4-Nitrobenzoyl)-propionic Acid (IV).—The intermediate diethyl-α-(*p*-nitrobenzoyl) succinate prepared from II (20.5 g.) and ethyl bromoacetate was obtained as a pale yellow oil and hydrolyzed directly with mixed acetic and hydrochloric acids, yield 16 g., m.p. 150–151° after recrystallization from water.

Anal. Calcd. for $C_{10}H_9O_5N$: C, 53.81; H, 4.07. Found: C, 53.38; H, 4.13.

β-Bromo-β-(4-nitrobenzoyl)-propionic Acid (V).—The bromination of IV was carried out as described for a series of aroylpropionic acids.[4] From 5 g. of III, there was obtained 6.5 g. of the bromo acid, m.p. 118–119.5° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{10}H_8O_5NBr$: N, 4.63. Found: N, 4.89.

β-(*p*-Nitrobenzoyl)-acrylic Acid (VI).—Dehydrohalogenation of the bromo acid (V) (4.6 g.) with acetic acid and sodium acetate gave the acrylic acid, yield 2.5 g., m.p. 173.5–174.5° after recrystallization from water.

Anal. Calcd. for $C_{10}H_7O_5N$: C, 54.30; H, 3.19; N, 6.33. Found: C, 54.38; H, 3.23; N, 6.18.

***p*-Nitro-ω-piperidinopropiophenone Hydrochloride.**—*p*-Nitroacetophenone (16.5 g.) was added gradually in one-half hour to a refluxing solution of 12.2 g. of freshly prepared piperidine hydrochloride and 4.5 g. of paraformaldehyde in

(1) See references 2–5, D. Papa, E. Schwenk, F. Villani and E. Klingsberg, THIS JOURNAL, **70**, 3356 (1948).

(2) Nisulfadine and Nisulfazole, R. H. Major and H. L. Douglas, *J. Kansas Med. Soc.*, **43**, 287 (1942); R. H. Major, *Am. J. Med.*, 1, 484 (1946). Derivatives of nitrobenzene and nitrofuran, M. D. Eaton, C. T. Huang and C. G. Levenson, *Proc. Soc. Exptl. Biol. Med.*, **71**, 501 (1949); M. C. Dodd, D. L. Cramer and W. C. Ward, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 313 (1950); M. C. Rebstock, G. W. Moersch, A. C. Moore and J. M. Vandenbelt, THIS JOURNAL, **73**, 3666 (1951); and others.

(3) M. Kotake, T. Saken and S. Senoh, THIS JOURNAL, **73**, 1832 (1951).

(4) E. B. Knott, *J. Chem. Soc.*, 455 (1945).

(5) Recently M. Goldman and E. I. Becker, *Nature*, **170**, 35 (1952), described a procedure for the preparation of aroylacrylic acids applicable to compounds containing a negative substituent such as the *p*-nitro group.

(6) (a) C. Mannich and M. Dannehl, *Arch. Pharm.*, **276**, 206 (1938); (b) H. Jager and M. Arens, *Chem. Ber.*, **83**, 152 (1950).

30 cc. of 2B ethanol. Then an additional 3 g. of paraformaldehyde was added, the reaction mixture refluxed for 15 minutes and filtered hot. The product separated from the cooled filtrate, yield 4 g., m.p. 193–194° after recrystallization from ethanol–acetone.

Anal. Calcd. for $C_{14}H_{19}O_3N_2Cl$: N, 9.38. Found: N, 9.64.

p-Nitro-ω-dimethylaminopropiophenone Hydrochloride.—To a refluxing solution of 40.75 g. of dimethylamine hydrochloride, 22.5 g. of paraformaldehyde, 1.5 cc. of concentrated hydrochloric acid in 200 cc. of 2B ethanol, 82.5 g. of *p*-nitroacetophenone was added portionwise over a period of 1 hour. The reaction mixture was refluxed an additional 15 minutes, cooled and the keto base filtered, yield 20 g., m.p. 190–191° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{11}H_{15}O_3N_2Cl$: N, 10.83. Found: N, 10.86.

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Some Notes on the Chemistry of Arsafluorinic Acid[1]

BY RICHARD J. GARASCIA AND I. VICTOR MATTEI

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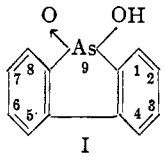
Arsafluorinic acid (I) has been the object of only scant attention. Aeschlimann, *et al.*,[2] were the first to report its preparation from ring closure of biphenyl-2-arsonic acid.



I

The chemistry of the system was somewhat extended by Cookson and Mann[3] who prepared several 9-substituted arsafluorenes. Recently, Feitelson and Petrow[4] reported a more varied series of compounds obtained by ring-closure methods and by direct substitution. This last publication appeared when we were in the final stages of some research in the same field. Though our efforts were not so extensive as those of Feitelson and Petrow, many of the compounds reported by them had been prepared by us, and agreement on the data concerning these was, in general, very good. There were some points of difference, however, and some new material which may be of interest in view of the paucity of information pertaining to the system,

The parent compound, arsafluorinic acid, was synthesized according to the method of Aeschlimann by treating biphenyl-2-arsonic acid with concentrated sulfuric acid for ten minutes at 100°. The compound obtained, however, had consistently a melting point of 327–328°. Since Cookson and Mann had reported a melting point of 299°, the product was submitted to further examination. Conversion to 9-chloro- and 9-iodoarsafluorene gave products melting at described temperatures.[2] The neutral equivalent, determined by titration with standard alkali in an alcohol–water medium using phenolphthalein indicator, gave values (260, 259) close to the calculated molecular weight of the compound. Arsenic analysis gave results consistent with the calculated content. Finally, hydrolysis and oxidation of 9-chloroarsafluorene by addition of 30% hydrogen peroxide to the suspension of the compound in hot potassium hydroxide solution gave, on acidification, arsafluorinic acid melting at 328–328.2°. The purity of the compound was then confirmed. Feitelson and Petrow indicate the melting temperature to be above 300°.

A simpler method for preparing the 9-chloro derivative was discovered. It consists in suspending arsafluorinic acid in glacial acetic acid, heating to 80° and adding phosphorus trichloride dropwise with stirring until the arsinic acid dissolves. Cooling effects the separation of 9-chloroarsafluorene in good yield and purity. This procedure was also applied, using chloroform as a solvent and phosphorus tribromide, to prepare for the first time 9-bromoarsafluorene, melting at 178°. Nitration of arsafluorinic acid to give the 2-nitro compound was accomplished by a method very similar to that described by Feitelson and Petrow,[4] but these authors do not comment on the surprising ease of nitration. The reaction is carried out at 5° with little more than the calculated quantity of nitric acid. This facility for nitration is unexpected in view of the electronegativity of the arsinic acid grouping. Dinitration is imminent and is, indeed, readily accomplished under mild conditions.

From the nitroarsinic acid, 2-nitro-9-chloroarsafluorene was prepared by the action of phosphorus trichloride. These haloarsines are useful compounds for purification and characterization since they represent soluble, crystallizable materials with good melting points. In the same way, 3-nitroarsafluorinic acid, obtained by ring closure of 5-nitrobiphenyl-2-arsonic acid, was converted to 3-nitro-9-chloroarsafluorene. Similarly, in the case of intermediates used in ring closing attempts, 5-nitrobiphenyl-2-dichloroarsine and 4'-nitrobiphenyl-2-dichloroarsine were prepared.

Reduction of the 2-nitro compound to the amine was accomplished with alkaline ferrous hydroxide in a manner similar to that already described[4] except that boiling-water temperature was used in the final stage. This amine decomposed without melting and had a clean yellow color instead of the pink color described for it. We suggest that the pink color of the material obtained by Feitelson and Petrow was due to the presence of some dinitroarsafluorinic acid in the starting material since we have obtained a light red product from attempts to reduce the dinitro compound with hot alkaline ferrous hydroxide. In the latter case evidence is incomplete, but our observations are at variance with those of Feitelson and Petrow who claim to have been unable to effect reduction of the dinitro-arsinic acid either with ferrous hydroxide or catalytic hydrogenation. Our light red material is probably not the diamine, but represents at least a partially reduced stage, perhaps the nitroamine.

Experimental

Preparation of Haloarsines. General Procedure.—Approximately 2 g. of the arsonic or arsinic acid was suspended

(1) Abstracted from a thesis presented by I. Victor Mattei in partial fulfillment of the requirements for the Master of Science degree at Xavier University.

(2) J. A. Aeschlimann, N. D. Lees, N. P. McLeland and G. N. Nicklin, *J. Chem. Soc.*, **127**, 66 (1925).

(3) G. H. Cookson and F. G. Mann, *ibid.*, 2888 (1949).

(4) B. N. Feitelson and V. Petrow, *ibid.*, 2279 (1951).

in 10 ml. of either glacial acetic acid or chloroform. The mixture was heated on a water-bath and the appropriate phosphorus trihalide (1–2 ml.) was added dropwise with shaking until the suspension completely dissolved. The solution was warmed 10–15 minutes on the water-bath, filtered, and allowed to cool. The crystalline material depositing was recrystallized, usually from chloroform. In this manner were prepared 9-chloroarsafluorene (I), 9-bromoarsafluorene (II), 2-nitro-9-chloroarsafluorene (III), 3-nitro-9-chloroarsafluorene (IV), 5-nitrobiphenyl-2-dichloroarsine (V) and 4'-nitrobiphenyl-2-dichloroarsine (VI). Details are given in Table I. Melting points were obtained with an aluminum block using a calibrated thermometer. Arsenic analysis was accomplished according to the procedure of Robertson.[5]

TABLE I

PREPARATION OF SOME HALOARSINES

Compound	Reaction solvent[b]	Recrystn. solvent[b]	Yield, %[a]	M.p., °C.	Arsenic, % Calcd.	Found
I	A	B	43.2	160–161	...	...
II	B	B	65.1	174–175	24.48	25.55
III	A	B	79.3	186–187	24.43	24.36
IV	A	B	80.1	199–200	24.43	24.47
V	A	B	70.9	105–106	21.84	21.78
VI	B	C	76.5	81–82	21.84	21.35

[a] Yield calculated from weight of recrystallized product. [b] Key to solvents: A, glacial acetic acid; B, chloroform; C, benzene–petroleum ether.

(5) G. R. Robertson, THIS JOURNAL, **43**, 182 (1921).

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The Preparation of Two Fluorinated *p*-Dihalobenzenes[1]

BY MAX HELLMANN AND ANDREW J. BILBO

RECEIVED MAY 22, 1953

A number of benzene derivatives containing fluorine and other halogens have been reported in the literature.[2] None of these compounds, however, contain two halogen atoms, other than fluorine, in positions para to each other. More recently Finger and co-workers[3] prepared 1,4-dichloro-2,5-difluorobenzene and 1,4-dibromo-2,5-difluorobenzene as the first compounds of this type to be made.

In this paper two new compounds of this series are reported containing one and four fluorine atoms, respectively. They are 1,4-dichloro-2-fluorobenzene, which was prepared from 2,5-dichloroaniline by the Schiemann reaction,[2] and 1,4-dibromo-2,3,-5,6-tetrafluorobenzene, which was obtained by brominating *sym*-tetrafluorobenzene. Finger and his associates had prepared this tetrafluorobenzene but found it relatively resistant to further substitution such as nitration and chlorination.[3] Our attempts to brominate this compound failed under mild conditions, but by using fuming sulfuric acid as a solvent, a good yield of the desired product was obtained. The identity of both new compounds was established by chemical analysis and by their ultraviolet absorption spectra.

(1) This paper is based on work sponsored by the Ordnance Corps, United States Department of the Army.

(2) For references up to 1946 see A. Roe, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 193–228.

(3) G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort and R. R. Blough, THIS JOURNAL, **73**, 145 (1951).

The ultraviolet absorption data of the two new fluorinated *p*-dihalobenzenes and their non-fluorinated analogs are presented in Table I. The shapes of the ultraviolet absorption curves for these new compounds agree with those generally found for aromatic compounds.[4] It is evident from these data that the introduction of fluorine atoms does not affect the main absorption bands appreciably. The secondary bands appear to be intensified in the fluorinated compounds, but they do not show any significant shifts. More detailed data on the ultraviolet absorption spectra of these and other fluorinated benzenes will be published at a later date.

TABLE I

ULTRAVIOLET ABSORPTION DATA

Compound	Primary band Wave length, Å.	Primary band Molar absorbance	Secondary band Wave length, Å.	Secondary band Molar absorbance
			2650	300
1,4-Dichlorobenzene	2248	12,900	2728	390
			2805	330
			2665	780
1,4-Dichloro-2-fluorobenzene	2240	11,400	2718	1080
			2795	1030
			2655	290
1,4-Dibromobenzene	2278	15,500	2733	300
			2821	195
1,4-Dibromo-2,3,5,6-tetrafluorobenzene	2275	18,400	2480	1750
			2700	1100

Experimental

1. **1,4-Dibromo-2,3,5,6-tetrafluorobenzene.**—The bromination was performed in a 100-ml. three-neck flask equipped with a mercury-sealed stirrer, condenser and a dropping funnel. Into this flask 14 ml. of bromine, 15 ml. of 60% fuming sulfuric acid and 0.5 g. of aluminum bromide were introduced. The mixture was stirred and 10 g. of 1,2,4,5-tetrafluorobenzene was added dropwise. An exothermic reaction occurred with the evolution of white fumes. After the addition was completed, the flask was heated in a water-bath at 50–60° for 4 hours. The contents were then carefully poured over cracked ice. The product settled out as a brownish solid which was filtered and washed successively with sodium carbonate, sodium bisulfite and water. It was then recrystallized from a methanol–water mixture and dried at room temperature; yield 16 g. (78%), m.p. 76–77°.

Anal. Calcd. for $C_6F_4Br_2$: F, 24.68; Br, 51.91; mol. wt., 307.9. Found: F, 24.7; Br, 51.7; mol. wt., 296.

2. **1,4-Dichloro-2-fluorobenzene.**—A suspension of 49.6 g. of 2,5-dichloroaniline hydrochloride in 40 ml. of concentrated hydrochloric acid and 80 ml. of water was stirred and cooled to −5°. A solution of 19.7 g. of sodium nitrite in 60 ml. of water was added dropwise while the temperature was maintained at −5°. After the addition was completed, the solution was stirred for 5 minutes. Any solid that remained at this point was removed by filtration at 0°. To the clear filtrate 42 ml. of 40% fluoboric acid was added rapidly. The resulting suspension of the diazonium fluoborate was stirred vigorously at about 5° for 30 minutes and filtered. The precipitate was washed with 25-ml. portions of 5% fluoboric acid, methanol and ether. The salt was then spread out on a large filter paper and dried in air; yield 46.6 g. (72%).

The diazonium fluoborate was decomposed in a system containing two flasks connected by a bent tube of large bore. The salt was introduced into one flask and the other was cooled in an ice-bath. The receiving flask was connected to a trap, cooled in ice, which had an outlet to the hood. The decomposition was performed by intermittent heating with a Bunsen burner until no more white fumes were given

(4) L. Doub and J. M. Vandenbelt, *ibid.*, **69**, 2714 (1947).

off. The product which had collected in the receiving flask and the trap was poured back into the decomposition flask from which it was steam distilled. The distillate was extracted with ether, washed with sodium carbonate and dried over Drierite. After removing the ether, the remaining liquid was distilled under reduced pressure; b.p. 91–92° at 60 mm., 168–169° at 750 mm., m.p. 4°, yield 23.5 g. (80%).

Anal. Calcd. for $C_6H_3Cl_2F$: C, 43.68; H, 1.83; Cl, 42.98. Found: C, 43.7; H, 1.9; Cl, 42.8.

3. **Measurement of Spectra.**—The absorption spectra were determined on solutions in 95% ethanol by means of a Cary Recording Spectrophotometer (Model 12), using 2-cm. matched fused quartz absorption cells against the solvent as reference.

Acknowledgment.—The authors wish to acknowledge the aid of Dr. G. M. Wyman and his associates who made the ultraviolet absorption measurements reported here.

NATIONAL BUREAU OF STANDARDS
WASHINGTON, D. C.

Low Pressure Hydrogenation and Several Properties of Methyl and *n*-Butylketene Dimers[1]

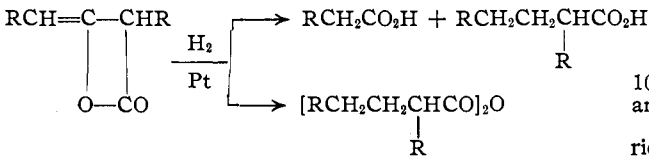
BY CARL M. HILL AND MARY E. HILL

RECEIVED APRIL 7, 1953

It has been demonstrated in this Laboratory that hydrogenation of mono-substituted alkylketene dimers at high pressures and temperatures and in the presence of Raney nickel catalyst produces dialkyl glycols.[2] It was thought profitable to report the response of ketene dimers of this type to hydrogen at low pressures and in the presence of Adams platinum catalyst. It was desired also to study the influence which a reactive solvent might have on the nature of the reduction products.

Treatment of methylketene dimer with hydrogen at 4.8 atm. and in platinum catalyst and petroleum ether gave 2-methylvaleric and propionic acids. Similar results were observed when *n*-butylketene dimer dissolved in petroleum ether was treated with hydrogen at 3.5 atm.

From an experiment in which *n*-butylketene dimer was treated with hydrogen at 3.4 atm. and in acetic acid anhydride, 2-*n*-butyloctanoic acid anhydride and acetic acid were isolated. It is probable that 2-*n*-butyloctanoic acid was formed as an intermediate product but was dehydrated by the acetic anhydride to form 2-*n*-butyloctanoic acid anhydride and acetic acid.



Where R = CH_3 and *n*-C_4H_9.

Experimental[3]

Preparation of Ketene Dimers.—The dimers were prepared by dehydrohalogenation of propionyl and *n*-caproyl chlorides with triethylamine.[4]

Characterization of Ketene Dimers.—Methylketene dimer reacted with concentrated ammonia to yield α-propionylpropionamide, m.p. 83–84° (reported[5] m.p. 82°); with aniline to give α-propionylpropionanilide, m.p. 115–116°; and with water to form diethyl ketone, from which the semicarbazone was prepared. Melting point of the semicarbazone was 135–136°; m.p. of the semicarbazone prepared from an authentic sample of diethyl ketone was 135–136°; mixed m.p. 135–136°. *n*-Butylketene dimer reacted with 15% sodium hydroxide solution to yield di-*n*-amyl ketone, b.p. 225° (755 mm.) and m.p. 14–15°; reported[6] m.p., 14–15°.

Catalytic Hydrogenation of Methylketene Dimer.—A mixture of 5.14 g. (0.04 mole) of methylketene dimer (b.p. 50–52° (9 mm.)) dissolved in 50 ml of petroleum ether and 0.3 g. of platinum oxide was treated with hydrogen at 4.8 atm. for four hours. The catalyst was separated and the solvent removed by distillation. Distillation of the residue from a Claisen flask gave two fractions: propionic acid (9.5%), b.p. 140° (755 mm.), $n^{20}D$ 1.3950, neutral equivalent calcd. for $C_3H_6O_2$: 74, found: 75; and 2-methylvaleric acid (75%), b.p. 88–90° (8 mm.) and 192° (750 mm.), d^{20}_4 0.9309, $n^{20}D$ 1.4170, MR_D (calcd.) 31.45, (found), 31.41, neutral equivalent calcd. for $C_6H_{12}O_2$: 116, found, 115. Reported[7] b.p., d^{20}_4 and $n^{20}D$ of 2-methylvaleric acid are 192–193.6° (748 mm.), 0.9230 and 1.4136, respectively.

Bromination of Methylketene Dimer.—A solution of 6.5 g. of dry bromine in 10 ml. of carbon tetrachloride was added dropwise to a solution of 5 g. of methylketene dimer in 40 ml. of carbon tetrachloride at 0°. Three grams of the reaction product was added slowly to a chilled suspension of 10 ml. of absolute ethanol and 5 g. of pulverized sodium acetate. Removal of the ethanol and distillation of the residue gave 2 g. of product, b.p. 86–88° (4 mm.), d^{20} 1.3200. Saponification equivalent of the product calculated on basis of one ester group and one reactive bromine is 119; found, 119.

Anal. Calcd. for $C_8H_{13}O_3Br$: Br, 33.75. Found: Br, 34.00.

Catalytic Hydrogenation of *n*-Butylketene Dimer.—A mixture of 10.8 g. (0.06 mole) of *n*-butylketene dimer (b.p. 115–116° (4 mm.)) dissolved in 50 ml. of petroleum ether and 0.2 g. of platinum oxide was treated with hydrogen at 3,5 atm. for 45 minutes. Two reduction products were isolated: *n*-caproic acid (22%), b.p. 74–76° (5 mm.), $n^{20}D$ 1.4170 ($n^{20}D$ observed for an authentic sample of *n*-caproic acid, 1.4169), d^{20}_4 0.8580; m.p. of amide 100–101° (reported[8] m.p. for *n*-caproamide 101°), neutral equivalent calcd. for $C_6H_{12}O_2$: 116, found, 111; and 2-*n*-butyloctanoic acid (72%), b.p. 156–158° (7 mm.), d^{20}_4 0.8923, $n^{20}D$ 1.4390, MR_D (calcd.) 59.17, (found) 59.09; neutral equivalent calcd. for $C_{12}H_{24}O_2$: 200, found 197; amide m.p. 108–109°; m.p. of the amide prepared from an authentic sample of 2-*n*-butyloctanoic acid, 108–109°; mixed m.p. 107–108°.

Catalytic hydrogenation of this dimer was repeated using 8.5 g. (0.04 mole) of the dimer, 0.15 g. of platinum oxide, 30 ml. of pure acetic acid anhydride and 3.4 atm. of hydrogen pressure. The theoretical amount of hydrogen was absorbed within 15 minutes. Products isolated were: 2-*n*-butyloctanoic acid anhydride (73%), b.p. 175–177° (3 mm.), d^{20}_4 0.8913, $n^{20}D$ 1.4440, equivalent weight calcd. for $C_{24}H_{46}O_3$: 191, found 197; and 2 g. of acetic acid. The 2-*n*-butyloctanoic anhydride was further identified by treatment with concentrated ammonia. This gave 2-*n*-butyloctanoamide, m.p. 108–109°, mixed m.p. 107–108°; and 2-*n*-butyloctanoic acid, b.p. 134–135° (4 mm.); amide m.p. 107.5–108.5°.

Reaction of *n*-Butylketene Dimer with Hydrogen Chloride.—Dry hydrogen chloride gas was bubbled through 3 g. of *n*-butylketene dimer at 0° for 2 hours. Distillation of the product gave 1 g. of α-caproylacaproyl chloride boiling at 198–200° (4 mm.).

Anal. Calcd. for $C_{12}H_{21}O_2Cl$: Cl, 15.23. Found: Cl, 15.32.

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(1) The experimental portion of this paper is based largely on the doctoral thesis, "Studies of Ketenes and Their Derivatives," of C. M. Hill, Cornell University, 1941.

(2) C. M. Hill, M. E. Hill, H. I. Schofield and L. Haynes, THIS JOURNAL, **74**, 166 (1952); C. M. Hill, L. Haynes and M. E. Hill, *ibid.*, 3423 (1952).

(3) All melting points are corrected.

(4) J. C. Sauer, THIS JOURNAL, **69**, 2444 (1947).

(5) H. Pingel, *Ann.*, **245**, 87 (1888).

(6) R. R. Briese and S. M. McElvain, THIS JOURNAL, **55**, 1698 (1933).

(7) M. Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933).

(8) I. Simon, *ibid.*, **38**, 47 (1929).

Methoxyindan and Methoxytetralin Esters[1]

BY E. C. HORNING AND G. N. WALKER[2]

RECEIVED APRIL 10, 1953

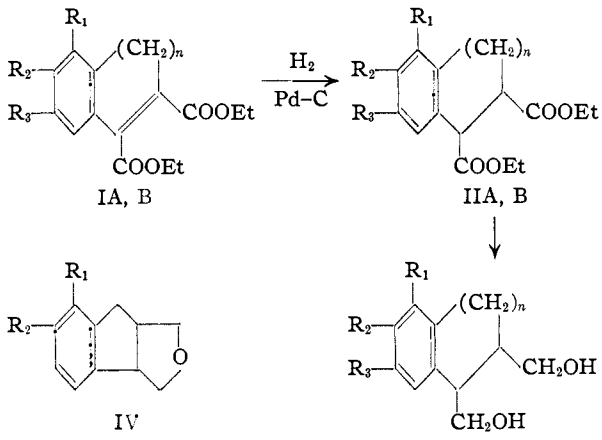
In the course of studying colchicine and its degradation products, several methoxyindene, methoxydihydronaphthalene and methoxybenzsuberene derivatives were prepared through the glyoxylate cyclization method. These compounds were bicyclic systems in which the B-ring was five, six or seven-membered, and the two acid groups were in the same relative position in each case. A route was sought for the introduction of a C-ring, using as a starting point 1,4-diols derived from these materials.

Compound IA and an acid–ester corresponding to IA were prepared as described earlier.[3] Compound IB was prepared by the polyphosphoric acid cyclization of the glyoxylate derived from ethyl γ-(3,4-dimethoxyphenyl)-butyrate. The sole product of the cyclization (in 92% yield) was the diester IB. This may be compared with the effect produced by the use of concentrated sulfuric acid in the cyclization; under such circumstances the product is the corresponding anhydride. This again demonstrates that polyphosphoric acid is capable of inducing glyoxylate cyclizations without transesterification or hydrolysis of the ester group.

The unsaturated esters IA and IB, as well as the acid–ester related to IA, were hydrogenated with ease (5% palladium–carbon catalyst). A related benzsuberan, 2,3,4-trimethoxybenzsuberan-5,6-dicarboxylic acid, was obtained by the catalytic reduction of a synthetic sample of 2,3,4-trimethoxybenzsuber-5-ene-5,6-dicarboxylic anhydride, followed by hydrolysis of the anhydride group. This seven-membered dicarboxylic acid may be converted to its anhydride by heating with acetic anhydride, but the acid is quite stable. This behavior may be contrasted with that of the corresponding seven-membered dicarboxylic acid containing a 5,6-double bond; this acid is unknown owing to its ready dehydration to form the corresponding anhydride.

With these materials as possible starting points, model experiments were carried out with IIA and IIB for the next step. Lithium aluminum hydride reduction in both cases gave the expected 1,4-diol, IIIA and IIIB. Compound IIIA was chosen for further model experiments directed to the lengthening of the carbon chains for C-ring formation. With phosphorus tribromide, a halogen-containing intermediate was formed, but attempts to use this product in alkylation reactions or in reaction with sodium cyanide gave in each case a neutral crystalline solid corresponding in properties and analysis to the tricyclic ether IV. While this was an interesting result, it was not in the desired direction, and this phase of the work was discontinued.

Acknowledgment.—We are indebted to Mrs. Sarah M. Woods for the analytical data.



A: R_1, R_2 = OCH_3; R_3 = H; n = 1
B: R_2, R_3 = OCH_3; R_1 = H; n = 2

Experimental[4]

Diethyl 6,7-Dimethoxy-3,4-dihydronaphthalene-1,2-dicarboxylate.—A mixture of 2.0 g. of glyoxylate (prepared from the condensation of ethyl oxalate with ethyl γ-(3,4-dimethoxyphenyl)-butyrate in ether with sodium ethoxide, 81% yield) and 8 g. of polyphosphoric acid was stirred vigorously. When the warm solution cooled to room temperature (10 minutes), the mixture was treated with ice and water and the product was extracted with ethyl acetate. The chilled extract was washed in turn with 5% sodium hydroxide solution, water, 5% acetic acid solution and 5% sodium bicarbonate solution. Evaporation of the solvent, after drying, gave 1.7 g. (92%) of crude crystalline ester. Recrystallization from methanol gave pale yellow crystals, m.p. 103–105°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.61; H, 6.61.

Hydrolysis of the diester with 15% sodium hydroxide solution (two hours at 95–100°), followed by dilution and acidification gave a yellow solution which on heating deposited red crystals of the anhydride, m.p. 192–193°, in agreement with the literature.

Catalytic Reductions.—Hydrogenation of IA[3] in ethyl acetate with a 5% palladium–carbon catalyst proceeded smoothly at room temperature under low pressure (30–40 lb.) to yield (quantitative) **1,2-dicarbethoxy-4,5-dimethoxyindan** as an oil. This ester was not characterized but was used immediately for further reaction. The reduction of an acid-ester corresponding to IA, prepared as described previously,[3] was carried out in the same way in acetic acid solution. The product in this case was 1-carboxy-2-carbethoxy-4,5-dimethoxyindan (based on the most probable structure for the acid-ester precursor) as a colorless solid, m.p. 149–151° (from methanol) (*Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.16. Found: C, 61.29; H, 6.09). The diester IB was hydrogenated in ethyl acetate solution in the same way as IA; the product was **1,2-dicarbethoxy-6,7-dimethoxytetralin**, as a colorless solid, m.p. 73–74.5° (from ether) (*Anal.* Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.48; H, 6.87). A sample of synthetic 2,3,4-trimethoxybenzsuber-5-ene-5,6-dicarboxylic anhydride[5] was hydrogenated in ethyl acetate solution at 60°; the crude product was hydrolyzed with hot sodium hydroxide solution, and after acidification there was isolated **2,3,4-trimethoxy-5,6-dicarboxybenzsuberan** as a colorless solid, m.p. 188–189.5° (from aqueous methanol). (*Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.10; H, 6.33.) From this acid by heating with acetic anhydride there was obtained the corresponding anhydride, **2,3,4-trimethoxybenzsuberan-5,6-dicarboxylic anhydride**, as a colorless solid, m.p. 176–178.5° (from ethyl acetate). (*Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.73; H, 5.92. Found: C, 63.00; H, 5.88.)

1,2-Di-(hydroxymethyl)-4,5-dimethoxyindan.—A solution of 47.2 g. of 1,2-dicarbethoxy-4,5-dimethoxyindan in

(1) Supported in part by a grant-in-aid from the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

(2) From the doctoral thesis of G. N. Walker submitted to the Graduate School of the University of Pennsylvania.

(3) E. C. Horning, J. Koo and G. N. Walker, THIS JOURNAL, **73**, 5826 (1951).

(4) All melting points are corrected.

(5) E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker, G. N. Walker, R. Horowitz and G. E. Ullyot, *ibid.*, **72**, 4840 (1950).

400 ml. of dry ether was added dropwise to a stirred mixture of 15.0 g. of lithium aluminum hydride in 400 ml. of ether over one hour. After stirring for an additional half-hour, the mixture was chilled and treated with water and dilute sulfuric acid. The product was isolated in the usual way as a crude red oil. Trituration with ether with chilling gave 29.1 g. (84%) of nearly colorless crystalline product. Recrystallization from water provided a colorless analytical sample, m.p. 100–102°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.64; H, 7.56.

The same diol was obtained in 38% yield by the lithium aluminum hydride reduction of the monoethyl ester of 1,2-dicarboxy-4,5-dimethoxyindan. To determine whether a different stereochemical configuration would result when a chemical reduction was carried out with 1,2-dicarbethoxy-4,5-dimethoxyindan, the following experiment was performed. A 5.0-g. quantity of IA was reduced with zinc dust in 20 ml. of aqueous acetic acid (2:1 aq.) at 95–100°. The neutral product, 4.4 g. of oil, was reduced with lithium aluminum hydride (2.0 g.) in 250 ml. of ether. The product was identical with that obtained from IIA; a mixed melting point was not depressed.

1,2-Di-(hydroxymethyl)-6,7-dimethoxytetralin.—The reduction of 4.0 g. of 1,2-dicarbethoxy-6,7-dimethoxytetralin with 2.1 g. of lithium aluminum hydride in dry ether yielded 2.3 g. (77%) of colorless crystalline product (by trituration with ether). An analytical sample was secured by recrystallization from water; m.p. 127–128.5°.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.34; H, 7.82.

6,7-Dimethoxy-3,3a,8,8a-tetrahydroindeno(1,2-c)furan (*R.I. 1437*).—Treatment of 5.0 g. of 1,2-di-(hydroxymethyl)-4,5-dimethoxyindan with 20.5 g. of phosphorus tribromide in 75 ml. of dry benzene under reflux for 45 minutes gave a neutral oil (2.5 g.) as a product. This material gave an immediate precipitate with alcoholic silver nitrate solution. Numerous efforts were made to replace the halogen by reaction under standard conditions with sodium cyanide and with ethyl malonate. In each case the product was a colorless crystalline solid, m.p. 82–83.5° (from ether). This material was halogen-free; it did not react with bromine or potassium permanganate solutions, and was recovered unchanged after refluxing with 25% potassium hydroxide solution. From these properties and the analytical data, structure IV was assigned to this material.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.51; H, 7.28.

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Substitution in Polymethylbenzenes. III. A New Route to Isodurene Derivatives[1]

BY GABRIELLO ILLUMINATI AND GIANLORENZO MARINO

RECEIVED MAY 5, 1953

In connection with kinetic studies now in progress on hindered nitrohydrocarbons, we have found that 4-nitroisodurene[2] can be obtained by reduction of 4,6-dinitroisodurene and subsequent deamination of the resulting 4-nitro-6-aminoisodurene by the method previously described[3] for the preparation of 3-nitrodurene,

4,6-Dinitroisodurene has been reported by a number of early workers,[4] but the melting point given by Jannasch and Weiler, 180–181°, is different from the values ranging from 156 to 165°, given by the other authors, and appears never to have been duplicated. We have nitrated isodurene in chloroform solution with nitric acid in sulfuric acid under essentially the same conditions as for the nuclear nitration of durene.[1] Our results are in good agreement with those of Jannasch and Weiler.

Since pure isodurene is not a readily available compound,[5] we have also tried to prepare 4,6-dinitroisodurene from other sources. Smith and Cass[6] have shown that the tetramethylbenzene fraction obtained from the distillation of the product of methylation of xylene is a mixture of durene and isodurene, from which most of the durene can be frozen out. Thermal analysis of the system durene–isodurene[5a] shows that at the eutectic point, −28.1°, the system contains only 8% of durene. Smith and Taylor[7] have already used isodurene-rich mixtures for the preparation of isodurene compounds, by mercuration of the mixture and purification of the acetoxymercuriisodurene thus obtained by differential crystallization. We have found that on nitration of a durene–isodurene mixture with a composition close to the one corresponding to the eutectic point, a crude 4,6-dinitroisodurene is obtained which can be purified by only three crystallizations from ethanol. The yield of the dinitro compound, m.p, 181.5–183.5°, was 43% based on the isomeric starting material. Since preliminary experiments with identical samples of isodurene-rich isomeric mixtures indicated that nitration was a more reliable route than mercuration for the preparation of certain isodurene derivatives, 4,6-dinitroisodurene, rather than 4-acetoxymercuriisodurene, was chosen as the starting material for the preparation of 4-nitroisodurene.

On reduction of 4,6-dinitroisodurene by sodium disulfide we have obtained pure 4-nitro-6-aminoisodurene in quantitative yields. The latter compound, m.p. 139.5–140.5°, proved to be different from the product obtained by Noelting and Stoecklin,[8] m.p. 87–88°, on nitration of isoduridine and described as nitroaminoisodurene. Noelting and Stoecklin reported results of analyses but gave no proof of structure for their product. Since nitration of polymethylbenzenes often led to side-chain substitution depending on experimental conditions[9] and nitration of arylamines may give arylnitramines,[10] the compound of Noelting and Stoecklin could be either a ω-nitroisoduridine or isodurylnitramine. On the other hand, the structure of the compound described in this paper as 4-nitro-6-aminoisodurene appears to be conclusively established both by the specific method of preparation used here and by its deamination to 4-nitroisodurene.

Crude, low-melting 4-nitroisodurene was effectively decolorized and purified with the least loss

(1) Part II of this series: G. Illuminati and M. Palmucci Illuminati, THIS JOURNAL, **75**, 2159 (1953).

(2) L. I. Smith and F. L. Taylor, *ibid.*, **57**, 2460 (1935).

(3) G. Illuminati, *ibid.*, **74**, 4951 (1952).

(4) E. Ador and A. Rilliet, *Ber.*, **12**, 329 (1879); O. Jacobsen, *ibid.*, **15**, 1853 (1882); W. R. Orndorff and Young, *Am. Chem. J.*, **15**, 267 (1890); P. Jannasch and M. Weiler, *Ber.*, **27**, 3441 (1894).

(5) (a) L. I. Smith and F. H. MacDougall, THIS JOURNAL, **51**, 3001 (1929); (b) S. F. Birch, R. A. Dean, F. A. Fidler and R. A. Lowry, *ibid.*, **71**, 1362 (1949); (c) C. D. Shacklett and H. A. Smith, *ibid.*, **73**, 766 (1951); (d) D. A. McCaulay and A. P. Lien, *ibid.*, **74**, 6246 (1952).

(6) L. I. Smith and O. W. Cass, *ibid.*, **54**, 1609 (1932).

(7) L. I. Smith and F. L. Taylor, *ibid.*, **57**, 2370 (1935).

(8) E. Noelting and L. Stoecklin, *Ber.*, **24**, 564 (1891).

(9) R. Willstätter and H. Kubli, *ibid.*, **42**, 4151 (1909).

(10) See, for example, W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1948, p. 320.

of material by chromatographic adsorption on alumina.

Experimental[11]

Materials.—Pure isodurene was prepared according to Smith's method.[12] On careful fractionation of the product through a Fenske column, the middle fraction, b.p. 195.5–195.6°, $n^{20}D$ 1.5130, was collected and used for nitration.

The isodurene-rich isomeric mixture used as a convenient starting material for the preparation of large amounts of 4,6-dinitroisodurene was obtained by submitting the tetramethylbenzene filtrate, after separation of durene in the usual manner[13] to a number of further freezing processes each followed by centrifugation with an International Equipment Co. refrigerated centrifuge at successively lower equilibrium temperatures down to −23°. After each centrifugation, the equilibrium liquid was separated from the solid (durene) by filtration, except for the last two processes at −20 and −23°, respectively, in which the equilibrium liquid was decanted. The clear liquid thus obtained was directly used for nitration. From 130 g. of starting tetramethylbenzene filtrate, 95 g. of such a liquid was obtained.

Nitration Experiments.—These experiments were carried out in essential accordance with the procedure described in Part II,[1] with the exception of the mode of addition of the nitrating reagent. In the present work, better results were obtained when a solution of nitric acid in 98% sulfuric acid was prepared first and then added to the chloroform solution of the hydrocarbon.

(a) **Nitration of Isodurene.**—On dinitration of 1.005 g. of isodurene (0.0075 mole) with a stoichiometric amount of nitric acid, 1.31 g. of crude 4,6-dinitroisodurene was obtained. After two crystallizations from ethanol, the yield was 0.95 g. (57.5%) of white needles, m.p. 181.5–183.5°. After two further crystallizations, a constant melting point value of 182.5–183.5° was observed.

Unlike durene[1] and prehnitene,[14] isodurene shows no sharp color change at the end of the reaction with a stoichiometric amount of nitric acid.

(b) **Nitration of the Isodurene-rich Isomeric Mixture.**—A four-batch dinitration of 20.0 g. of the isodurene-rich isomeric mixture, obtained at −23° as described above, was carried out with a stoichiometric amount of nitric acid in a straight-wall beaker of 15-cm. height and 4-cm. width, to give a combined yield of 25.9 g. of crude product, m.p. 160–175°. After three crystallizations from ethanol, the yield of 4,6-dinitroisodurene was 14.4 g. (43%), m.p. 181.5–183.5°.

4-Nitro-6-aminoisodurene.—To a boiling solution of 14.4 g. of 4,6-dinitroisodurene (0.064 mole) in 400 ml. of ethanol, a solution of sodium disulfide (prepared from 50 g. of crystalline sodium sulfide and 6.5 g. of sulfur in 145 ml. of water) was gradually added. The mixture was refluxed for an over-all time of five hours; then most of the alcohol was removed by distillation and the residue was poured into ice water. After filtration, the collected product was dissolved in hot 10% hydrochloric acid and the resulting solution was filtered, if necessary. This solution was made alkaline by gradual addition of concd. ammonia, and the product which separated was collected by filtration and dried. A beautiful yellow powder, m.p. 139.5–140.5°, was obtained; the yield was 12.1 g. (97.5%).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.51; H, 7.65; N, 14.49.

4-Nitroisodurene.—4-Nitro-6-aminoisodurene was diazotized and the resulting diazo-salt was treated with 50% hypophosphorous acid according to the procedure previously described for the corresponding durene compound.[3] The reaction mixture was kept in ice water for a fortnight and, after filtration, the collected product was thoroughly mixed with chloroform. The chloroform solution thus obtained was filtered from any inorganic material left behind and then worked up in the usual manner.[3] From 7.77 g. of nitroamino compound (0.040 mole), 5.37 g. of a crude, brown-yellow product was obtained. For decolorization and purification, the latter was dissolved in 90 ml. of dry petroleum ether (b.p. 40–60°), and the resulting solution was applied on a column of 90 g. of alumina for adsorption. Elution was continued with a 5% solution of absolute ethanol in dry petroleum ether until a brown-yellow band due to impurities reached the bottom of the column. On evaporation of the combined elution liquids, a very pale-colored crystalline residue of 5.18 g. (72.2%) of 4-nitroisodurene, m.p. *ca.* 40°, was obtained. On recrystallization from methanol, the melting point raised to 41–42°.

With only a small percentage decrease in the final yield, the reduction of the diazo-salt can be made faster by keeping the reaction mixture at room temperature for two days or so.

Acknowledgments.—The authors are very grateful to Prof. V. Caglioti for encouragement. Thanks are also due to the Humble Oil and Refining Co., Baytown, Texas, for the generous gift of a large sample of tetramethylbenzene filtrate in a later part of the present work.

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(11) All melting points are uncorrected.

(12) L. I. Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 360.

(13) Reference 12, p. 248.

(14) Unpublished studies.

Density and Refractive Index of Uranyl Fluoride Solutions[1]

BY JAMES S. JOHNSON AND KURT A. KRAUS

RECEIVED APRIL 8, 1953

In the course of an ultracentrifugal investigation of uranyl fluoride solutions, their densities and refractive indices were measured as a function of concentration.

The measurements were carried out near 25 and 30° and if necessary extrapolated to 25.0 and 30,0° from the observed temperature coefficients. Most density data were obtained pycnometrically (25-cc. samples) and a few with gradient tubes.[2] The refractive index measurements were carried out with a Bausch and Lomb dipping refractometer (calibrated with "known" solutions) using sodium-D light (reproducibility ±0.00004),

The materials used and the analytical procedures were described earlier.[3] Although the accuracy of the density measurements was approximately one part in 10,000, the accuracy of the determinations at high UO_2F_2 concentration is considerably less, in view of the uncertainty in the uranium analyses (±0.2% in the uranium concentration).

1. **Density.**—The density data, which are listed in Table I, could be fitted to the quadratic equation

$$1/d = 1/d_0 + aF_2 + bF_2^2 \qquad (1)$$

where d is the density of the solution, d_0 the density of the pure solvent and F_2 the weight fraction of UO_2F_2. The empirical constants a and b were obtained from the intercept and slope of a plot of $(1/d - 1/d_0)/F_2$ *vs.* F_2, which is a straight line. At 25°, $a = -0.9120$ and $b = 0.0567$ and at 30°, $a = -0.9126$ and $b = 0.0569$ give satisfactory fit as shown in Table I. Dean[4] earlier measured densities of UO_2F_2 solutions in the range 13 to 66

(1) This document is based on work performed for the Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) (a) K. Linderstrom-Lang and H. Lanz, *Compt. rend. trav. lab. Carlsberg*, **21**, 315 (1938); (b) C. Anfinsen, "Preparation and Measurement of Isotopic Tracers," J. Edwards, Ann Arbor, Michigan, 1947, p. 61.

(3) J. S. Johnson and K. A. Kraus, THIS JOURNAL, **74**, 4436 (1952).

(4) G. R. Dean, Report CC 2092, September, 1944.

TABLE I

DENSITY AND REFRACTIVE INDEX OF URANYL FLUORIDE SOLUTIONS

Wt. % UO_2F_2	Density 25° d	Density 25° $\Delta d^a \times 10^4$	Density 30° d	Density 30° $\Delta d^a \times 10^4$	Refractive index 25° $n^{25}D$	Refractive index 25° $\Delta n^a \times 10^5$	Refractive index 30° $n^{30}D$	Refractive index 30° $\Delta n^a \times 10^5$	Mole refraction (cc.) (25°)
1.002					1.33319	−1	1.33266	−4	17
2.495	1.0202[b]	0			1.33417	0	1.33366	−5	17.0
4.985	1.0443	0	1.0429	0	1.33586	0	1.33531	−2	17.0
5.025	1.0448	−1			1.33597	−8			17.1
7.481					1.33764	−2	1.33705	−2	17.1
9.607					1.33925	−10	1.33864	−7	17.2
10.20	1.0983	0	1.0967	0	1.33963	−5	1.33907	−7	17.1
15.01					1.34333	−6	1.34275	−7	17.04
20.09	1.2164	+2	1.2146	0	1.34756	−5	1.34692	−2	17.09
20.48	1.2219[b]	−2			1.34788	−2	1.34721	+3	17.01
24.89					1.35188	−1	1.35114	+9	17.06
30.10	1.3632	0			1.35705	0			17.09
30.18	1.3632	+13	1.3607	+15	1.35705	+6	1.35636	+11	17.21
33.39					1.36059	+1	1.35988	+5	17.09
40.30	1.5509	+4	1.5481	+6					
40.27					1.36888	−5	1.36825	−9	17.14
46.36					1.37726	−1	1.37647	+6	17.15
50.27	1.7893	+2	1.7859	+1	1.38316	+14	1.38239	+18	17.13
50.90					1.38439	−5	1.38370	−11	17.15
56.90					1.39503	+1	1.39418	+10	17.13
57.10					1.39542	0	1.39457	+9	17.13
61.12					1.40392	−26	1.40303	−15	17.14
61.63	2.1627	−1	2.1589	−15	1.40475	+2	1.40407	−9	17.11

[a] Δd and Δn are the differences: calculated values minus experimental values. [b] Measured by gradient tube method.

weight per cent. His densities agree with those calculated by equation 1 to *ca.* 0.1% except for the saturated solution, where his points scatter considerably more. Since his densities are reported to four significant figures, the agreement clearly is within his experimental error and indicates that there is no systematic error in the uranium analyses.

Assuming that the density of uranyl fluoride solutions follows equation 1, the apparent molal volume ϕ_v at 25° was computed by the equation

$$\phi_v = M_2(1/d_0 + a + bF_2) = 308.07(0.0909 + 0.0567F_2) = 28.0 + 17.5F_2 \quad (2)$$

where $M_2 = 308.07$ is the molecular weight of uranyl fluoride.

Since it had been shown earlier[3,5] that uranyl fluoride in the concentration range studied does not appreciably dissociate into ions (*i.e.*, essentially is a non-electrolyte under these conditions), the large variation of ϕ_v with concentration is surprising. For non-electrolytes ϕ_v would have been expected to change little with concentration.[6] It is of interest that extrapolation of ϕ_v to $F_2 = 1$ yields $\phi_v = 45.5$ cc. which may be compared with the molal volume $V = 48.3$ cc. of solid UO_2F_2 which was calculated from the crystallographic value of the density ($\rho = 6.38$).[7]

2. Refractive Index.—The results of the refractive index measurements are also listed in Table I. The refractive indices were fitted to the equation

$$n^t_D = n^{\circ t}_D + \alpha c + \beta c^{3/2} \quad (3)$$

where c is the concentration (molarity), α and β are constants, and where n^t_D and $n^{\circ t}_D$ are the measured refractive indices of the solutions and of water at temperature t, respectively. Satisfactory fit of the data to equation 3 was obtained at 25° using $\alpha = 0.02055$ and $\beta = -0.00185$ and at 30° using $\alpha = 0.02049$ and $\beta = -0.00183$. The deviations between experimental and calculated values are shown in Table I. It is believed that the scatter is due, to a large extent, to the inaccuracies in the analyses of the uranium solutions.

Values of the mole refraction (R) of UO_2F_2 were calculated according to the equation[8]

$$R = \frac{(n^2-1)}{(n^2+2)} \times \frac{1}{d}\left(\frac{1000}{m} + M_2\right) - \frac{(n^0)^2-1}{(n^0)^2+2} \times \frac{1}{d_0} \times \frac{1000}{m} \quad (4)$$

where m is the molality of the solution. The results of the calculations are also listed in Table I. Within the accuracy of the data, R appears to be constant ($R = 17.1 \pm 0.1$ cc.) and hence does not reflect the considerable change in the degree of dimerization of uranyl fluoride which occurs in this concentration range.

(5) J. S. Johnson and K. A. Kraus, unpublished.

(6) See for example, H. S. Harned and B. B. Owen, "Electrolytic Solutions," Second Edition, Reinhold Publ. Corp., New York, N. Y., 1950, p. 260.

(7) W. H. Zachariasen, *Acta Cryst.*, 1, 277 (1948).

(8) W. Geffcken, *Z. physik. Chem.*, B**5**, 81 (1929).

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Preparation of β-H-Perfluoro Alkanesulfonic Acids

BY R. J. KOSHAR, P. W. TROTT AND J. D. LAZERTE

RECEIVED JUNE 1, 1953

The synthesis of β-H-perfluoroethanesulfonic acid by the reaction of sodium bisulfite with tetrafluoro-

TABLE I

β-H-PERFLUORO ALKANESULFONIC ACIDS

Sulfonic acid	Conv.,[a] %	Yield, %	B.p. °C.	B.p. Mm.	Neut. equiv. Calcd.	Neut. equiv. Found	Anal. of sodium salt: Na, % Calcd.	Na, % Found	S, % Calcd.	S, % Found
$CF_3CFHCF_2SO_3H$	93	64	111–113	20	232	228	..	..	..	..
$C_3F_7CFHCF_2SO_3H$	83	79	119–120	14	332	317	6.50	6.55	9.04	9.19
$C_5H_{11}CFHCF_2SO_3H$	74	73	119–120	3	432	415	5.07	5.25	7.05	7.21

[a] Based on olefin reacted.

ethylene has been reported by Barrick.[1] Several higher molecular weight β-H-perfluoro alkanesulfonic acids have now been prepared in good yield by the reaction of sodium bisulfite with perfluoropropene, perfluoropentene-1 and perfluoroheptene-1. A summary of the preparation and properties of these sulfonic acids is presented in Table I.

These sulfonic acids are viscous liquids, soluble in both water and diethyl ether. They are very hygroscopic and form solid hydrates when exposed to moist air. They are strong acids as indicated by their reaction with NaCl to liberate HCl. The acids as well as their sodium salts are highly surface active in aqueous media, *e.g.*, a solution containing 1% by weight of $C_5F_{11}CFHCF_2SO_3H$ gave a surface tension of 38 dynes per centimeter at 25°. A preliminary investigation was made into the thermal and hydrolytic stability of the sodium salts. The dry salts are thermally stable up to 350° but undergo extensive decomposition in aqueous base at about 250°.

Experimental

Perfluoropropene, perfluoropentene-1 and perfluoroheptene-1 were prepared by the method of Hals, Reid and Smith.[2] Preparation of the β-H-perfluoro alkanesulfonic acids was carried out according to the following typical experiment: A mixture of 90 g. (0.6 mole) of perfluoropropene, 60 g. (0.5 mole) of sodium bisulfite, 27.4 g. of borax, 120 cc. of water and 0.8 g. of benzoyl peroxide was charged to a stainless steel autoclave. The contents of the autoclave were heated with agitation at 110–120° for nine hours. Ten grams of unreacted perfluoropropene was bled from the autoclave at room temperature. The reaction mixture was then evaporated to dryness and the resulting salts extracted with hot ethanol. There was isolated 115 g. of crude ethanol-soluble $CF_3CFHCF_2SO_3Na$. About 100 g. of this vacuum-dried salt was mixed with 150 g. of 95% H_2SO_4 and 40 g. of SO_3 (Sulfan β), and distilled under reduced pressure. Fractionation of the distillate gave 68 g. of $CF_3CFHCF_2SO_3H$ boiling at 111–113° (20 mm.).

(1) P. L. Barrick, U. S. Patent 2,403,207 (July 2, 1946).

(2) L. J. Hals, T. S. Reid and G. H. Smith, THIS JOURNAL, **73**, 4054 (1951).

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A Convenient Synthesis of 2-β-Hydroxyethylaminofluorene[1]

BY EUGENE SAWICKI

RECEIVED MAY 11, 1953

The literature contains a method for the preparation of 2-β-hydroxyethylaminofluorene,[2,3] but it is troublesome and gives a poor yield of product. It has now been found that the compound can be obtained readily in high yield by the decomposition of β-chloroethyl N-2-fluorenylcarbamate in alkaline solution.

The infrared spectra of β-chloroethyl N-2-fluorenylcarbamate (I), 3-(2′-fluorenyl)-2-oxazolidone (II), 2-β-hydroxyethylaminofluorene (III) have been determined. The carbonyl band of II lies at 5.76μ while that of the starting carbamate lies at 5.72μ. As II has no O–H or N–H stretching vibration bands, the structure assignment of the compound as an oxazolidone is substantiated. III has no C=O stretching vibration band but has N–H and O–H bands at 2.93 and 2.77 μ, respectively. The starting carbamate has a N–H band at 2.90μ. This substantiates the structure of III as 2-β-hydroxyethylaminofluorene.

Experimental[4]

β-Chloroethyl N-2-Fluorenylcarbamate.—To an ice-cold stirred solution of 1.81 g. of 2-aminofluorene[5] in 10 ml. of pyridine was added dropwise 1.1 ml. of β-chlorethyl chlorocarbonate. The solution was stirred an additional half hour at 0–10° and then poured into 200 ml. of cold 25% sulfuric acid. An oil was formed which solidified after two hours. Crystallization from heptane gave 2.73 g. (95% yield) of colorless microneedles, m.p. 134–134.5°.

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.67; H, 4.86. Found: C, 67.05; H, 5.09.

3-(2′-Fluorenyl)-2-oxazolidone.—A solution of 1.6 g. of potassium hydroxide in 40 ml. of ethanol was added to 2.88 g. of β-chloroethyl N-2-fluorenylcarbamate dissolved in 150 ml. of hot ethanol. The stirred solution remained clear for a short time and then a thick crystalline precipitate was formed. The stirred mixture was immediately cooled to room temperature. Stirring was continued for an additional half hour. Excess water was added and then the white crystalline precipitate was filtered. Crystallization from methyl cellosolve gave 2.38 g. (95% yield) of colorless plates, m.p. 239–240°.

Anal. Calcd. for $C_{16}H_{13}NO_2$: N, 5.58. Found: N, 5.88.

2-β-Hydroxyethylaminofluorene.—A solution of 3.2 g. of potassium hydroxide in 80 ml. of ethanol was added to a hot solution of 2.88 g. of β-chloroethyl N-2-fluorenylcarbamate in 40 ml. of ethanol. A thick crystalline precipitate of the oxazolidone was formed which dissolved with decomposition on refluxing vigorously for two hours. Three-fourths of the alcohol was distilled off. Excess water was added to the residue. Crystallization from hexane gave 2.0 g. (89% yield) of colorless plates, m.p. 148–149°. Davis, *et al.*,[3] reported yellow plates, m.p. 150°.

Acknowledgment.—The author is indebted to Dr. Francis E. Ray for his encouragement and interest in this work and to Miss Mary Louise Van Natta of the Chemistry Department of the University of Florida for determining the infrared spectra.

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(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).

(3) W. Davis, J. L. Everett and W. C. J. Ross, *ibid.*, 1331 (1950).

(4) All melting points are uncorrected. Infrared absorption spectra were measured with a Perkin-Elmer Model 21 Infrared Spectrophotometer.

(5) W. E. Kuhn, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 448.

β-Bromo-α-chloro-β-formylacrylic Acid

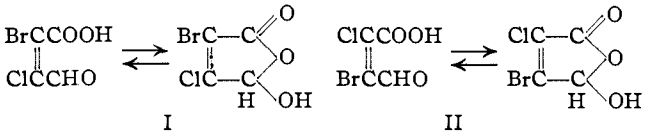
BY E. KUH AND R. L. SHEPARD

RECEIVED FEBRUARY 25, 1953

The method described by Simonis[1] of treating furfural with an excess of bromine in aqueous solution to obtain mucobromic acid is useful for the preparation of small quantities of that compound for laboratory purposes. On a larger scale, however, this procedure is inconvenient not only because of the large quantity of bromine used, but also because it has to be added all at once in spite of the exothermic character of the reaction. To arrive at a practical procedure for larger quantities we tried using an amount of bromine just in excess of the one-mole equivalent that appears in the final compound and then employing chlorine to regenerate bromine from the hydrobromic acid formed in the course of the reaction, thus making it available for further bromination of furfural.

In carrying out this procedure we obtained in almost quantitative yield, not the expected mucobromic acid, but a compound with similar properties and a molecular weight of 213, microanalysis of which showed it to be a bromochloroformylacrylic acid.

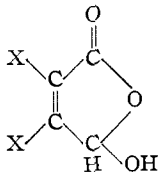
An acid of the same empirical formula had been obtained previously by Hill[2] in very small quantity in a tedious way. Starting with ethyl tetrachlorotetrahydrofuroate, he obtained 4,5-dichlorofuroic acid from a fraction of the pyrogenically decomposed ester.[3] By reducing this compound to 4-chlorofuroic acid and oxidizing the latter with bromine in aqueous solution, he obtained what he called mucochlorobromic acid and assigned to it the formula of α-bromo-β-chloro-β-formylacrylic acid (I).



I II

Using this procedure of Hill, we obtained only traces of his acid until we followed the advice of Vander Wal[4] to use 3,4-dichloro-2-furoic acid instead of 4,5-dichloro-2-furoic acid to make 4-chloro-2-furoic acid. It was then an easy task to obtain reasonable quantities of I and to compare it with the acid formed in our reaction. It was essential to have more material than could be obtained by Hill's procedure because the melting and mixed melting point did not serve to distinguish or to identify the two products. The infrared absorption spectra, however, showed that the two acids are different compounds and indicated that we had obtained β-bromo-α-chloro-β-formylacrylic acid (II).

The infrared spectra of mucochloric and mucobromic acids, which were included for comparison, show clearly that each exists, not as an open chain formylacrylic acid, but in the form of a ring as



Neither acid shows any acid carbonyl absorption around 1700 cm.$^{-1}$ but rather each has carbonyl absorptions characteristic of strained ring carbonyls; mucobromic acid a singlet at 1767 cm.$^{-1}$ and mucochloric acid a doublet at 1770 and 1782 cm.$^{-1}$ (see Fig. 3). Neither acid shows any aldehyde absorption around 1690 cm.$^{-1}$. Furthermore, the hydroxyl absorptions at 3300 cm.$^{-1}$ for mucobromic acid and at 3312 cm.$^{-1}$ for mucochloric acid are of too high frequency to be hydroxyl absorptions of carboxyl groupings which absorb at about 3100 cm.$^{-1}$. The hydroxyl absorptions of these two compounds are correct, however, for alcoholic –CHOH absorptions (see Fig. 1).

Likewise the infrared spectra of I and II show that each exists entirely in the same ring structure as mucochloric and mucobromic acids, since the spectrum of each shows strained ring carbonyl and alcoholic –CHOH absorptions and no carboxyl carbonyl or carboxyl hydroxyl absorptions. The infrared spectra of I and II are similar enough to indicate clearly that they both have the same ring structure, but their spectra are sufficiently different to show that they are not identical compounds. The fact that II and mucochloric acid both have a carbonyl doublet with identical absorptions at 1770 and 1782 cm.$^{-1}$ shows that the environment of the carbonyl group is the same in the two cases. Moreover, both I and mucobromic acid have a single carbonyl absorption at 1774 cm.$^{-1}$ in the former and at 1767 cm.$^{-1}$ in the latter. This infrared evidence shows that I is β-chloro-α-bromo-β-formylacrylic acid and that II is the β-bromo-α-chloro derivative.

In chemical respects, too, the new acid shows quite significant differences when compared with I. If II, for example, reacts with sodium nitrite, the yield of nitromalonic aldehyde is much larger than from I and equals exactly the yield obtained from mucobromic acid under the same conditions. In this connection it should be mentioned that from mucochloric acid only very small quantities of nitromalonic aldehyde are formed.

The mechanism of the reaction leading to II is not quite clear. The over-all equation according to which it takes place is

$$2C_5H_4O_2 + Br_2 + 9Cl_2 + 6H_2O \longrightarrow 2C_4H_2O_3BrCl + 16HCl + 2CO_2$$

During the first stages, at least, the conditions for the formation of mucobromic acid prevail, but no trace of a dibromo acid is ever found in the final product. It is, therefore, reasonable to conclude that, at some stage of the oxidation, there is an exchange of one bromine atom for chlorine, a phenomenon similar to that already observed by Hill in

(1) H. Simonis, *Ber.*, **32**, 2084 (1899).

(2) H. B. Hill and J. Torrey, Jr., *Am. Chem. J.*, **22**, 89 (1899).

(3) Hill claimed erroneously that this acid was 3,5-dichlorofuroic acid. Vander Wal (ref. 4) proved it to be 4,5-dichlorofuroic acid which by reduction yields 4-chloro-2-furoic acid not, as Hill claimed, 3-chloro-2-furoic acid.

(4) R. J. Vander Wal, *Iowa State College J. Sci.*, **11**, 128 (1936).

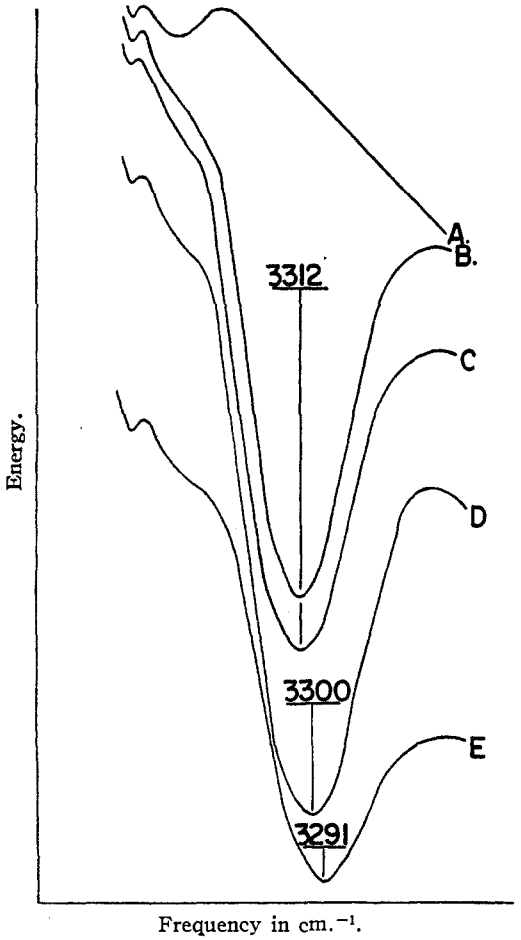


Fig. 1.—A, radiation curve; B, mucochloric acid; C, β-bromo-α-chloro-β-formylacrylic acid; D, mucobromic acid; E, α-bromo-β-chloro-β-formylacrylic acid.

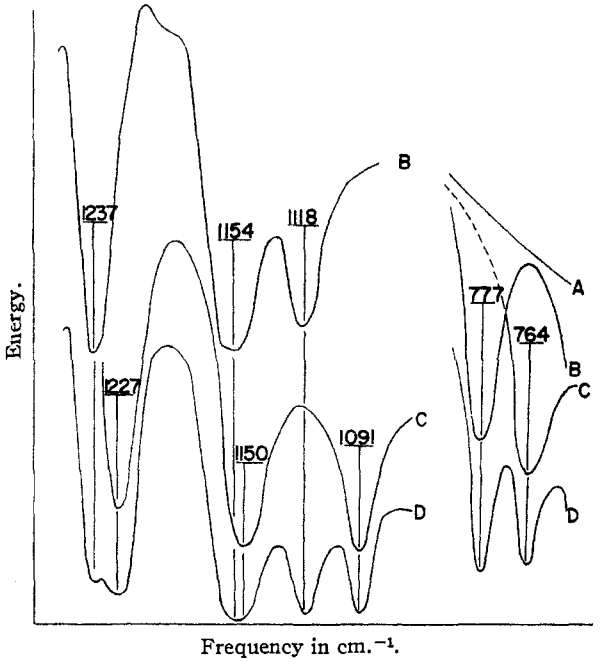


Fig. 2.—A, radiation curve; B, mucochloric acid; C, mucobromic acid; D, mixture, mucochloric and mucobromic acids.

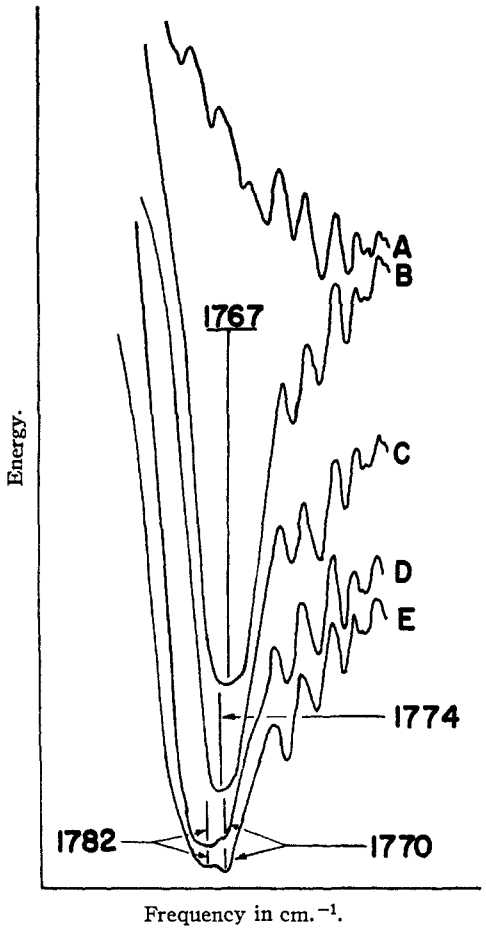


Fig. 3.—A, radiation curve; B, mucobromic acid; C, α-bromo-β-chloro-β-formylacrylic acid; D, mucochloric acid; E, β-bromo-α-chloro-β-formylacrylic acid.

the dibromocrotonolactones.[5] However, when mucobromic acid was treated with chlorine in hydrochloric acid solution at elevated temperatures, no mucobromochloric acid or bromine was obtained.

Though it was not probable, because of the invariable ratio of bromine and chlorine in our final product, that it consisted of a mixture of mucochloric and mucobromic acids, we recrystallized a molar mixture of both acids from benzene. We actually obtained crystals of the same shape and almost the same α and β refractive indices. The infrared absorption curve, however, indicated clearly that this was a mixture and chemically not unique. In Fig. 2 covering the absorption region of 750–1250 cm.$^{-1}$ frequency, it is shown that the absorption of the mixture is simply the sum of the absorptions of the two components.

Experimental

β-Bromo-α-chloro-β-formylacrylic Acid.—The reaction was run in a round-bottom flask with five necks fitted with an efficient agitator, a long reflux condenser, a dropping funnel with a capillary stem, a subsurface gas feed tube and a thermometer. It is essential that the capillary of the dropping funnel always remains below the surface of the reaction mixture and that the flow of the furfural never stops, otherwise the furfural turns into tar.

The flask was charged with 150 g. of 48% hydrobromic acid, 175 ml. of water and 72 g. of bromine. The bromine

(5) H. B. Hill and R. N. Cornelison, *Proc. Am. Acad. of Arts and Sciences*, **XXIX**, 89 (1899).

dissolved completely in the liquid, forming a complex which could be heated above the boiling point of bromine. The excess of bromine (including that contained in the hydrobromic acid) is necessary because a certain loss of bromine is unavoidable on a laboratory scale. It is carried away by the rapid current of hydrochloric acid (and CO_2) formed in the reaction.

The contents of the flask was heated to 65° and 96 g. of furfural added at such a rate that the steady flow through the capillary took about 2 to 2.5 hours. The furfural reacts exothermically with the bromine. The temperature was allowed to reach 75° and the bromine started to reflux. As soon as the deep red color of the liquid became lighter, a fast current of chlorine was passed through the liquid. The flow of furfural and chlorine has to be adjusted in a ratio of 1:3 by weight. The temperature was kept between 75 and 85° by external cooling. When about $^2/_3$ of the furfural had been added, the evolution of large quantities of hydrogen chloride began. Almost no cooling was then needed to keep the temperature at 80–85°. After all of the furfural was in, the temperature was raised to 95° and the chlorine flow cut in half. Chlorine was then added until the whole usage was about 290 g. (90–94% of the theoretical 4.5 mole equivalents). There remained in the flask a pale yellow liquid which on cooling formed a stiff slurry of almost white crystals. This crude product was purified by crystallization from hot water. The yield was 90–94% of theory; m.p. of the purified compound, 122.5°. Titration with caustic showed a molecular weight of 212 (theory, 213).

Anal. Calcd. for $C_4H_2O_3BrCl$: C, 22.5; H, 0.95; Br + Cl, 54.07. Found: C, 22.7; H, 1.02; Br + Cl, 53.7.

Acknowledgments.—We are indebted to Dr. R. J. Vander Wal for suggesting the use of 3,4-dichloro-2-furoic acid to make Hill's 4-chloro-2-furoic acid and for his kindness in supplying a copy of his thesis. We wish to thank Dr. D. N. Kendall for making and interpreting the infrared absorption curves, and O. E. Sundberg for the microanalysis.

CHEMICAL RESEARCH DEPT.
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Kinetics of the Hydrolysis of *p*-Nitrosodimethylaniline[1]

BY F. M. MILLER AND MARTHA L. ADAMS

RECEIVED MAY 4, 1953

The cleavage of *p*-nitrosodialkylanilines by base, a classical preparative method for dialkylamines, has often been considered to be a typical aromatic nucleophilic displacement reaction.[2] There has been, however, beyond gross similarities, no avail-

$$p\text{-ON—}C_6H_4N(CH_3)_2 + NaOH \longrightarrow p\text{-ON—}C_6H_4ONa + (CH_3)_2NH$$

able evidence to support this contention. Further, since this is one of the few known examples of a reaction in which the group displaced is activated by a nitroso group, it was of interest to examine the reaction kinetically.

Experimental

Materials.—*p*-Nitrosodimethylaniline was prepared by nitrosation of dimethylaniline,[3] and obtained as green crystals from ligroin with a melting point of 86°.[4] *p*-Nitrosophenol was obtained by hydrolysis of the nitrosoaniline,[5] and purified by recrystallization from water to a constant melting point of 124–128°.[6]

Method.—It was found from the absorption spectra of *p*-nitrosodimethylaniline in 50% alcohol–water and of *p*-nitrosophenol in the same solvent, which was also approximately 0.2 *M* in sodium hydroxide, that at a wave length of 675 mμ there is a maximum absorption due to *p*-nitrosodimethylaniline and a corresponding minimum in the curve for *p*-nitrosophenol. Using a Coleman spectrophotometer, the optical densities of various mixtures of *p*-nitrosodimethylaniline and *p*-nitrosophenol were determined, and a standard curve drawn.

One-tenth molar solutions of *p*-nitrosodimethylaniline in 50% alcohol–water were prepared frequently by weighing out the calculated amount of the substance. In carrying out an experimental run, definite quantities of this 0.100 *M* *p*-nitrosodimethylaniline solution were measured into the reaction flask by means of a buret. A calculated amount of potassium chloride was added to maintain a constant ionic strength of 0.203. The flask and contents were allowed to reach bath temperature and a calculated quantity of standard sodium hydroxide, also at bath temperature, added with stirring from a pipet. At convenient intervals samples of the reaction mixture were withdrawn by means of a pipet and diluted to give a concentration of approximately 0.01 *M* or less. The extent of dilution nearly stopped the reaction. The diluted samples were immediately transferred to the spectrophotometer cuvettes and readings of the optical density taken at 675 mμ. The concentrations of *p*-nitrosodimethylaniline were then determined from the standard curve, and the concentration of the withdrawn sample calculated using the appropriate dilution factor. Runs were made at 30 and 50 ± 0.05°.

Results and Discussion

Typical data for reactions at 30 and 50° are listed in Tables I and II, respectively, and plots of these data are given in Fig. 1. The results of several runs at various concentrations are given in Tables III and IV. From the average values of the rate constants at the two temperatures the energy of activation was calculated to be 13 kcal. and log *PZ* to be 6.

TABLE I

TYPICAL DATA FOR A REACTION AT 30°

Time, sec.	Optical density	$(b-x)$ (p-$ONC_6H_4N(CH_3)_2$)	$(a-x)$ (NaOH)	$\log \frac{a-x}{b-x}$
0	...	0.0750	0.203	0.432
360	0.511	.0599	.188	.497
615	.495	.0572	.185	.510
1065	.471	.0535	.181	.529
1515	.460	.0517	.180	.542
1810	.450	.0505	.178	.548
2340	.430	.0476	.176	.568
2595	.420	.0455	.173	.580

TABLE II

TYPICAL DATA FOR A REACTION AT 50°

Time, sec.	Optical density	$(b-x)$ (p-$ONC_6H_4N(CH_3)_2$)	$(a-x)$ (NaOH)	$\log \frac{a-x}{b-x}$
0	...	0.0500	0.199	0.600
135	0.520	.0413	.190	.663
380	.479	.0365	.186	.707
610	.440	.0325	.182	.748
945	.400	.0282	.177	.798
1880	.310	.0187	.168	.954

The second-order character of the rate constants, and the values of the Arrhenius parameters are in

(1) Abstracted from the thesis presented by M. L. Adams to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Master of Science.

(2) (a) A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 377; (b) W. A. Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1950, p. 497; (c) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

(3) W. J. Hickenbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1936, p. 287.

(4) C. Wurster and L. Roser, *Ber.*, **12**, 1823 (1879).

(5) E. ter Meer, *ibid.*, **8**, 623 (1875).

(6) E. Bamberger, *ibid.*, **33**, 1955 (1900).

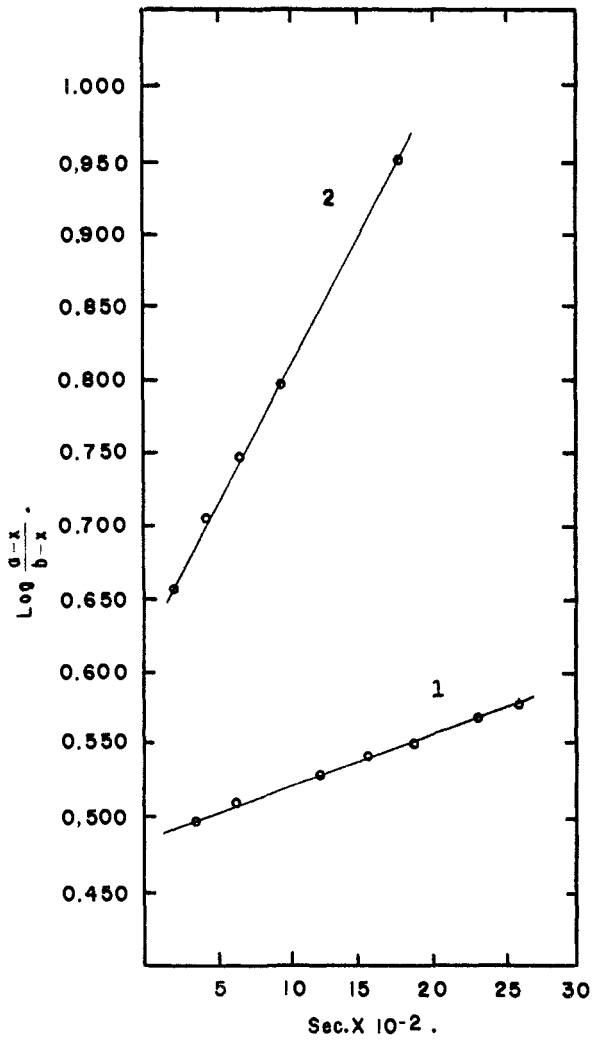

Fig. 1.—Rate curves for the hydrolysis of *p*-nitrosodimethylaniline: 1, at 30°; 2, at 50°.

TABLE III

VALUES OF THE SPECIFIC REACTION RATE AT 30°

NaOH	*p*-ONC$_6$H$_4$N(CH$_3$)$_2$	$k \times 10^3$ (l. mole^{-1} sec.$^{-1}$)
0.203	0.100	5.96
.203	.075	6.23
.102	.095	7.27
.143	.085	7.51
.203	.050	7.16
	Av.	6.4 ± 0.7

TABLE IV

VALUES OF THE SPECIFIC REACTION RATE AT 50°

NaOH	*p*-ONC$_6$H$_4$N(CH$_3$)$_2$	$k \times 10^3$ (l. mole^{-1} sec.$^{-1}$)
0.075	0.075	2.46
.203	.050	2.82
.199	.050	2.58
.203	.070	2.20
.199	.090	2.10
	Av.	2.4 ± 0.4

agreement with similar data for known aromatic nucleophilic displacement reactions.[2c] Therefore, the cleavage of *p*-nitrosodimethylaniline may now be considered as an example of this reaction type, and the mechanism of the reaction may be thought of as that of a typical aromatic nucleophilic displacement reaction,[2] although, as pointed out by Berliner,[7] it is not yet possible to decide whether the formation or decomposition of the transition complex is the rate determining step. It is noteworthy that the values of the activation energy and log *PZ* for this reaction, in comparison with those for other reactions of this type, substantiate the statement of LeFevre[8] that one nitroso group will activate a group toward displacement roughly to the same extent as two nitro groups.

(7) E. Berliner and L. C. Monack, THIS JOURNAL, **74**, 1574 (1952).

(8) R. J. W. LeFevre, *J. Chem. Soc.*, 810 (1931).

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Copolymerization of Anthracene with 1,3-Butadiene[1]

BY C. S. MARVEL AND W. S. ANDERSON

RECEIVED JUNE 4, 1953

Recently Stockmayer and Peebles demonstrated the ability of benzene to copolymerize with vinyl acetate.[2] This prompts us to record the copolymerization of another aromatic hydrocarbon, anthracene, with 1,3-butadiene.

Copolymers prepared from butadiene (95 pts.) and anthracene (5 pts.) in the Mutual recipe[3] showed an intense ultraviolet absorption with maxima at 2575, 2645 and 2720 Å. which were not altered by repeated solution and reprecipitation of the copolymer. These absorption peaks resemble very closely those reported for 9,10-dihydroanthracene[4a] and for 9,10-dimethyl-9,10-dihydroanthracene,[4b] which indicates that the copolymerization involves the 9,10-positions in the anthracene molecule. Using the extinction coefficients for 9,10-dihydroanthracene for comparison, it is calculated that approximately 5% by weight of anthracene has been incorporated in a copolymer prepared to 25% conversion.

Agitation of anthracene with polybutadiene latex does not produce a polymer with these absorption maxima; hence the anthracene is not introduced by an addition to the polybutadiene.

Benzene was employed as a mutual solvent for butadiene and anthracene in these emulsion polymerizations. There were no absorption maxima which indicated incorporation of benzene units in the copolymer when anthracene was present or absent during such polymerizations.

That anthracene does give free-radical reactions has been demonstrated before. 2-Methylanthracene has been shown to copolymerize with styrene.[5] Anthracene itself inhibits the autoxidation of benzaldehyde.[6] The photodimerization of anthracene is well known,[7] and recently[8] the addition of free radicals to anthracene, both with and without con-

(1) The work discussed herein was performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

(2) W. H. Stockmayer and L. H. Peebles, Jr., THIS JOURNAL, **75**, 2279 (1953).

(3) J. W. Wilson and E. S. Pfau, *Ind. Eng. Chem.*, **40**, 530 (1948).

(4) (a) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951; (b) G. M. Badger, M. L. Jones and R. S. Pearce, *J. Chem. Soc.*, 1700 (1950).

(5) M. Magat and R. Bonême, *Compt. rend.*, **232**, 1657 (1951).

(6) H. L. J. Backstrom and H. A. Beatty, *J. Phys. Chem.*, **35**, 2530 (1931); G. E. K. Branch, H. J. Almquist and E. C. Goldsworthy, THIS JOURNAL, **55**, 4052 (1933).

(7) F. Fritzsche, *J. prakt. Chem.*, [1] **101**, 337 (1867).

(8) A. F. Bickel and E. C. Kooyman, *Rec. trav. chim.*, **71**, 1137 (1952).

current dimerization of the latter, has been reported. Hence one might have anticipated that anthracene would undergo copolymerization reactions.

Experimental

Preparation of Copolymers of Anthracene and 1,3-Butadiene.—A two-ounce screw-capped bottle provided with a rubber gasket was charged with 17.5 ml. of a 2.8% solution of a sodium fatty-acid soap (Office of Synthetic Rubber specifications), 1 ml. of a 3% aqueous solution of potassium persulfate, 0.5 g. of anthracene, 5 ml. of benzene, 0.025 g. of lauryl mercaptan and 12 g. of liquid butadiene (Phillips research grade). The air was swept out of the polymerization bottle by allowing the butadiene to evaporate until the charge contained 9.5 g. of butadiene. The bottle was then sealed and tumbled end-over-end at 50° in a constant-temperature bath for 11 hours. At that time the polymer which had formed was precipitated by adding 5 ml. of a saturated methanol solution of N-phenyl-β-naphthylamine and 5 ml. of a 13% solution of sulfuric acid saturated with sodium chloride. The polymer was washed thoroughly with water and dried in a desiccator under reduced pressure. The product was soluble in benzene and the conversion was 25%. This material was twice redissolved in carbon disulfide and precipitated with acetone. The inherent viscosity in benzene was 1.53.

Absorption Spectra.—One sample of the above copolymer was reprecipitated seven times by making a solution in carbon disulfide and pouring it into acetone. Another sample was reprecipitated ten times in this manner. These samples were dried under reduced pressure. Solutions in cyclohexane having a concentration of 8.5 g. of polymer per liter were examined on a Cary recording spectrophotometer, Model 11, using a 1.0-cm. cell. The absorbance at 2645 Å. was higher than at 2575 and at 2720 Å.

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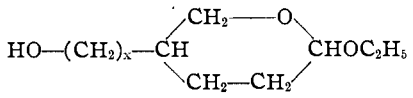
Synthesis and Polymerization of 6-Hydroxy-4-hydroxymethylhexanal Diethyl Acetal and 5-Hydroxy-4-hydroxymethylpentanal Diethyl Acetal[1]

BY C. S. MARVEL AND JOHN J. DRYSDALE

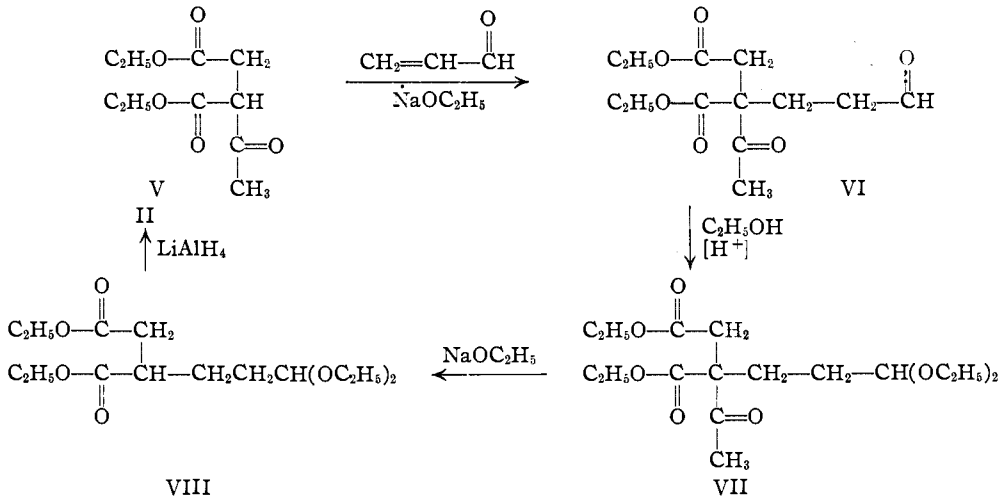
RECEIVED JUNE 15, 1953

The dihydroxyacetals, 5-hydroxy-4-hydroxymethylpentanal diethyl acetal (I) and 6-hydroxy-4-hydroxymethylhexanal diethyl acetal (II), have been polymerized to give low molecular weight, soluble polymers. Attempts to increase the molecular weights of the polymeric acetals have been unsuccessful and have led to the formation of gel. The cyclic acetals, 2-ethoxy-5-hydroxymethyltetrahydropyran (III) and 2-ethoxy-5-(β-hydroxyethyl)-tetrahydropyran (IV), were isolated from the polymerization mixtures of the dihydroxyacetals, I and II, respectively.



III, $x = 1$
IV, $x = 2$

6-Hydroxy-4-hydroxymethylhexanal diethyl acetal (II) was synthesized by the method outlined below.



Experimental[2]

5-Hydroxy-4-hydroxymethylpentanal Diethyl Acetal (I).—Compound I was synthesized by the method of Marvel and Hill,[3] b.p. 113–114° (0.06 mm.), $n^{20}D$ 1.4532. Infrared analysis in chloroform showed a hydroxyl band at 3378 cm.$^{-1}$.

α-Acetyl-α-(3,3-diethoxypropyl)-succinic Acid Diethyl Ester (VII).—One gram (0.043 mole) of sodium was dissolved in 1 liter of absolute ethanol in a 2-liter, 3-necked flask equipped with stirrer, reflux condenser and dropping funnel. Two hundred grams (0.92 mole) of diethyl α-acetylsuccinate was added and the ethanolic mixture was cooled to 0°. Stirring was started and 56 g. (1.0 mole) of acrolein was added dropwise over a period of 1 hour. The basic mixture was allowed to stir at 0° for a total of 3 hours. It was then acidified with dry hydrogen chloride and was allowed to stir for 2 more hours.

The mixture was neutralized with sodium bicarbonate, diluted with water, and extracted with ether. After removal of the ether at water-pump pressure, the residue was fractionated to give 132 g. of α-acetyl-α-(3,3-diethoxypropyl)-succinic acid diethyl ester (VII), b.p. 157–158° (1.3 mm.), $n^{20}D$ 1.4520, d^{31}_4 1.068.

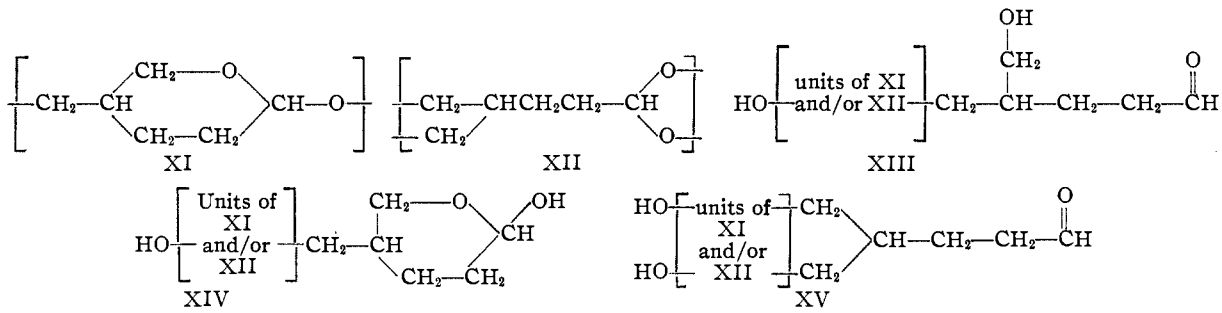
Anal. Calcd. for $C_{17}H_{30}O_7$: C, 58.93; H, 8.73. Found: C, 58.90; H, 8.39.

α-(3,3-Diethoxypropyl)-succinic Acid Diethyl Ester (VIII).—One hundred and thirty-two grams (0.38 mole) of compound VII was refluxed with 3.0 g. (0.044 mole) of sodium ethoxide in 1 liter of absolute ethanol for 2.75 hours. The mixture was chilled, neutralized with sodium bicarbonate, filtered, and the ethanol removed at water-pump pressure.

(1) A portion of the work discussed herein was performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

(2) Analyses were performed by Mrs. Katherine Pih, Mrs. Jean Fortney, Mrs. Lucy Chang and Jozsef Nemeth of the University of Illinois Microanalytical Laboratory. Infrared analyses were performed by Mrs. Elizabeth Leighly of the University of Illinois and by the Anderson Physical Laboratories, Champaign, Ill.

(3) C. S. Marvel and H. W. Hill, Jr., THIS JOURNAL, **73**, 481 (1951).



Distillation of the residue gave 58 g. (50%) of α-(3,3-diethoxypropyl)-succinic acid diethyl ester (VIII), b.p. 157–158° (3.8 mm.), $n^{20}D$ 1.4370–1.4378, d^{31}_4 1.022.

6-Hydroxy-4-hydroxymethylhexanal Diethyl Acetal (II).—Fifty-eight grams (0.19 mole) of compound VIII was reduced with 10 g. (0.0264 mole) of lithium aluminum hydride, according to the procedure of Marvel and Hill,[3] to give 31.5 g. (75%) of 6-hydroxy-4-hydroxymethylhexanal diethyl acetal, b.p. 152–153° (1 mm.). A small sample was distilled from sodium carbonate and analyzed, b.p. 131° (0.06 mm.), $n^{20}D$ 1.4610. Infrared analysis in chloroform showed a hydroxyl band at 3336 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 60.20; H, 10.70.

2-Ethoxy-5-hydroxymethyltetrahydropyran (III).—When 5-hydroxy-4-hydroxymethylpentanal diethyl acetal was polymerized (see below) at temperatures above 100° (1.5 mm.), a clear white liquid, 2-ethoxy-5-hydroxymethyltetrahydropyran, distilled from the reaction mixture, b.p. 95–97° (1.5 mm.), $n^{20}D$ 1.4563. Infrared analysis showed a hydroxyl group (3418 cm.$^{-1}$) and the absence of an aldehyde group.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.60. Found: C, 60.25; H, 10.36.

2-Ethoxy-5-(β-hydroxyethyl)-tetrahydropyran (IV).—A small sample of 6-hydroxy-4-hydroxymethylhexanal diethyl acetal was heated at reduced pressure for a short time and then fractionated to give a polymeric residue and a colorless liquid, 2-ethoxy-5-(β-hydroxyethyl)-tetrahydropyran (IV), b.p. 97° (1.6 mm.), $n^{21.5}D$ 1.4602. Infrared analysis on the pure liquid showed a hydroxyl band at 3418 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.03; H, 10.41. Found: C, 62.06; H, 10.52.

Polymerization of Compound I.—One gram of 5-hydroxy-4-hydroxymethylpentanal diethyl acetal (I), $n^{20}D$ 1.4530–32, was placed in a small tube connected with a distillation system, a small crystal of *p*-toluenesulfonic acid monohydrate was added, the pressure in the distillation system was reduced to 0.02 mm., and heat was applied by means of an oil-bath. The bath temperature was kept slightly below the reflux temperature of the cyclic acetal III until the reaction mixture became quite viscous. The bath temperature was then raised to 120° and heating was continued for a total of 15 minutes. The reaction mixture was cooled, neutralized with concentrated ammonia, and extracted with chloroform. The chloroform extract was decolorized with Darco and evaporated to dryness under reduced pressure. The average molecular weight of the polymer as determined in bornyl bromide was 1190 ± 100; inherent viscosity in chloroform was 0.14. Infrared analysis of a film of the polymer showed a hydroxyl absorption at 3440 cm.$^{-1}$ and a carbonyl absorption at 1736 cm.$^{-1}$. The polymer softened at 49° to give a transparent glass.

Anal. Calcd. for $(C_6H_{10}O_2)_{7x}(C_6H_{12}O_3)_{3x}$: C, 60.29; H, 8.93. Found: C, 60.28; H, 8.67.

The above data are consistent with a branched structure whose internal $C_6H_{10}O_2$ units may have structure XI and/or XII and whose end $C_6H_{12}O_3$ units may have structure XIII, XIV and/or XV, and in which the average ratio of internal to external units is 7/3.

Polymerization of compound I in the above manner with a reaction time of 2 hours produced a polymer which was approximately 80% insoluble in chloroform; inherent viscosity in chloroform of the soluble portion, 0.17.

Polymerization of II.—Five grams of the dihydroxy acetal (II) was placed in a 25-ml. pear-shaped flask and the flask attached to a small distillation system. The system was evacuated to 1 mm. and the flask immersed in an oil-bath maintained at 210–220°. After 27 hours, heat was applied to the distillation column and a small amount of the cyclic acetal IV removed. A sample of material removed from the reaction flask at this time had an inherent viscosity in chloroform of 0.04.

The reaction flask was heated for 24 hours more at 210–220° (39 mm.) to give a firm, light red, translucent solid, inherent viscosity in chloroform 0.10. Continued heating in the above manner failed to raise the observed viscosity but did produce increasing amounts of gel. This polymer was assumed to contain a branched structure and structural units similar to the polymeric acetal I.

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Synthesis of 3,5-Dibromophenylsilanes

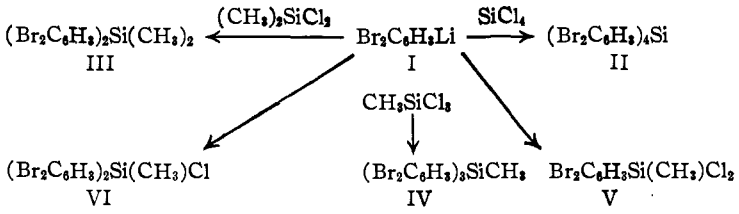
BY C. R. MORGAN, H. A. HOFFMAN AND F. E. GRANCHELLI

RECEIVED APRIL 10, 1953

In the course of an investigation of organosilanes of high density it became of interest to attempt the conversion of 1,3,5-tribromobenzene to 3,5-dibromophenylsilane derivatives. Following a brief unsuccessful effort to prepare a Grignard reagent from the tribromobenzene, we decided to employ 3,5-dibromophenyllithium (I) for reaction with the chlorosilanes. Gilman had reported[1] a 56% yield of 3,5-dibromobenzoic acid upon carbonation of the dibromophenyllithium compound, but no study was made of the optimum conditions for the halogen–metal interchange between *n*-butyllithium and 1,3,5-tribromobenzene. We have examined the effect of reaction time, as measured by the yield of 3,5-dibromobenzoic acid and find that in ether, with reaction times of 0.5, 1.0, 2.0 and 5.0 minutes, measured from the end of the addition of reagents, yields of 77, 78, 54 and 38%, respectively, were obtained. In petroleum ether, a one-minute reaction time gave only 18%. From the neutral portion of the reaction mixtures a product melting at 208.5–209° was isolated. This does not appear to correspond to the expected 3,5,3′,5′-tetrabromobiphenyl (m.p. 186°), but may be the tetrabromodiphenyl ketone.

Reactions of I were conducted with silicon tetrachloride, dimethyldichlorosilane and methyltrichlorosilane. The accompanying equations illustrate the methods used to prepare the various dibromophenylsilanes employing a one-minute reaction time for preparation of the lithium reagent. Yields of the tetrasubstituted silanes generally were good, but difficulties were encountered in con-

(1) H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2327 (1940).



trolling reaction conditions for monosubstitution of methyltrichlorosilane. In the initial attempts to prepare V none of the monosubstituted product was isolated, and only VI was obtained in 18% yield. Small yields of both V and VI were realized only by mixing, successively, small equivalent amounts of tribromobenzene and *n*-butyllithium solutions, followed by immediate addition to a large excess of the trichlorosilane. After separation of VI the distillation residue yielded a product melting at 247.5–248°, believed to be a pentabromoterphenyl.

Experimental[2]

***n*-Butyllithium.**—The procedure of Gilman[3] was used for preparation of *n*-butyllithium. In experiments where storage of the reagent was necessary, petroleum ether (Skellysolve A) was used as the solvent instead of diethyl ether.

Reaction Time Studies on Formation of 3,5-Dibromophenyllithium.—The apparatus used to study the optimum reaction time for the formation of 2,4-dibromophenyllithium (yield based on conversion to its acid) was a simple 250-ml. wide mouth erlenmeyer flask equipped with a 2-hole rubber stopper for helium inlet and outlet.

To 3.15 g. (0.01 mole) of 1,3,5-tribromobenzene in 100 ml, of diethyl ether or petroleum ether was added 20 ml. of 0.5 *N* *n*-butyllithium in diethyl ether solution. This mixture was allowed to stand for the prescribed reaction time under an atmosphere of dry helium at 25–28°. The reaction mixture was then poured onto a slurry of Dry Ice and diethyl ether. 3,5-Dibromobenzoic acid, m.p. 215–216°, was obtained from the aqueous extract of the ether solution.

One gram of a neutral product melting at 203–204° was isolated from the ether layer. The material was recrystallized from dioxane–water solution and then chromatographed in benzene solution on an alumina column, yielding a colorless product, m.p. 208.5–209°.

Anal. Calcd. for $C_{13}H_6Br_4O$: C, 31,36; H, 1.22; Br, 64.21, Found: C, 31.75, 31.30; H, 1.53, 1.58; Br, 64.17, 63.16.

Tetra-(3,5-dibromophenyl)-silane (II).—Using the simple reaction flask described in the preceding section, 1.57 g. (0.005 mole) of 1,3,5-tribromobenzene in 50 ml. of ether was treated with 10 ml. of 0.5 *N* *n*-butyllithium in petroleum ether solution. After one minute reaction time at 25°, 0.21 g. (0.00125 mole) of silicon tetrachloride in 5 ml. of ether was added with swirling. The mixture was allowed to stand for 15 minutes. The solvent was then distilled and the residue treated with petroleum ether producing a gummy precipitate which was crystallized from acetone. Recrystallization from benzene gave crystals melting at 298–302°. The yield was 0.52 g., 43%, based on tribromobenzene.

Anal. Calcd. for $C_{24}H_{12}Br_8Si$: C, 29.79; H, 1.25; Br, 66.07. Found: C, 29.74; H, 1.34; Br, 65.72.

Dimethyldi-(3,5-dibromophenyl)-silane (III).—The process above was repeated using 0.25 g. (0.0025 mole) of dimethyldichlorosilane in place of silicon tetrachloride. The reaction mixture was stripped of ether, extracted with benzene and the benzene solution concentrated to give 0.98 g. of product, 75% yield based on tribromobenzene. After two recrystallizations from ethanol, the melting point was 113–114°.

Anal. Calcd. for $C_{14}H_{12}Br_4Si$: C, 31.84; H, 2.29; Br, 60.55. Found; C, 31.99; H, 2.35; Br, 60.14.

(2) All melting points are uncorrected.

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

Methyltri-(3,5-dibromophenyl)-silane (IV).—The above preparation was repeated using 0.15 g. (0.0015 mole) of methyltrichlorosilane. A total of 0.86 g, of product was obtained (76%, based on tribromobenzene), melting at 214–215° after two recrystallizations from benzene.

Anal. Calcd. for $C_{19}H_{12}Br_6Si$: C, 30.51; H, 1.62; Br, 64.12. Found: C, 30.87; H, 1.98; Br, 63.84.

Methyldi-(3,5-dibromophenyl)-chlorosilane (VI) and Pentabromoterphenyl (?).—1,3,5-Tribromobenzene, 7.5 g. (0.0237 mole) in 125 ml. of ether, was placed in a 250-ml. addition funnel. The funnel was so arranged to have outlet through one neck of a 2-liter three-necked flask equipped with a rapidly run trubore stirrer and a condenser, and fitted with inlet and outlet for a vigorous stream of dry nitrogen,

In the flask was placed a solution of 28 g. (0.174 mole) of methyltrichlorosilane in 250 ml. of diethyl ether. After cooling the flask in an ice-bath, 50 ml. of 0.475 *N* *n*-butyllithium in petroleum ether was added as quickly as possible from a pipet with rapid stirring by means of the emptying pipet. One minute after the end of this addition, at which time the solution passed through a bright yellow to slightly dark color the dropping funnel was emptied quickly into the rapidly stirred chlorosilane solution. The funnel was swept out with dry nitrogen, the stopcock was closed, and the interchange was repeated on a second portion of 1,3,5-tribromobenzene. This solution was run into the flask and the final reaction mixture was allowed to stir for one-half hour as it warmed up to room temperature.

The ether was removed and the yellow liquid residue containing precipitated lithium chloride was treated with 125 ml. of hot benzene and filtered in a nitrogen atmosphere. The benzene was stripped under vacuum, using a small column and take-off, the whole apparatus being under dry nitrogen introduced at the ebulliator. The product was then fractionated under vacuum, using a small integral pot still of 25-ml. capacity with attached condenser. After a small forerun, a white crystalline solid came over which, from its subliming properties, appeared to be tribromobenzene. (This was later shown to be correct since its melting point was 119–120°, and the material gave no depression in a mixed melting point with authentic 1,3,5-tribromobenzene.) The difficulty in removing the tribromobenzene necessitated interruption of the distillation to clean the fraction cutter.

A third fraction, 2.34 g., was then obtained at 185° and 0.1 mm. This product (VI) solidified in the receiver, and represented a yield of 18%. The di-substituted silane was recrystallized from petroleum ether three times. After drying in vacuum, the white prisms melted at 109–110°.

Anal. Calcd. for $C_{13}H_9SiClBr_4$: C, 28.47; H, 1.65; Cl, 6.47. Found: C, 28.96; H, 1.71; Cl, 6.38.

After collecting the third fraction, the distillation was stopped and the residue was dissolved in hot benzene. Upon concentration and cooling, a precipitate was obtained which was crystallized from benzene solution (m.p. 246–247°). Recrystallization from dioxane–water solution yielded 1 g. of product, m.p. 247.5–248°.

Anal. Calcd. for $C_{18}H_9Br_5$: C, 34.61; H, 1.44; Br, 64.00. Found: C, 34.79; H, 1.79; Br, 63.73.

Methyl-(3,5-dibromophenyl)-dichlorosilane (V).—Using the apparatus described by Gilman,[1] there was placed 75 ml. of an ether solution of 0.64 *N* *n*-butyllithium in funnel A and 15 g. (0.047 mole) of 1,3,5-tribromobenzene in 250 ml. of diethyl ether in funnel B. In flask II, immersed in an ice–salt-bath, was placed 55.9 g. (0.38 mole) of methyltrichlorosilane in 250 ml. of diethyl ether. A nitrogen atmosphere was maintained in both reaction flasks. From funnel A, 5 ml. of solution was added to flask I, immediately followed by addition of 18 ml. of the tribromobenzene solution. The mixture then was added instantly to flask II with vigorous stirring.

This sequence of additions was carried out fifteen times until all reactants were consumed. The ice-bath was then removed and the mixture was stirred until it reached room temperature (30 minutes). Ether was stripped at atmospheric pressure over a steam-bath, and the residue was treated with hot, dry benzene and filtered under a nitrogen atmosphere.

The benzene solution was then distilled, first at atmospheric pressure to remove all solvent, followed by vacuum distillation at 0.1–0.05 mm. In the first fraction there was collected 0.1 g. of a low boiling liquid, b.p. 35–55°, which was not identified. A second fraction, 0.50 g., was collected at 65–75° and this solidified in the receiver. Some tribromobenzene was also obtained, but because of its tendency to condense as a solid on the walls of the fraction cutter its partial separation from this product was effected. The third fraction was collected at 185°, and consisted of 2.5 g. of (VI).

The last two fractions were redistilled, and the more volatile fraction was collected at 65° and 0.1 mm. Distillation was not continued beyond this point. The product solidified in the receiver and was found to melt at 44–45°.

Anal. Calcd. for $C_7H_6SiBr_2Cl_2$: C, 24.06; H, 1.73; Si, 8.04. Found: C, 24.27; H, 1.78; Si, 7.80.

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Pentaphenylethanol

BY WILLIAM A. MOSHER AND MELVIN L. HUBER[1]

RECEIVED FEBRUARY 26, 1953

In connection with other work it was desirable to prepare substantial quantities of pentaphenylethanol, a compound reported by Schmidlin and Wohl[2] from the reaction of phenylmagnesium iodide and β-benzopinacolone under forcing conditions. This same reaction had been attempted previously but with negative results[3] and other reactions which were expected to yield pentaphenylethanol gave other products.[4] Only two other references to the compound have been found,[5] and in these small amounts of a compound corresponding to the Schmidlin and Wohl substance were reported. No proof of structure has yet been presented.

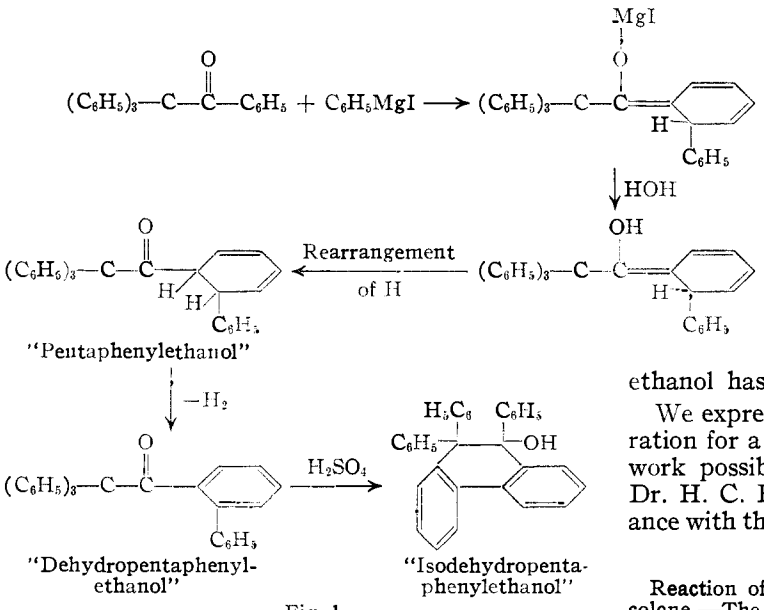

Fig. 1.

Schmidlin and Wohl[2] found that their substance ($C_{32}H_{26}O$) was converted to $C_{32}H_{24}O$ by treatment with hydrochloric acid, acetyl chloride, or phosphorus pentachloride and the new substance was called "dehydropentaphenylethanol." We have recently established the structure of "dehydropentaphenylethanol" as *o*-biphenylyl triphenylmethyl ketone,[6] and this information now permits attack on the structure of the original substance.

When the compound from the reaction of phenylmagnesium iodide and β-benzopinacolone is catalytically dehydrogenated at its melting point with palladium on charcoal, *o*-biphenylyl triphenylmethyl ketone, identical with "dehydropentaphenylethanol," is formed. The original substance shows a strong infrared absorption for carbonyl but hydroxyl absorption is absent. These facts are consistent with a 1,4-addition of the Grignard reagent to the conjugated system of the carbonyl and the aromatic ring, in the matter described by Kohler and Nygaard[7] with diphenylbenzalacetophenone, followed by rearrangement of hydrogen. Figure 1 indicates the complete series of reactions. The only uncertainty is the location of the double bonds in the rather unstable, partially hydrogenated ring. Our formulation is based on the simplest tautomeric shifts.

We have some evidence that the original enol may be present; before recrystallization the infrared absorption is strong at the hydroxyl band and the material decolorizes permanganate. A simple recrystallization removed the hydroxyl absorption completely both from the solid and from the mother liquor.

It seems safe to say that "pentaphenylethanol" as previously reported is actually a dihydroketone, probably 1-triphenylacetyl-2-phenyl-1,2-dihydrobenzene. Pentaphenylethanol has not yet been prepared.

We express our appreciation to Research Corporation for a F. G. Cottrell Grant which made this work possible and to Mrs. Margaret Kraus and Dr. H. C. Beachell of this Department for assistance with the infrared data.

Experimental

Reaction of Phenylmagnesium Iodide and β-Benzopinacolone.—The method was essentially that of Schmidlin and Wohl[2]: 100 g. of benzene, 13 g. (0.54 mole) of magnesium turnings, 102 g. of phenyl iodide (0.5 mole) and 400 ml. of dry ether were used to prepare the Grignard reagent, which was filtered, added to a flask containing 20 g. (0.057 mole) of β-benzopinacolone (m.p. 179–80°) and refluxed for 20 hours. The reaction mixture was cooled in an ice-bath and carefully decomposed with a mixture of ice and water containing 46 ml. of concd. hydrochloric acid. After shaking in a separatory funnel, the solid which separated in the ether layer was filtered off and washed. Recrystallization of this product from acetic acid and then from benzene or a mixture of benzene and petroleum ether (b.p. 65–110°) gave a white solid melting at 175–176°. *Anal.* Calcd. for

(1) F. G. Cottrell Research Fellow. From the Ph.D. Dissertation of M. L. Huber, Univ. of Delaware School of Graduate Studies, 1950. Presented before Division of Organic Chemistry, American Chemical Society, Chicago, September 7, 1950.

(2) J. Schmidlin and J. Wohl, *Ber.*, **43**, 1145 (1910).

(3) M. Gomberg and L. H. Cone, *ibid.*, **38**, 2454 (1905); **39**, 1461, 1469 (1906).

(4) J. Schmidlin, *ibid.*, **39**, 4200 (1906); **43**, 1137 (1910); W. Schlenk and R. Ochs, *ibid.*, **49**, 608 (1916); W. E. Bachmann, THIS JOURNAL, **53**, 2759 (1931).

(5) W. Schlenk and H. Mark, *Ber.*, **55**, 2298 (1922); H. Gilman and R. E. Fothergill, THIS JOURNAL, **51**, 3149 (1929).

(6) W. A. Mosher and M. L. Huber, *ibid.*, **73**, 795 (1951).

(7) E. P. Kohler and E. M. Nygaard, *ibid.*, **52**, 4129 (1930).

$C_{32}H_{26}O$: C, 90.11; H, 6.14. Found: C, 90.24; H, 5.90.

Infrared absorption spectra in nujol mull were taken using a Baird split beam recording spectrophotometer. The above compound showed very strong absorption at 6 microns, the carbonyl absorption band, and no absorption at 2.9 microns, the hydroxyl band. The compound was unsaturated to bromine and to potassium permanganate.

Dehydrogenation of Pentaphenylethanol.—The above material (0.2 g.) heated at 170–180° with 0.02 g. of palladium on charcoal catalyst[8] yielded *o*-biphenylyl triphenylmethyl ketone, m.p. and mixed m.p. 175–176°,[7] and a small amount of an unidentified product.

Isolation of the Enol Form.—When the crude, ether-insoluble material from the Grignard reaction above, filtered after hydrolysis, was carefully washed with dilute hydrochloric acid (about 2 *M*) and chloroform and then ether, the residue gave an infrared spectrum with absorption at 2.9 μ, indicative of hydroxyl. Tests with bromine in carbon tetrachloride and potassium permanganate in acetone indicated unsaturation. All attempts to recrystallize this material yielded either the unsaturated ketone described above, m.p. 175–176°, or *o*-biphenylyl triphenylmethyl ketone.

(8) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1130 (1940).

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2,2-Dimethyl-3-aminopentane and its Reaction with Nitrosyl Chloride

BY WILLIAM A. MOSHER, JAMES C. COX, JR., AND JAMES KREITZER

RECEIVED FEBRUARY 21, 1953

Although rearrangement was expected, we undertook the reaction of 2,2-dimethyl-3-aminopentane with nitrosyl chloride as a possible method of preparing 2,2-dimethyl-3-chloropentane. The amine was prepared by the reduction of the corresponding ketoxime. On treatment of the amine in ether solution with gaseous nitrosyl chloride as employed by Bartlett and Knox[1] the only product isolated was identical with the nitrosochloride from 2,3-dimethyl-2-pentene.

Markownikoff[2] reported the preparation of 2,2-dimethyl-3-aminopentane by reduction of the secondary nitro compound formed by the nitration of 2,2-dimethylpentane. This nitro compound gave on hydrolysis with alkali a ketone erroneously identified as ethyl *t*-butyl ketone on the basis of correspondence with reported physical constants.[3] Markownikoff's ketone must actually have been methyl neopentyl ketone since it gave a semicarbazone of m.p. 175°; the reported values for this derivative from ethyl *t*-butyl ketone[4] and methyl neopentyl ketone[5] are, respectively, 144 and 176°.

Apparently 2,2-dimethyl-3-aminopentane has not been previously reported. The following physical properties were determined in the present study: b.p. 128.0° (760 mm.), n^{25} 0.7615, $n^{15}D$ 1.4306, $n^{20}D$ 1.4287, $n^{30}D$ 1.4249, viscosity at 25°, 24.86 millipoises; surface tension, capillary rise 23.3 dynes/cm. The phenylthiourea melts at 151° and the 3,5-dinitrobenzoate at 149–151°.

Experimental

Preparation of Ethyl-*t*-butylcarbinol.—This compound was prepared from *t*-butylmagnesium chloride and propionaldehyde in the usual manner; yield 45%, b.p. 135° (757 mm.), $n^{25}D$ 1.4180, phenylurethan m.p. 83°.[6] A 45% recovery of propionaldehyde, presumably through enolization, was observed.

Oxidation of Ethyl-*t*-butylcarbinol.—The oxidation was carried out as described by Mosher and Langerak[7] with chromic anhydride in aqueous acetic acid. The ketone was distilled through a column of 15 theoretical plates; yield 88–90%, b.p. 125°,[3] $n^{25}D$ 1.4013, m.p. of semicarbazone 144°,[4,8] of 2,4-dinitrophenylhydrazone 143°,[8] and oxime 84–85°.[8]

Reduction of the Ketoxime.—A total of 190 g. of ketoxime was reduced in the following manner: ethyl *t*-butyl ketoxime, 16.3 g. (0.13 mole), was dissolved in 300 ml. of *n*-amyl alcohol and heated to boiling under reflux; 21 g. of metallic sodium, cut into thin strips, was added slowly. Refluxing was continued for three hours. The reaction mixture was allowed to cool and then poured into 500 ml. of water. The amyl alcohol layer, containing most of the amine, was separated and acidified with concd. hydrochloric acid, the acidified washings were combined, made basic with 10% sodium hydroxide and extracted with several portions of ether. The ether extracts were dried over solid potassium hydroxide, the ether distilled and the amine purified by fractionation. The yields were 75–90% of theory. Chloroplatinate salt: calcd. for $(C_7H_{18}NCl)_2PtCl_4$: Pt, 30.49. Found: Pt, 30.45. Hydrochloride m.p. 221: calcd. for C_7H_8NCl: Cl, 23.38. Found: Cl, 23.35. Phenylthiourea m.p. 151°: calcd. for $C_{14}H_{22}N_2S$: N, 11.19. Found: N, 11.30. 3,5-Dinitrobenzoate m.p. 149–151°: calcd. for $C_{14}H_{19}O_6N_3$: N, 12.87. Found: N, 12.77.

Reaction of 2,2-Dimethyl-3-aminopentane with Nitrosyl Chloride.—This reaction, including the preparation of nitrosyl chloride, was carried out as described by Bartlett and Knox.[1] The reaction temperature was −10° and ether was employed as solvent. Gaseous nitrosyl chloride was added until the persistence of a brown color indicated that an excess had been added. The ether solution was washed with water, dried with sodium sulfate, and evaporated. The solution was blue-green, indicating the presence of a completely substituted double bond,[9] the recrystallized product melted at 124°. For comparison purposes, methylethylisopropylcarbinol was prepared by the reaction of ethylmagnesium bromide on methyl isopropyl ketone and the alcohol formed was dehydrated with potassium acid sulfate. Fractionation gave 2,3-dimethyl-2-pentene, b.p. 97–98°, $n^{20}D$ 1.4212,[10] confirmed by ozonolysis into acetone and methyl ethyl ketone and only a trace of acetaldehyde. The nitrosochloride of 2,3-dimethyl-2-pentene was prepared as above: m.p. and mixed m.p. with the product from 2,2-dimethyl-3-aminopentane, 124°. *Anal.* Calcd. for $C_7H_{14}ONCl$: Cl, 21.67. Found: Cl, 21.80.

(1) P. D. Bartlett and L. H. Knox, THIS JOURNAL, **61**, 3184 (1939).

(2) B. V. Markownikoff, *Ber.*, **33**, 1906 (1900).

(3) A. Wischnegradsky, *Ann.*, **178**, 103 (1875).

(4) A. Favorskii, *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912).

(5) R. J. McCubbin and H. Adkins, THIS JOURNAL, **52**, 2547 (1930).

(6) J. Leroide, *Ann. chim. phys.*, [9] **16**, 366 (1921); F. C. Whitmore and W. S. Forster, THIS JOURNAL, **64**, 2966 (1942).

(7) W. A. Mosher and E. O. Langerak, *ibid.*, **71**, 286 (1949).

(8) F. C. Whitmore, C. I. Noll and V. C. Meunier, *ibid.*, **61**, 684 (1939).

(9) *Cf.* J. L. Simonsen, "The Terpenes," Vol. I, Second Edition, Cambridge Univ. Press, Cambridge, 1947, p. 168.

(10) M. P. Doss, "Physical Constants of the Principal Hydrocarbons," Third Edition, The Texas Co., New York, N. Y., 1942, p. 24.

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A Synthesis of 3,2′-Nornicotyrine[1]

BY HENRY RAPOPORT AND MELVIN LOOK

RECEIVED MAY 25, 1953

Recently[2] it has been shown that the use of N-nitroso-N-(3-pyridyl)-isobutyramide (I) in the Gomberg (or diazo) reaction affords a reasonable method for introducing the 3-pyridyl radical into

(1) Reported in part in *Abstracts Papers Am. Chem. Soc.*, **122**, 14M (1952).

(2) H. Rapoport, M. Look and G. J. Kelly, THIS JOURNAL, **74**, 6293 (1952).

an aromatic system, the specific example being the preparation of 3-phenylpyridine. An interesting extension of this method has now been found in the introduction of the 3-pyridyl radical into a pyrrole nucleus, thus providing a convenient synthesis of 3,2′-nornicotyrine (III).

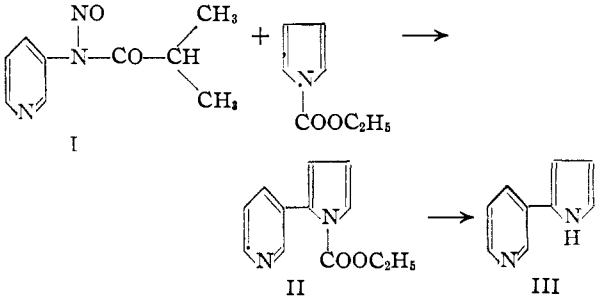
In considering the applicability of such an approach to the synthesis of a pyridylpyrrole, two essential questions had to be answered, *viz.*, can the pyrrole nucleus be substituted employing this reaction and, if so, at what position(s) does substitution occur.

A search of the literature revealed only one instance in which a pyrrole compound had been successfully employed in the Gomberg reaction. This was the work of Rinkes,[3] who prepared 2-phenylpyrrole from the reaction of N-nitrosoacetanilide with 1-carbethoxypyrrole followed by hydrolysis of the carbethoxyl group. We have confirmed his results and obtained a parallel reaction with 3,3-dimethyl-1-phenyltriazene in place of N-nitrosoacetanilide. The 2-phenylpyrrole thus obtained melts at 129–130° and is apparently the pure 2-isomer.

Whether any of the 3-isomer is an accompanying impurity in the original reaction mixture is difficult to say since 3-phenylpyrrole has not been reported. Although the preparation of 2-phenylpyrrole by thermal rearrangement of 1-phenylpyrrole[4] admits to the possibility (and probability) of some of the 3-isomer as a side-product, synthesis from ethyl benzoylacetate, ammonia and α,β-dichloroethyl ethyl ether must give only the 2-isomer.[5] In each case[3,4,5] the melting points are identical, and we are led to the conclusion that the Gomberg reaction apparently gave exclusive (or overwhelming) substitution of the pyrrole nucleus at the 2-position. This is surprising in view of the fact that with substituted benzenes[6] and pyridine,[7] all possible isomers are formed.

Attempts were next made to replace 1-carbethoxypyrrole with 1-methylpyrrole in the Gomberg reaction. However, coupling took place without nitrogen elimination and the product was 1-methyl-2-phenylazopyrrole. This is not too surprising when one considers that 1-methylpyrrole readily forms azo compounds with diazonium salts, whereas 1-carbethoxypyrrole does not. Parallel results were obtained in the benzene series where phenols and naphthols in the Gomberg reaction give azo compounds rather than nitrogen elimination.[8]

These observations indicated that the pyrrole nucleus could be substituted in the Gomberg reaction if 1-carbethoxypyrrole was used and that the entering substituent took the 2-position. To apply this reaction to the synthesis of a pyridylpyrrole related to the nicotine series, N-nitroso-N-(3-pyridyl)-isobutyramide (I) was allowed to react with 1-carbethoxypyrrole. The product, isolated by distillation in 23% yield, was N-carbethoxy-3,2′-nornicotyrine (II), which was hydrolyzed with alkali to 3,2′-nornicotyrine (III),



m.p. 98–100°. Again in this reaction apparently none (or extremely little) of the isomeric 3-substituted pyrrole was formed. Since 3,3′-nornicotyrine is the higher melting and less soluble of the two isomers,[9] its presence in even small amount would be detectable.[9a]

This reaction thus appears to offer an interesting alternative method, with some possibility of variation, for the synthesis of certain compounds related to nicotine.

Experimental[10]

2-Phenylpyrrole.—A mixture of 11.6 g. (0.08 mole) of 3,3-dimethyl-1-phenyltriazene[11] and 50 ml. of N-carbethoxypyrrole[12] were warmed on the steam-bath (protected from atmospheric moisture) until gas evolution ceased. The solution was then steam distilled (four liters of distillate collected), the distillate was extracted with four 250-ml. portions of ether, the combined ether extracts were washed with sodium carbonate and dried over magnesium sulfate, and the ether was evaporated. Distillation of the residue gave 5.1 g., 30% yield, of 1-carbethoxy-2-phenylpyrrole, b.p. 150–155° (12 mm.). Hydrolysis by the procedure of Rinkes[3] gave a quantitative yield of 2-phenylpyrrole, m.p. 129–130° (reported[3,4,5] m.p. 129–130°).

1-Methyl-2-phenylazopyrrole.—Using N-nitrosoacetanilide[13] or the triazene[11] and N-methylpyrrole (du Pont, redistilled) and the same coupling and isolation procedure as given above, 1-methyl-2-phenylazopyrrole, an orange liquid, was the only isolable product, b.p. 120–130° (3 mm.).[14]

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.4; H, 6.0; N, 22.6. Found: C, 71.6; H, 6.4; N, 22.1.

The picrate was prepared with ethanolic picric acid and recrystallized from absolute ethanol, m.p. 148–149°.

Anal. Calcd. for $C_{17}H_{14}O_7N_6$: C, 49.3; H, 3.4; N, 20.3. Found: C, 49.0; H, 3.3; N, 20.6.

N-Carbethoxy-3,2′-nornicotyrine.—N-Nitroso-N-(3-pyridyl)-isobutyramide was prepared from 10 g. (0.06 mole) of N-(3-pyridyl)-isobutyramide and nitrosyl chloride as described previously,[2] except that the extraction of the aqueous solution was made with three 100-ml. portions of cold, peroxide-free ether. The combined extracts, after washing with 100 ml. of 2% sodium hydroxide and 100 ml. of saturated sodium chloride solution, were dried over magnesium sulfate, and evaporated at reduced pressure and room tem-

(3) I. J. Rinkes, *Rec. trav. chim.*, **62**, 116 (1943).

(4) A. Pictet and P. Crepieux, *Ber.*, **28**, 1904 (1895); G. Plancher and E. Ghigi, *Gazz. chim. ital.*, **55**, 757 (1925); C. F. H. Allen, M. R. Gilbert and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937); H. Adkins and H. L. Coonradt, THIS JOURNAL, **63**, 1563 (1941).

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(6) D. F. De Tar and H. J. Scheifele, Jr., THIS JOURNAL, **73**, 1442 (1951).

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(8) R. Huisgen and R. Horeld, *Ann.*, **562**, 137 (1949).

(9) (a) J. P. Wibaut and H. P. L. Gitsels, *Rec. trav. chim.*, **57**, 755 (1938); (b) E. Späth and P. Kainrath, *Ber.*, **71**, 1276 (1938).

(10) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California.

(11) J. Elks and D. H. Hey, *J. Chem. Soc.*, 441 (1943).

(12) W. Tschelinzeff and B. Maxaroff, *Ber.*, **60**, 194 (1927).

(13) H. France, I. M. Heilbron and D. H. Hey, *J. Chem. Soc.*, 369 (1940).

(14) This compound, prepared by methylation of 2-phenylazopyrrole, has been reported as boiling at 140° (21 mm.) and forming a picrate, m.p. 151° [G. Plancher and E. Soncini, *Gazz. chim. ital.*, **32**, II, 464 (1902)].

perature. To the residue was added 51 g. (0.37 mole) of N-carbethoxypyrrole and the mixture was allowed to stand at 0° for three days and room temperature for an additional day, at which time gas evolution had ceased. Ether was added, the solution was washed with dilute sodium carbonate and then steam distilled until four liters of distillate was collected. The distillate was extracted with four 250-ml. portions of ether and the ether extracts were dried and distilled giving recovered N-carbethoxypyrrole at 100° (50–55 mm.) and 2.5 g. of N-carbethoxy-3,2′-nornicotyrine at 141–143° (2 mm.). Similar extraction of the steam distillation residue gave an additional 0.5 g.; total, 3.0 g., 23% yield.

The picrate was prepared with ethanolic picric acid and recrystallized from ethanol, m.p. 146–147°.

Anal. Calcd. for $C_{18}H_{15}O_9N_5$: C, 48.5; H, 3.4; N, 15.7. Found: C, 48.6; H, 3.3; N, 15.7.

3,2′-Nornicotyrine.—To a solution of 1.3 g. of sodium hydroxide in 2.6 ml. of water was added 2.7 g. of the N-carbethoxy compound and sufficient ethanol to make a homogeneous solution. After standing at room temperature overnight, the solution was freed from ethanol by concentration at reduced pressure, the residue was extracted with three 50-ml. portions of ether, and the combined ether extracts were dried over magnesium sulfate and evaporated. Distillation of the residue gave 0.9 g. (50%) of 3,2′-nornicotyrine, b.p. 146–147° (1 mm.), which solidified in the receiver and melted at 98–100° on crystallization from benzene (5 ml.)–petroleum ether (1 ml.) (m.p. variously reported[9,15] from 99 to 101°).

Addition of saturated ethanolic picric acid gave a picrate which was crystallized from ethanol, m.p. 203–205° dec. (reported[9,15] m.p. from 202 to 204°).

(15) M. L. Swain, A. Eisner, C. F. Woodward and B. A. Brice, THIS JOURNAL, **71**, 1341 (1949); F. Lions and E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 110 (1940).

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An Anomalous Result of an Attempted Dakin Reaction

BY DAVID H. ROSENBLATT AND ROBERT W. ROSENTHAL

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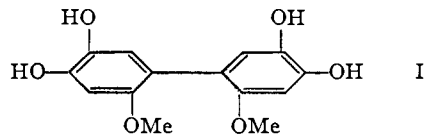
In connection with some studies being made in these laboratories, the synthesis of 4-methoxycatechol was undertaken. Kvalnes[1] reported, without giving any details of the synthesis, that he had obtained 4-methoxycatechol, m.p. 48–50°, in good yield by means of the Dakin[2] reaction, *i.e.*, replacement of the aldehydo or aceto group in ortho or para phenolic aldehydes or ketones with a hydroxyl group by means of hydrogen peroxide. When we added hydrogen peroxide to an aqueous solution of 2-hydroxy-5-methoxybenzaldehyde and sodium hydroxide, a precipitate was formed which softened at 200° and carbonized at 300°. Changing the reaction temperature from room temperature to 45°, and providing a nitrogen atmosphere to exclude oxygen, did not affect the results. The experiment was repeated twice, using lithium hydroxide and potassium hydroxide, respectively, and it was observed that, regardless of the hydroxide used, if the reaction mixture were allowed to stand for several days, the same precipitate was the only isolable product. Its solubility in hot water is compatible with the assumption that it is a polyhydroxy compound, but the high melting point of the material (m.p. 267–270° dec.) and its insolubility in ether suggest that it is not a simple nuclearly substituted catechol.

Raudnitz[3] has reported that the reaction between potassium persulfate and *p*-cresol yields 2,2′-dimethyl-5,5′-dihydroxydiphenyl, and Burton and Hopkins[4] have found that the oxidation of 4-methylcatechol by ferric acetate or silver oxide yields 4,5,4′,5′-tetrahydroxy-2,2′-dimethyldiphenyl and further oxidation products. These two analogous reactions suggest that the substance is a bis-(4-methoxycatechol) such as I or an isomer.



I

In an attempt to isolate the previously reported 4-methoxycatechol, a large quantity of the sodium salt of 2-hydroxy-5-methoxybenzaldehyde was treated with hydrogen peroxide according to Surrey's[5] procedure for making 3-methoxycatechol. Only a trace of a compound having the m.p. (48–50°) of 4-methoxycatechol[1] was found.

Experimental

2-Hydroxy-5-methoxybenzaldehyde.—This compound (b.p. 129° (12 mm.), lit. 124° (12 mm.)) was prepared by the Reimer–Tiemann reaction from *p*-methoxyphenol, as reported by Rubenstein.[6] The semicarbazone melted at 224–225°.

Bis-(4-methoxycatechol).—To a solution of 3.04 g. (0.02 mole) of 2-hydroxy-5-methoxybenzaldehyde in 20 ml. of 1 *N* KOH at room temperature was added in one portion 3.3 g. of 26% hydrogen peroxide in 30 ml. of water. The mixture became gradually brown, then cherry red, and was then heated for 15 minutes on a water-bath at 60°. The mixture was allowed to cool and stand overnight, whereupon 0.83 g. of precipitate was obtained. The precipitate was recrystallized three times from water slightly acidified with hydrochloric acid, m.p. 267–270°. When the mother liquor was allowed to stand several more days additional precipitate was isolated.

Anal. Calcd. for $C_{12}H_4(OCH_3)_2(OH)_4$: C, 60.4; H, 5.04; OCH_3, 22.3; mol. wt., 278; active H, 1.44, Found: C, 60.3, 59.8; H, 5.1, 5.1; OCH_3, 21.9; mol. wt.,[7] 279.6; active H, 1.46.

The same procedure with 1 *N* lithium hydroxide solution gave a similar result and a cleaner product.

4-Methoxycatechol.—To a mixture of 25 g. of 2-hydroxy-5-methoxybenzaldehyde and 83 ml. of 2 *N* sodium hydroxide at room temperature, 25 g. of 26% hydrogen peroxide in 145 ml. of water was added dropwise. The solution darkened and by the end of the addition, the temperature had risen to 60°. After the reaction mixture cooled, sodium chloride was added and the solution was extracted with chloroform. On standing the aqueous layer yielded several crops of the high-melting compound reported in this work. The solvent was removed from the chloroform extract and the residue was extracted with boiling water. A white precipitate, melting at 258–262°, which was evidently more of the biphenyl compound, formed from the extract overnight. The mother liquor was stored in the refrigerator and after several weeks a few large translucent crystals formed. This precipitate was filtered, dissolved in hot benzene, and reprecipitated with petroleum ether. The compound was yellow and melted at 49–51° (lit. 48–50°),

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(3) H. Raudnitz, *Ber.*, **63B**, 517 (1930).

(4) H. Burton and H. Hopkins, *J. Chem. Soc.*, 2445 (1952).

(5) A. Surrey, *Org. Syntheses*, **26**, 90 (1946).

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(7) Determined by modification of the method of Signer (*Ann.*, **478**, 246 (1930)), the details of which were reported by the Analytical Branch of the Chemical Corps Chemical and Radiological Laboratories, Army Chemical Center, Maryland (Abstracts of Papers, 123rd Meeting American Chemical Society, March,, 1953, p. 5B).

Acknowledgment.—The authors wish to thank Mr. Thomas Parr, III, and Pfc. Vyto Adomaitis for their aid in carrying out some of the syntheses. Analyses were performed by various members of the Analytical Branch of the Chemical Corps Chemical and Radiological Laboratories, Army Chemical Center, Maryland.

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Optical Rotation of Peptides. VII. α- and γ-Dipeptides of Glutamic Acid and Alanine[1]

BY HOWARD SACHS AND ERWIN BRAND

RECEIVED MAY 15, 1953

Previous papers in this series[2] dealt with the synthesis and specific rotations of a number of alanine and lysine peptides. In this paper, the synthesis and specific rotations (in 0.5 *N* HCl) of eleven isomeric dipeptides containing glutamic acid (symbol: H·Glu·OH)[3] and alanine (H·Ala·OH)[3] are presented. Detailed data on the residue rotations[4] of glutamic acid and alanine residues in these peptides will be reported subsequently.

The dipeptides were prepared by coupling the appropriate N-carbobenzyloxyamino acid with amino acid benzyl esters according to the method of Boissonnas[5]; the resulting N-carbobenzyloxy dipeptide benzyl esters were reduced to the free peptides with palladium and hydrogen. Alanine peptides (H·Ala-Glu·OH) were obtained by coupling Z·Ala·OH with glutamic acid dibenzyl ester[6] (H·Glu·OBz). Glutamic acid α-peptides were synthesized from the carbobenzyloxy γ-benzyl ester[7] (Z·Glu·OH) and the γ-peptides from the carbobenzyloxy α-benzyl ester[6] (Z·Glu·OBz).

In the Van Slyke carboxyl nitrogen determination (ninhydrin),[8] γ-dipeptides of glutamic acid should yield 1 mole of COOH nitrogen (COOH, N), while the α-peptides should yield none. That this is the case for these two types of glutamic acid dipeptides, synthesized by the methods outlined above, can be seen from Table II (compounds 15–22).

In the Van Slyke amino nitrogen determination (nitrous acid), the α-peptides give correct analytical values (1 mole of amino N, *cf.* Table II, compounds 12–18). With the γ-peptides, both amino and peptide nitrogens react (2 moles of amino N, Table II, compounds 19–22). This observation constitutes an important distinction between α- and γ-peptides of glutamic acid. The underlying mechanism will be discussed elsewhere in connection with additional data.[9]

The purity of these peptides was further confirmed by chromatography; α- and γ-isomers are readily separable by this method (*cf.* Table II, column R_{Glu}).

It has been established[10] that the synthesis of dipeptides of glutamic acid *via* its carbobenzyloxy anhydride (Z·Glu·O),[11] yields mixtures of α- and γ-peptides. It was thought that the synthesis of pure γ-peptides could be accomplished *via* the γ-azide of carbobenzyloxyglutamic acid, (Z·Glu·OH)[10,12–14]. However, we have found[15] that this procedure is not unequivocal, but leads to mixtures of α- and γ-peptides; from these mixtures, pure α- and γ-peptides can sometimes be obtained by fractional crystallization.[15]

In view of the difficulties encountered in the preparation of γ-peptides, it is essential that, in every case, homogeneity be established by all of the analytical procedures described above.

Experimental[16]

Starting Materials.—The syntheses and properties of some of the starting materials have been previously described: L- and D-alanine,[17] H·Ala·OBz (L) and (D) (ref. 17, compounds 5, 6), L- and D-glutamic acid,[6] H·Glu·OBz (L) and (D), and Z·Glu·OBz (L) (ref. 6, compounds 1, 2 and 5). Other starting materials used were: Z·Ala·OH (L) and (D),[11] Z·Glu·OH (L)[7] and H·Glu·OH (L)[7] (carboxyl nitrogen[8] content (ninhydrin, 100°, 7 min., *p*H 2.5): Calcd. for $C_{12}H_{15}O_4N$ (237.2): carboxyl N, 5.9. Found: carboxyl N, 5.9).

Carbobenzyloxy Dipeptide Benzyl Esters (Compounds 1–11).—The free COOH group of the carbobenzyloxyamino acids (Z·Ala·OH, Z·Glu·OH, Z·Glu·OBz) is converted into a tertiary amine salt. The tertiary amine salts, in turn, are converted with ethyl chlorocarbonate into the mixed an-

(1) From a dissertation to be submitted by Howard Sachs in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. Erwin Brand deceased July, 1953.

(2) Paper VI, E. Brand, B. F. Erlanger and H. Sachs, THIS JOURNAL, **74**, 1851 (1952).

(3) The following abbreviations and symbols are used (*cf.* E. Brand, *Ann. N. Y. Acad. Sci.*, **47**, 187 (1946); ref. 2, Table I, footnote *a*; ref. 6, footnote 2): Z, carbobenzyloxy, $C_6H_5CH_2OCO$; Bz, $C_6H_5CH_2$; Ala, $NHCH(CH_3)CO$, C_3H_6ON; Glu, $NHCH(CH_2CH_2COOH)CO$, $C_5H_7O_3N$; peptide linkage indicated by dash, -; configuration follows compound in parentheses, ( ). When the γ-carboxyl group of glutamic acid is substituted, the following symbol is used for the residue: Glu(OH). *e.g.*, N-carbobenzyloxy-γ-alanine benzyl ester, Z·Ala·OBz (L); N-carbobenzyloxy-D-glutamic acid γ-benzyl ester, Z·Glu(OH)·OH (D); N-carbobenzyloxy-L-alanyl-D-glutamic acid dibenzyl ester, Z·Ala-Glu(OBz)·OBz (LD); N-carbobenzyloxy-α-benzyl γ-L-glutamyl-D-alanine benzyl ester, Z·Glu(OBz)·OBz (LD); γ-L-glutamyl-D-glutamic acid, H·Glu(OH)·OH (LD); α-L-glutamyl-L-alanine, H·Glu-Ala(OH)·OH (2L)

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(16) We are indebted for analytical work to T. Zelmenis (total and amino N).

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TABLE I

CARBOBENZYLOXY DIPEPTIDE BENZYL ESTERS; ANALYTICAL DATA AND SPECIFIC ROTATIONS IN GLACIAL ACETIC ACID

No.	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. (cork)	Nitrogen, % Calcd.	Nitrogen, % Found	$[\alpha]^{23}D$ c, 2
	α-Dipeptide derivatives						
1	Z·Ala-Glu·OBz (LL) └OBz	$C_{30}H_{32}O_7N_2$	532.6	104–105	5.3	5.2	−16.6°
2	Z·Ala-Glu·OBz (LD) └OBz	$C_{30}H_{32}O_7N_2$	532.6	112–113	5.3	5.2	− 3.7
3	Z·Ala-Glu·OBz (DL) └OBz	$C_{30}H_{32}O_7N_2$	532.6	112–113	5.3	5.3	+ 3.8
4	Z·Glu-Ala·OBz (LL) └OBz	$C_{30}H_{32}O_7N_2$	532.6	102–104	5.3	5.3	−21.2
5	Z·Glu-Ala·OBz (LD) └OBz	$C_{30}H_{32}O_7N_2$	532.6	120–121	5.3	5.3	+ 2.6
6	Z·Glu-Glu·OBz (LL) └OBz └OBz	$C_{39}H_{40}O_9N_2$	680.7	104–105	4.1	4.1	−10.4
7	Z·Glu-Glu·OBz (LD) └OBz └OBz	$C_{39}H_{40}O_9N_2$	680.7	91–92	4.1	4.2	− 0.5
	γ-Dipeptide derivatives						
8	Z·Glu·OBz (LL) └Ala·OBz	$C_{30}H_{32}O_7N_2$	532.6	124–126	5.3	5.2	−16.2[c]
9	Z·Glu·OBz (LD) └Ala·OBz	$C_{30}H_{32}O_7N_2$	532.6	124–125	5.3	5.2	+14.7[b]
10	Z·Glu·OBz (LL) └Glu·OBz └OBz	$C_{39}H_{40}O_9N_2$	680.7	140.5–142	4.1	4.0	− 5.2
11	Z·Glu·OBz (LD) └Glu·OBz └OBz	$C_{39}H_{40}O_9N_2$	680.7	129.5–131	4.1	4.2	+ 3.3

[a] For an explanation of the symbols, *cf.* ref. 3. [b] At 25°. [c] At 26°.

TABLE II

DIPEPTIDES OF GLUTAMIC ACID AND ALANINE; ANALYTICAL DATA,[a] *R* VALUES AND SPECIFIC ROTATIONS IN 0.5 *N* HCl

No.	Compound[b]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Nitrogen, % Found	Amino N,[c] % Calcd.	Amino N,[c] % Found	Carboxyl N,[d] % Calcd.	Carboxyl N,[d] % Found	R_f[e]	R_{Glu}[f]	$[\alpha]^{24}D$ c, 1–2
	α-Peptides											
12	H·Ala-Glu·OH (LL)	$C_8H_{14}O_5N_2·H_2O$	236.2	11.8	11.8	5.9	5.9	0.0	0.0	0.3	1.1	− 9.3
13	H·Ala-Glu·OH (LD)	$C_8H_{14}O_5N_2$	218.2	12.8	12.9	6.4	6.4	.0	.0	.3	1.2	+32.4[g]
14	H·Ala-Glu·OH (DL)	$C_8H_{14}O_5N_2$	218.2	12.8	12.6	6.4	6.5	.0	.0	.3	1.1	−32.9[g]
15	H·Glu-Ala·OH (LL)	$C_8H_{14}O_5N_2$	218.2	12.8	12.7	6.4	6.6	.0	.0	.4	1.7	+ 7.3[h]
16	H·Glu-Ala·OH (LD)	$C_8H_{14}O_5N_2$	218.2	12.8	12.9	6.4	6.4	.0	.0	.4		+79.7
17	H·Glu-Glu·OH (LL)[i]	$C_{10}H_{16}O_7N_2$	276.2	10.1	10.0	5.1	5.3	.0	.0	.1	1.2	+18.2
18	H·Glu-Glu·OH (LD) └OH └OH	$C_{10}H_{16}O_7N_2$	276.2	10.1	10.2	5.1	5.0	.0	.0	.1		+56.4
	γ-Peptides											
19	H·Glu·OH (LL)[j] └Ala·OH	$C_8H_{14}O_5N_2$	218.2	12.8	12.8	6.4	12.3	6.4	6.4	0.4	1.1	−11.5
20	H·Glu·OH (LD) └Ala·OH	$C_8H_{14}O_5N_2$	218.2	12.8	13.0	6.4	12.0	6.3	6.4	.4	1.1	+63.1
21	H·Glu·OH (LL)[k] └Glu·OH	$C_{10}H_{16}O_7N_2$	276.2	10.1	10.1	5.1	10.1	5.1	5.0	.1	0.9	+ 3.8
22	H·Glu·OH (LD) └Glu·OH	$C_{10}H_{16}O_7N_2$	276.2	10.1	10.2	5.1	10.1	5.1	4.9	.1	0.9	+36.7[l]

[a] Compounds 12–14, 19–22 dried at 100° *in vacuo*, compounds 15, 17, 18 at 78°, compound 16 at 56°. [b] For an explanation of the symbols, *cf.* ref. 3. [c] Reaction time with nitrous acid was 3 minutes. [d] Reaction time with ninhydrin was 7 minutes at *p*H 2.5; *cf.* ref. 8. [e] After 40 hours; phenol–H_2O–NH_3 (ref. 18). [f] After 90 hours; butanol–acetic acid–H_2O (ref. 19). [g] At 23°. [h] At 27°. [i] Previously prepared (*cf.* ref. 11) with $[\alpha]^{18}D$ +19.9° (2.0% in H_2O + 1 equiv. HCl); we find $[\alpha]^{23}D$ +20.0° (0.9% in H_2O + 1 equiv. HCl). [j] Previously prepared (*cf.* ref. 13) with $[\alpha]^{18}D$ −22.1° (5.0% in H_2O); probably contained some α-isomer. We find $[\alpha]^{23}D$ −27.0° (5.3% in H_2O). [k] Previously prepared (*cf.* ref. 12) with $[\alpha]^{17}D$ +6.0° (1.1% in H_2O + 1 equiv. HCl); probably contained some α-isomer. [l] At 22°.

hydrides of ethylcarbonic acid. The peptide linkage is then formed by the action of amino acid esters on these anhydrides

$$Z\text{·Ala·ONHR}_3 \longrightarrow Z\text{·Ala·O·CO(OC}_2H_5) +$$

$$H\text{·Glu·OBz} \longrightarrow Z\text{·Ala-Glu·OBz} + CO_2 + C_2H_6OH$$
$$\text{└OBz} \qquad\qquad \text{└OBz}$$

Tri-*n*-butylamine (2.4 ml., 0.01 mole) is added to 0.01 mole of carbobenzyloxyamino acid in 20 ml. of dioxane, cooled to 5–10°, and 0.95 ml. (0.01 mole) of ethyl chlorocarbonate added. After standing at this temperature for 30 minutes, 25 ml. of a cooled (10°) dioxane solution, containing 0.013 mole of amino acid benzyl ester hydrochloride and 0.013 mole of tri-*n*-butylamine, is added. The reaction mixture is kept in the ice-box overnight; then 100 ml. of ethyl acetate, followed by 150 ml. of 0.5 *N* HCl, is added. The ethyl acetate layer is washed successively with 0.5 *N* HCl, 5% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, crystalline products are obtained, which are recrystallized first from ethyl acetate-

petroleum ether, and then from methanol–H_2O. The yield of pure compounds varies from 3.2 to 5.5 g. (60–80%, based on the carbobenzyloxyamino acid used).

Dipeptides (Compounds 12–22).—The carbobenzyloxy dipeptide benzyl esters are hydrogenated in the usual way,[2] using 80–90% acetic acid as solvent (a volume of 150 ml. per 0.015 mole of compound). Reduction is complete in approximately six hours. The peptides are recrystallized from H_2O (compounds 13, 14, 20), H_2O–ethanol (compounds 14, 15, 17, 18, 19, 21, 22), or 90% methanol and ether (compounds 12, 16). The yield of the individual pure peptides varies from 2.3 to 3.5 g. (70–85%).

Chromatography of Peptides.—Ascending, one dimensional, paper partition chromatography is employed using Whatman No. 1 paper and two solvent systems, (a) phenol–water–NH_3,[18] and (b) butanol–acetic acid–water (50:10:40).[19] A wad of filter paper is attached to the top of the paper cylinder.[20] This makes it possible to develop the chromatograms for 44–96 hours.

All peptides traveled as single spots in both systems. The α- and γ-isomers are readily separable in solvent system (b) as indicated by the R_{Glu} values in Table II.

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Benzyl Esters of Glutamic Acid[1]

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Benzyl esters of glutamic acid (symbol, H·Glu·OH)[2] are useful intermediates in peptide synthesis. The preparation and properties of the L- and D-isomers of the α- and of the dibenzyl esters are presented in this paper.

Experimental[3]

The starting materials, L- and D-glutamic acid,[4] had specific rotations $[\alpha]^{25}D$ +31.6° (1.0% in 6 *N* HCl), and $[\alpha]^{26}D$ −31.3° (1.3% in 6 N HCl), respectively. All melting points are corrected.

1. H·Glu(OBz)·HCl (L).—A suspension of 10 g. (0.068 mole) of L-glutamic acid in 150 ml. of benzyl alcohol is warmed to 55°, agitated with a magnetic stirrer while dry HCl is passed in for one hour, and the temperature permitted to rise. The mixture is transferred to a still, and 75 ml. of benzene added, which is distilled off with most of the H_2O at a bath temperature of about 40°. The mixture is now left *in vacuo* (approximately 10 mm.) for one hour at a bath temperature of 85°. Then, dry HCl is again passed in for one hour as described above. Unchanged glutamic acid hydrochloride (about 2 g.) is now filtered off, benzene added, and the process described previously is repeated. Dry HCl is passed in for a third time; after removal of about one-half of the benzyl alcohol *in vacuo* (steam-bath), the di-ester hydrochloride is precipitated with ether (5–7 volumes), and recrystallized from methanol–ether. The yield of pure compound is 15 g. (61%, not counting the recovered glutamic acid), m.p. 100–102°, $[\alpha]^{22}D$ +9.4° (1.5% in 0.1 *N* HCl).

Anal. Calcd. for $C_{19}H_{21}O_4N$·HCl (363.8): N, 3.9; amino N, 3.9. Found: N, 3.9; amino[5] N, 3.9.

2. H·Glu(OBz)·HCl (D).—This compound is obtained by the same procedure and in similar yield from D-glutamic acid as the L-isomer; m.p. 100–102°, $[\alpha]^{25}D$ −9.0° (2.0% in 0.1 *N* HCl).

Anal. Calcd. for $C_{19}H_{21}O_4N$·HCl (363.8): N, 3.9; amino N, 3.9. Found: N, 3.9; amino[5] N, 4.0.

3. H·Glu(OBz)·OBz (L).—Ten grams (0,027 mole) of compound 1, H·Glu(OBz)·HCl (L), is dissolved in 100 ml. of glacial acetic acid. Ten ml. (0.12 mole) of constant boiling HI (sp. gr. 1.7) is added and the solution kept at 50° for 5.5 hours. The reaction mixture is taken down *in vacuo* and the resulting oil repeatedly (at least twice) treated with 50 ml. of benzene, which each time is distilled off *in vacuo*. The dark brown sirup is then taken up in 60 ml. of cold (−10°) 95% ethanol containing 7 ml. (0.029 mole) of tri-*n*-butylamine. Additional tri-*n*-butylamine (3–4 ml.) is added to bring the *p*H (moist *p*H paper) to approximately 7, whereupon the product begins to crystallize out. After storing in the ice-box overnight, the product is filtered off and washed copiously with absolute ethanol and ether to give 5.7 g. of crystalline material. The crystals are dissolved at room temperature in 11 ml. of water containing 0.034 mole of HCl, decolorized with charcoal, and an equal volume of absolute ethanol is added. Upon neutralization with tri-*n*-butylamine, crystallization takes place; the mixture is then cooled (0°) for several hours. The yield of pure compound is 4.3 g. (67%), m.p. 147–148°, $[\alpha]^{25}D$ +12.2° (2.9% in 0.1 *N* HCl).

Anal. Calcd. for $C_{12}H_{15}O_4N$ (237.2): N, 5.9; amino N, 5.9; carboxyl nitrogen,[6] 0.0. Found: N, 5.9; amino N, 5.9; carboxyl nitrogen,[6] 0.0,

4. H·Glu·OBz (D).—This is obtained from compound 2 by the same procedure and yield as the L-isomer; m.p. 147–148°, $[\alpha]^{25}D$ −11.9° (2.0% in 0.1 *N* HCl).

Anal. Calcd. for $C_{12}H_{15}O_4N$ (237.2): N, 5.9; amino N, 5.9; carboxyl nitrogen,[6] 0.0. Found: N, 5.9; amino N, 6.1; carboxyl nitrogen,[6] 0.0.

5. Z·Glu·OBz (L).—5.0 g. (0.021 mole) of H·Glu·OBz (L) (compound 3) is suspended in a cooled (0°), and vigorously stirred solution of 3.45 g. (0.025 mole) of K_2CO_3 in 20 ml. of water. When almost all of the ester has dissolved, 4.25 g. (0.025 mole) of carbobenzyloxy chloride is added in four portions over a period of 30 minutes, maintaining the *p*H at approximately 8 by addition of a 10% K_2CO_3 solution (total of 15–20 ml.); and stirring is continued for an additional 10 minutes. The reaction mixture is extracted twice with 30 ml. of ether, and acidified with 6 *N* HCl, yielding a heavy oil which solidifies on standing. The product is recrystallized from CCl_4 or ethanol–water; yield of pure compound[7] is 5.5–6.6 g. (70–85%), with m.p. 95–96°, $[\alpha]^{24}D$ −10.4° (1.7% in glacial acetic acid).

(1) From a dissertation to be submitted by Howard Sachs in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. Erwin Brand deceased July, 1953.

(2) For symbols and abbreviations, see the preceding paper by H. Sachs and E. Brand, THIS JOURNAL, **75**, 4608 (1953). *E.g.*, D-glutamic acid-α-benzyl ester, H·Glu-OBz (D); L-glutamic acid-γ-benzyl ester, H·Glu·OH (L); L-glutamic acid dibenzyl ester hydrochloride, H·Glu(OBz)·OBz·HCl (L); N-carbobenzyloxy-L-glutamic acid α-benzyl ester, Z·Glu(OBz)·OBz (L).

(3) We are indebted for analytical work to T. Zelmenis (total and amino N).

(4) D-Glutamic acid was prepared by the enzymatic resolution of acetyl-DL-glutamic acid according to V. E. Price, J. B. Gilbert and J. P. Greenstein, *J. Biol. Chem.*, **179**, 1169 (1949). It was also obtained from DL-pyrrolidone carboxylic acid by alkaloid resolution (G. Hillmann and A. Elies, *Z. physiol. Chem.*, **283**, 31 (1948)); we are indebted to Dr. R. Dische for this material.

(5) The compound requires a reaction time of 10 minutes in the Van Slyke, manometric, amino N procedure.

(6) *Cf.* D. D. Van Slyke, R. T. Dillon, D. A. MacFadyen and P. Hamilton, *J. Biol. Chem.*, **141**, 627 (1941); reaction time with ninhydrin was for seven minutes at *p*H 2.5.

(7) A mixture of Z·Glu·OBz and Z·Glu·OH was obtained as an oil by M. Bergmann, L. Zervas and L. Salzmann (*Ber.*, **66**, 1288 (1933)), by treating N-carbobenzyloxy-L-glutamic anhydride with benzyl alcohol at 100°. W. J. LeQuesne and G. T. Young (*J. Chem. Soc.*, 1954 (1950)) fractionated the mixture with Na_2CO_3 and obtained a solid, m.p. 78–81°, which they considered to be Z·Glu·OBz (L).

Anal. Calcd. for $C_{20}H_{21}O_6N$ (371.4): N, 3.8; neut. equiv., 371. Found: N, 3.7; neut. equiv.,[8] 374.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 124-260).

(8) Obtained by titration in alcohol; *cf.* E. Brand, B. F. Erlanger and H. Sachs, THIS JOURNAL, **74**, 1851 (1952).

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Separation Factors for Expressing the Relative Adsorbabilities of Liquids on Adsorbents[1]

BY ROBERT W. SCHIESSLER AND CARLETON N. ROWE[2]

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Separation factors are used as criteria for the evaluation of various fractional separation processes. By analogy to relative volatility in fractional distillation, the adsorption separation factor, α, is defined as the ratio of relative adsorbabilities and may be expressed as

$$\alpha = (N_A/N_B)^a/(N_A/N_B)^l \qquad (1)$$

where

N = mole fraction
A and B = components
a = adsorbed phase
l = liquid phase

Experimental determination of the adsorbed phase composition cannot be made since a completely satisfactory method for the physical separation of the adsorbed and liquid phases has not been found, In consequence, only one application of the separation factor concept to the adsorption of binary liquid mixtures has been found in the literature. Mair, Westhaver and Rossini[3] have reported separation factors for a number of low molecular weight hydrocarbons. These were determined by a rather indirect method through the use of adsorption columns. A lengthy mathematical treatment of the fractionation process and an independent determination of the adsorbent capacity through the vapor phase were required to employ the fractionation data in an expression similar to equation 1.[4]

(1) American Petroleum Institute Research Project 42. Advisory Committee: H. Sutherland (Chairman), E. M. Barber, J. R. Bates, L. C. Beard, Jr., G. H. Denison, L. M. Henderson, R. F. Marschner, L. A. Mikeska and J. H. Ramser.

(2) American Petroleum Institute Research Fellow. Abstracted from an M.S. thesis by Carleton N. Rowe, 1953.

(3) B. J. Mair, J. W. Westhaver and F. D. Rossini, *Ind. Eng. Chem.*, **42**, 1279 (1950).

(4) The separation factor may be expressed[3] in terms of volume fractions by converting equation 1 as

$$\alpha = \frac{(N_A/N_B)^a}{(N_A/N_B)^l} = \frac{(n_A/n_B)^a}{(n_A/n_B)^l} = \frac{\left[\frac{(dv/M)_A}{(dv/M)_B}\right]^a}{\left[\frac{(dv/M)_A}{(dv/M)_B}\right]^l} = \frac{(v_A/v_B)^a}{(v_A/v_B)^l} = \frac{(V_A/V_B)^a}{(V_A/V_B)^l}$$

where α, N, A, B, a and l have the meanings stated previously

n = moles
v = volume *as liquid* of a component in either the liquid phase or the adsorbed phase
d = *liquid* density of the pure components
M = molecular weight
V = volume fraction

Separation factors determined by the column method tend to be in error since they generally vary with composition due to non-ideality, and wide composition ranges are covered in the column technique.

The present investigation was undertaken to find a direct and more accurate method for determining adsorption separation factors. Jones and Outridge,[5] and Mair, Westhaver and Rossini[3] have observed that the adsorbent capacity determined by equilibration through the vapor phase is nearly constant for pure liquids having widely different chemical compositions and properties, This has been confirmed in the present work for activated alumina and silica gel. Table I shows the average adsorbent capacities in cc, adsorbed per gram adsorbent for a number of liquids.

TABLE I

ADSORBENT CAPACITIES

Liquid	Alumina Capacity, cc./g.	Alumina Deviation from av., %	Silica gel Capacity, cc./g.	Silica gel Deviation from av., %
Methylcyclohexane	0.213	−0.5	0.357	−1.4
n-Heptane	.218	+1.9	.356	−1.7
Benzene	.217	+1.4	.365	+0.8
Cyclohexane	...	...	.349	−3.6
5-*n*-Butylnonane	.209	−2.3	...	...
Water	.211	−1.4	.383	+5.8
Av.	.214	1.5	.362	2.6

Defining the adsorbed phase in terms of the adsorbent capacity,[6,7] an expression may be derived for determining the separation factor in a static system. In the derivation, the assumption is made that the volumes are additive. Let

A = component preferentially adsorbed
V_A^l = vol. fctn. of A in original liquid mixture
V_A^l = vol. fctn. of A in liquid phase at equilibrium
V_A^a = vol. fctn. of A in adsorbed phase at equilibrium
X = vol. of original liquid mixture in cc.
Y = vol. of liquid phase at equilibrium in cc.
W = weight of adsorbent
z = capacity of adsorbent, cc./g,
Z = Wz, total capacity of W g. of adsorbent in cc.

The material balance for component A at equilibrium is

$$V_A^l X = V_A^l Y + V_A^a(X - Y) \qquad (2)$$

but, as previously defined

$$Z = (X - Y) \qquad (3)$$

thus

$$V_A^l X = V_A^l(X - Z) + V_A^a Z \qquad (4)$$

Rearranging

$$V_A^a = (V_A^l - V_A^l)X/Z + V_A^l \qquad (5)$$

Since the separation factor may be determined from volume fractions[4] and since $V_B^a = 1 - V_A^a$, equation 1 reduces to

$$\alpha = V_B^l V_A^a / V_A^l(1 - V_A^a) \qquad (6)$$

(5) D. C. Jones and L. Outridge, *J. Chem. Soc.*, 1574 (1930).

(6) The assumption that the adsorbent capacity determined by vapor phase equilibration is analogous to the adsorbed phase when the adsorbent is immersed in liquid is slightly erroneous due to the reduction of the vapor pressure of the liquid trapped in fine capillaries.[5]

(7) Mair, Westhaver and Rossini[3] used the adsorbent capacity determined through the vapor phase in their estimation of separation factors from column data.

Substituting equation 5 in equation 6, recalling that $V_A^1 + V_B^1 = 1$, and subtracting 1 from both sides for simplification

$$\alpha - 1 = \frac{(V_A^1 - V_A)X}{V_A^1[V_B Z - (V_A^1 - V_A)X]} \qquad (7)$$

Equation 7 is an expression of the separation factor in terms of readily determined quantities.

Error due to any non-additivity in volume can be reduced by employing an experimentally-determined density–composition curve to find the value for X used in equation 7.

Expressions similar to equation 7 may be derived using mole fraction or weight fraction, but both involve the density of a liquid mixture having the composition of the adsorbed phase. Assuming density to be linear with composition, or experimentally determining a density–composition curve, it is possible to calculate the separation factor using either mole fraction or weight fraction, but the equations are more complex. From the nature of the separation factor expression, any non-additivity in volume will lead to the same error, independent of the method of expressing the compositions.

A comparison of separation factors determined by the column method and the static method can be made for *n*-hexane/benzene mixtures on silica gel. Mair, Westhaver and Rossini[3] have determined separation factors for this hydrocarbon pair by the use of the column method. These values are shown graphically in Fig. 1. Equilibria data for the same hydrocarbon pair and the same type adsorbent (Davison Chemical Corporation, No. 22-08, "through 200 mesh") in a static system have been reported by Lombardo.[8] From these data we have calculated separation factors, also plotted in Fig. 1.

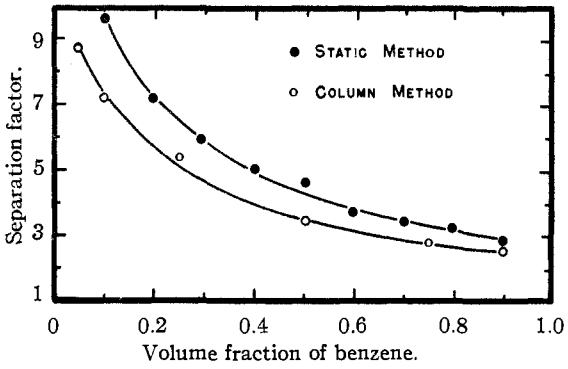

Fig. 1.—Separation factors for benzene/*n*-hexane mixtures.

The results indicate that the separation factors determined by the static method are higher than those determined by the column method. Since both methods assume additivity in volumes, and since both methods define the adsorbed phase in terms of the adsorbent capacity as determined by equilibration through the vapor phase, any deviations from these two assumptions could not account for the differences between the two curves. Due to the broad composition range covered in the column method, involving a broad range of separation factors, it is believed that the separation factors determined by the static method are more accurate. Furthermore, the attainment of equilibrium was determined experimentally in the static method, and must be assumed in the column method.

(8) R. J. Lombardo, Ph.D. Thesis, The Pennsylvania State College (1951). An equation similar to 5 was employed to determine the composition of the adsorbed phase.

Experimental

The experimental work consisted of determining the adsorbent capacities listed in Table I.

Adsorbents.—Activated alumina (Alcoa, F-20 grade, 80–200 mesh) was pretreated by heating to 200° for 16 hours in a 10 mm. i.d. column with passage of a slow stream of nitrogen gas through the column. Silica gel (Davison Chemical Corporation, No. 11-08-08-01, 28–200 mesh) was heated to 175° for 20 hours in the same apparatus.

Test Liquids.—Table II lists the liquids, their sources, refractive indices and vapor pressures at room temperature. Methylcyclohexane was purified by distillation in a helix packed column of 35–40 plates at a reflux ratio of 15/1 and passed over silica gel. Cyclohexane was passed over silica gel twice before use. The distilled water was boiled to remove any dissolved gases.

TABLE II

TEST LIQUIDS

Liquid	Source	$n^{25}D$	Approx. v.p. at 25°, mm.
Methylcyclohexane	Phillips, Tech. Grade, 95 mole % pure	1.4213[a]	48.0
Cyclohexane	Eastman, Practical	1.4236[a]	96.0
n-Heptane	Pure, Westvaco	1.3851	49.0
Benzene	Phillips, 99.97% pure	1.4976	95.2
Distilled water	Laboratory	1.3321	23.8
5-*n*-Butylnonane	API Project 42 Penn. State	1.4246	0.2

[a] Refractive index following purification.

Procedure for Determining Adsorbent Capacity.—The pretreated adsorbent was placed in a weighed covered Petri dish, and then dish and contents were weighed to the nearest ±0.0001 g. to give the weight of the adsorbent. The Petri dish and adsorbent were placed in a desiccator along with pure liquid in another open Petri dish. The desiccator was evacuated until the vapor pressure of the liquid was approached. The desiccator was then sealed and equilibration allowed to proceed. At 24-hour intervals, the adsorbent plus adsorbate was weighed to the nearest ±0.0001 g. until no increase in weight was observed. The weight of the adsorbate divided by the density of the liquid at room temperature gave the volume of the liquid adsorbed.

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A Study of the Quantitative Dinitrophenylation of Amino Acids and Peptides

BY W. A. SCHROEDER AND JOANN LEGETTE

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During an investigation of peptides in partial hydrolysates of gelatin,[1] the method of Sanger[2] has been used not only for the identification of the N-terminal amino acids but also for the identification and estimation of the other amino acids of the peptides. According to this method, the dinitrophenyl (DNP) peptide is completely hy-

(1) W. A. Schroeder, L. Hounen and F. C. Green, *Proc. Nat. Acad. Sci.*, **39**, 23 (1953).

(2) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

drolyzed and the N-terminal DNP-amino acid so released is extracted and identified. The remaining amino acids of the peptide which are present as the free amino acids in the hydrolysate are identified and estimated after conversion to the DNP-amino acids. When known amounts of DNP-peptides are hydrolyzed, one would not expect to recover an equimolar quantity of N-terminal DNP-amino acid because of the known partial destruction during hydrolysis. However, because there is no evidence that the other amino acids are destroyed during hydrolysis of a DNP-peptide, one would expect to be able to isolate them in amounts equimolar to the starting amount of DNP-peptide if their conversion to the DNP-derivative were quantitative. In most of our experiments this anticipated result was not realized and the DNP-amino acids, both terminal and other, failed to correspond to the amount of DNP-peptide. The present investigation was made in order to ascertain what conditions were required to produce quantitative dinitrophenylation of amino acids and peptides: this aim has to some extent been achieved. A correlation of the present results with some previously recorded in the literature will be presented in the discussion.

Experimental

Reagents.—The sources of amino acids were the same as those previously used.[3] Gly-DL-ala[4] and DL-ala-gly were obtained from Amino Acid Manufactures (University of California at Los Angeles), L-leu-gly-gly from Delta Chemical Works, and ala-ala-ala-ala (4 L) from Dr. Erwin Brand. Sodium bicarbonate was J. T. Baker analyzed C.P. grade and sodium carbonate was Baker and Adamson reagent grade. 2,4-Dinitrofluorobenzene (DNFB) was prepared by dinitration of fluorobenzene and purified both by distillation at reduced pressure and by chromatography on silicic acid–Celite. Absolute alcohol was obtained from U.S. Industrial Chemicals Co. Anhydrous ether from General Chemical Co. was distilled before use.

Dinitrophenylation Procedures.—All procedures for dinitrophenylation had certain common features despite variations which were introduced from time to time. One ml. of a standard solution which contained one micromole of amino acid or peptide per ml. was pipetted into a 100-ml. glass-stoppered flask, and sodium carbonate or bicarbonate was added followed by a solution of DNFB in 2 ml. of undistilled absolute alcohol. (Distilled alcohol gives extraneous zones on chromatograms of a blank dinitrophenylation.) The mixture was then mechanically shaken for 3 hr.

Three distinct procedures of dinitrophenylation were used. These differed in the quantities of reagents as shown in the following tabulation:

Reagent	Dinitrophenylation procedure First	Second	Third
$NaHCO_3$, mg.	100	....	20
Na_2CO_3, mg.	....	100	...
DNFB, ml.	0.1	0.1	0.02

Other variants on these three procedures will be given when the results are presented.

Extractive Procedures.—After any of the above procedures had been used, the reaction mixture was transferred to a separatory funnel with 10 ml. of water. In those experiments in which the amount of water and alcohol in the reaction mixture was increased, 20 ml. of water was used for the transfer. When sodium carbonate was used, the transfer of the large amount of dinitrophenol was expedited by using, in addition to the water, the 25 ml. of ether which was used for the first extraction (see below).

The **original extractive procedure** was as follows. The transferred reaction mixture was extracted with 4 × 25 ml. of ether to remove unreacted DNFB, acidified with one ml. of 6 *N* hydrochloric acid, and further extracted with 2 × 25 and 5 × 10 ml. of ether to remove the DNP-amino acid or DNP-peptide. The latter ether extracts were then washed with 3 × 10 ml. of water to each portion of which two drops of 6 *N* hydrochloric acid was added. Unless acid is added to the wash waters, some DNP-amino acids and DNP-peptides tend to re-enter the aqueous phase during washing.

The **revised extractive procedure** differed from the above only in that the transferred reaction mixture was acidified directly and the preliminary extraction of the basic solution to remove DNFB was omitted.

For the extraction of DNP-peptides, ethyl acetate replaced ether in the extraction of the acidified solutions.

Chromatographic Procedures.—During a dinitrophenylation, 2,4-dinitrophenol is formed to a greater or less extent. One cannot therefore determine directly the quantity of DNP-compound which has been extracted from the dinitrophenylation mixture, for example, by spectrophotometry. This interfering substance has been removed chromatographically.

The extracts of the dinitrophenylation mixtures were prepared for chromatography as previously described,[5] and each DNP-amino acid and DNP-peptide was then chromatographed in all particulars by the method of Green and Kay.[6] Each compound was developed with 6 or 7 *V* ml. of a developer appropriate to the group to which it belonged. Dinitrophenol is removed by 1 or 2 *V* ml. of any developer which is used in the method. DNP-Gly-ala and DNP-ala-gly were developed with 3AA-15A-L, DNP-leu-gly-gly with 2AA-10A-B and DNP-ala-ala-ala-ala with 3AA-15A-B (abbreviations as in Green and Kay[6]).

Spectrophotometric Procedures.—After the compound had been chromatographed and eluted, the eluent was evaporated and the residue of DNP-compound was taken up in glacial acetic acid for spectrophotometric determination. For spectrophotometric calculations, it has been assumed that the molecular extinction coefficient of DNP-amino acids and DNP-peptides is 1.61×10^4 liters per mole cm. at 340 ± 2 mμ in glacial acetic acid, except in the case of α,ε-di-DNP-lysine in which the determined value is 3.22×10^4 at 342 mμ and of DNP-proline in which the determined value is 1.75×10^4 at 360 mμ. If these coefficients are recalculated in terms of the ratio: concn. in micromoles per 100 ml. of soln./optical density for a 1-cm. length of soln., the values of 6.2, 3.1 and 5.7, respectively, are obtained. These are more convenient for calculation of quantity.

The assumed constants were arrived at from a study of values which had been determined for several compounds.[5] DNP-Aspartic acid which has been much used in the present study was found by determination to have exactly the assumed value.

Results and Discussion

Table I records the percentage of the theoretical amount of various DNP-amino acids and DNP-peptides which was isolated after the use of the several procedures described above.

In these experiments, one micromole of compound has been used because this quantity forms nicely visible zones on the chromatographic column and also is sufficient to require dilution to about 20 ml. before the spectrophotometric reading is taken. At such dilution, the blank correction introduced by the chromatographic procedure is inconsequential: it would reduce the values in Table I by no more than one per cent. and has not been applied. One correction, however, has been applied to give the results in Table I. It has been found that when such diverse DNP-derivatives as α,ε-di-DNP-lysine, DNP-aspartic acid, DNP-valine and DNP-phenylalanine are chromatographed, there is a loss of about 7% per chromatogram. It has been assumed that all the compounds listed

(3) W. A. Schroeder, L. M. Kay and R. S. Mills, *Anal. Chem.*, **22**, 760 (1950).

(4) Abbreviations follow the suggestions of E. Brand (*Ann. N. Y. Acad. Sci.*, **47**, 222 (1948), and F. Sanger (*Adv. Prot. Chem.*, **7**, 5 (1952)).

(5) W. A. Schroeder, THIS JOURNAL, **74**, 5118 (1952).

(6) F. C. Green and L. M. Kay, *Anal. Chem.*, **24**, 726 (1952).

TABLE I

PERCENTAGE OF THE THEORETICAL AMOUNT RECOVERED AFTER VARIOUS METHODS OF DINITROPHENYLATION

Amino acid or peptide[a]	Dinitrophenylation procedure: First[b]	Second[b]	Third[c]
Ala	97, 87, 90[d]	97, 102, 96, 101	100, 100
Asp	61, 60, 66, 69	83, 80, 84	93, 94
Glu	70, 61, 69, 68	86, 80, 83	96, 98
Gly	85, 80	95, 95	94, 98
Leu			97, 99[e]
Lys	78, 78, 80, 81	92, 86, 89	99, 96
Pro	72, 75	77	82, 76
Thr			99, 98
Ala-gly			95, 95
Gly-ala	82	88	82
Leu-gly-gly			85, 90
Ala-ala-ala-ala			82, 82

[a] One micromole of each was taken. [b] Original extractive procedure. [c] Revised extractive procedure. [d] Individual replicate values in chronological order of determination. [e] Original extractive procedure was used because contamination, apparently by DNFB, invalidates the results.

in Table I are lost to this degree in the course of one chromatogram and, hence, the values given have been corrected to this extent. It has not been possible to ascertain the cause of the losses which are suffered during chromatography. Experiments have shown, however, that it is not due to the action of light or to the use of ether in the procedure.

The proportions of water, alcohol, sodium bicarbonate and DNFB which were used in the first dinitrophenylation procedure are those which Sanger[2] used for dinitrophenylating insulin and they are very similar to his conditions for dinitrophenylating phenylalanine. It is evident from Table I that the dinitrophenylation is not quantitative in any instance and that the conversion of aspartic acid is especially poor. Mills[7] has also noted the difficulty with which aspartic acid is dinitrophenylated but he achieved quantitative results by increasing the time of reaction. He claims quantitative conversions for the other amino acids. Middlebrook[8] found that increase in reaction time did not improve the yield of DNP-aspartic acid but that the substitution of sodium carbonate for sodium bicarbonate did give quantitative recovery.

The second dinitrophenylation procedure (in which this substitution was used) very definitely improved the recoveries. The yield of DNP-alanine and DNP-glycine is almost quantitative and that of DNP-aspartic acid, DNP-glutamic acid and di-DNP-lysine is much improved; on the other hand, that of DNP-proline is little altered. The use of sodium carbonate has the disadvantage that rather large amounts of dinitrophenol are formed in this more basic solution although the dinitrophenol does not interfere chromatographically. In addition, artefacts appear on the chromatograms.

Within the framework of these two procedures, a number of variations were introduced. Thus, with the second procedure as a basis and with aspartic acid as a test substance, the time of reaction, the amount of sodium carbonate, and the method of extracttion were varied. The results may be tabulated as follows:

(7) G. L. Mills, *Biochem. J.*, **50**, 707 (1952).

(8) W. R. Middlebrook, private communication.

Time of reaction, hr.	Yield of DNP-aspartic acid, %
0.5	79, 79
3	83, 80, 84
7.5	83, 73
Amount of sodium carbonate, mg.	
30	83, 83
100	83, 80, 84
Extractive procedure	
Original	83, 80, 84
Revised	83, 88, 89

The reaction clearly is very rapid and essentially the same results are obtained over the period from 0.5 to 7.5 hours. Variation in the amount of sodium carbonate has no effect while the revised extractive procedure increased the yield slightly. Thus, of the above variations only the revised extractive procedure showed even minor improvement.

One variant of the first dinitrophenylation procedure was also tried in order to test the effect of light. Mills,[7] for example, recommends that photochemical reactions be reduced by shielding the DNP-derivatives from light. When aspartic acid was dinitrophenylated and carried through the procedure with the exclusion of all but the dimmest light required to carry out the various operations, the yield of 61% was not improved over those of 61, 60, 66 and 69% which were obtained under normal conditions of laboratory lighting. Our laboratories are lighted by fluorescent fixtures and the amount of natural light is negligible.

It was, of course, possible that the scale of the experiments was so small that manipulative losses were responsible for the poor yields. Consequently when the first dinitrophenylation procedure was used but the quantity of aspartic acid was increased from one to 10 micromoles, the yield also increased from an average of 64% to 81 and 79%. The definite improvement warranted further experiments. When 10 micromoles of aspartic acid was dinitrophenylated in 5 ml. of water and 10 ml. of alcohol which contained the usual 100 mg. of sodium bicarbonate and 0.1 ml. of DNFB, the recovery was 92%: when, under these same conditions, only one micromole of aspartic acid was used, the recovery was 94%. These results lead to the conclusion that the concentration of the reagents is important in improving the yield of the dinitrophenylation. Consequently, the third dinitrophenylation procedure was devised and the revised extractive procedure was used because it had given slightly higher yields.

Before discussing those results which were obtained with the third procedure and which are recorded in Table I, let us mention the effect of variation from the third procedure since in actual practice it is not always possible to use exactly these conditions. Aspartic acid was again chosen as the test substance because it seems to be one of the most difficult to dinitrophenylate. The variables which were introduced into the third procedure were time of reaction, amount of amino acid, amount of sodium bicarbonate, and extractive procedure. The following results were obtained:

Time of reaction, hr.	Yield of DNP-aspartic acid, %
0.5	86
1	91
3	93, 94
8	93
Amount of amino acid micromoles	
0.3	83, 84
1.0	93, 94
10.0	98, 97
Amount of sodium bicarbonate, mg.	
5	94
20	93, 94
Extractive procedure	
Original	85
Revised	93, 94

As previously noted, the reaction is rapid and the results are constant between 1 and 8 hr. Very probably the concentration of amino acid rather than incidental manipulative losses is responsible for the differences which appear when the amount of amino acid is altered. Thus, if one micromole is used but the concentration is reduced by using 5 ml. of water and 10 ml. of alcohol, the yield is only 85%. Further decrease in the amount of sodium bicarbonate is without effect but the revised extractive procedure apparently improves the recovery by a few per cent.

When the third procedure is used, the recoveries as shown in Table I are generally satisfactory. After this method was found to give improved results, the scope of the study was broadened to include other representative amino acids and some peptides. Of the amino acids, proline alone behaves much the same in each procedure and gives a rather low yield. Structural features may influence the result in this case as there is no reason to believe that the proline is impure. It is more difficult to assess the results from the peptides because studies of their purity have not been made.

The literature records only a few studies of the quantitativeness of the dinitrophenylation of amino acids. As already mentioned, the first procedure of the present study is essentially that of Sanger.[2] Porter and Sanger[9] studied the quantitative dinitrophenylation of valine but fail to describe experimental details. Mills[7] has obtained quantitative dinitrophenylation of all amino acids and Krol[10] has shown that glycine reacts quantitatively. In the light of the present results, Mills' description of procedure is significant. "Residual HCl (from a hydrolysate) was neutralized by the careful addition of a *slight excess* of sodium bicarbonate...." (Italics ours.) Likewise, Krol used only 30 or 40 mg. of sodium bicarbonate per 3 ml. of reaction mixture. Apparently, their quantitative results stemmed from their use of small amounts of sodium bicarbonate.

Several observations have been made which may throw some light on the reason why the reaction is more quantitative when the reagents are less concentrated. In the third procedure, the reaction mixture is homogeneous in contrast to the others. This may mean that the actual concentration of reagents is greater because the bicarbonate cannot have salted out the DNFB. Although, in both the first and third procedures, the DNFB is in excess at the end of the reaction, much less dinitrophenol is produced in the third procedure. The reduction of this competitive reaction may influence the course of the dinitrophenylation in the homogeneous reaction mixture. It may be noted that a homogeneous solution was present in that experiment in which an improved yield of DNP-aspartic acid was obtained simply by changing the amount of solvents in the original procedure from 1 to 5 ml. of water and from 2 to 10 ml. of alcohol. The change in conditions does not seem to involve the shifting of an equilibrium. Thus, when a known amount of DNP-aspartic acid was "dinitrophenylated" by both the first and the third procedures, the recovery was 94 and 95%, respectively. If an equilibrium were involved, the former value should be about 64%.

(9) R. R. Porter and F. Sanger, *Biochem. J.*, **42**, 287 (1948).
(10) S. Krol, *ibid.*, **52**, 227 (1952).

Applications

The third dinitrophenylation procedure has been used with success in the study of peptides from partial hydrolysates of gelatin.[1] The estimation of the amino acids other than the N-terminal amino acids of the peptides is generally better than 90% of the starting DNP-peptides. It is advisable, however, to use the original rather than the revised extractive procedure. When the original extractive procedure is used, dinitroaniline is removed during the extraction of the basic solution, but if the revised procedure is used, dinitroaniline is always present on the chromatograms and requires definite identification in order to distinguish it from DNP-phenylalanine. The source of the dinitroaniline is unknown and if the revised procedure is used, its presence on the chromatograms leads to unnecessary complications.

Conclusions

The investigation has shown that the quantitative dinitrophenylation of amino acids is best achieved by carrying out the reaction in a homogeneous solution of amino acid, sodium bicarbonate, DNFB, alcohol and water.

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Correlation between the Structure of Some Dinitrophenyl Peptides and their Chromatographic Behavior on Silicic Acid–Celite

BY W. A. SCHROEDER AND LEWIS R. HONNEN

RECEIVED MAY 14, 1953

During the determination of the N-terminal amino acid of lysozyme,[1] dinitrophenyl (DNP) peptides were detected in certain hydrolysates and

(1) F. C. Green and W. A. Schroeder, THIS JOURNAL, **73**, 1385 (1951).

were separated and identified in subsequent studies[2] by an extension of the methods which were devised by Green and Kay[3] for the separation and identification of DNP-amino acids. The investigation of these peptides demonstrated that the separation of unknown peptides would be greatly facilitated by a study of the chromatographic behavior of known DNP-peptides.

Consequently, although there was little intrinsic interest in any particular peptide, a variety of known DNP-peptides was chromatographed in order to give any conclusions more general validity. From the accumulated data it has been possible to deduce generalizations which permit the prediction of the chromatographic behavior of known DNP-peptides with considerable success or conversely which aid in the identification of tentatively identified DNP-peptides through the comparison of determined and predicted behaviors. This information which is the subject of the present report has been very useful in recent examinations of the peptides in partial hydrolysates of gelatin.[4]

Experimental

Sources of Peptides.—The peptides were obtained from the following sources: DL-ala-gly,[5] gly-DL-ala, gly-gly and gly-L-leu from Amino Acid Manufactures (University of California at Los Angeles); gly-L-try, gly-L-tyr, L-leu-gly, DL-leu-gly-gly and L-leu-L-tyr from Delta Chemical Works; L-ala-L-ala, tri-ala (3 L), tetra-ala (4 L), penta-ala (5 L), gly-L-ala-L-ala, gly-L-ala-gly, gly-L-lys-gly, L-lys-L-ala and L-lys-gly from Dr. Erwin Brand; tri-gly from Nutritional Biochemicals Corp.; gly-L-pro and L-hypro-gly from Dr. Emil L. Smith; lys-glu from Dr. Barbara Low; L-lys-L-val-L-phe-gly from Dr. James R. Vaughan, Jr.; di-DNP-L-lys-L-val-L-phe and di-DNP-L-lys-L-val from partial hydrolysis of di-DNP-L-lys-L-val-L-phe-gly; and D-pro-D-val from Dr. Sidney W. Fox.

Preparation of DNP-Peptides.—The method for the preparation of the DNP-peptides was similar to that of Sanger[6] for the preparation of DNP-insulin. A 5- or 10-mg. sample of peptide was placed in a 10-ml. glass-stoppered erlenmeyer flask and dissolved in one ml. of water. To this solution were added 100 mg. of J. T. Baker analyzed C.P. sodium bicarbonate and a solution of 0.1 ml. of 2,4-dinitrofluorobenzene (DNFB) (prepared by dinitration of fluorobenzene followed by distillation *in vacuo*) in 1.9 ml. of undistilled absolute alcohol (U.S. Industrial Chemicals Co.). After the reaction mixture had been shaken mechanically for 3 hr., it was transferred to a separatory funnel with 10 ml. of water and extracted with 4 × 25 ml. of ether (General Chemical Co.) to remove excess DNFB. Following acidification with one ml. of 6 *N* hydrochloric acid, the DNP-peptide was extracted with 2 × 15 and 4 × 10 ml. of ether or ethyl acetate. The nature of the DNP-peptide itself determined the choice of solvent; ethyl acetate was used if the distribution favored the aqueous phase and extraction with ether was unsatisfactory. The combined extracts were washed once with 10 ml. of water. (More recent experience has shown that it is advisable to acidify such wash water with a drop or two of 6 *N* hydrochloric acid in order to reduce re-extraction into the aqueous phase.) Finally, the solvent was evaporated from the extracts in preparation for the chromatography of the DNP-peptide. Sometimes, acidification of the reaction mixture caused precipitation of the DNP-peptide and then it was isolated by centrifugation. After washing with one ml. of water and recentrifuging, the precipitate was dissolved in acetone, transferred to a flask, and the solvent and traces of water were evaporated in preparation for chromatography.

The DNP-peptides so prepared were chromatographed without further purification and yet in only a few instances were zones of impurity observed on the chromatograms.

No attempt has been made to assess the yield of any DNP-peptide.

Chromatographic Procedures.—The chromatographic apparatus, the adsorbent, the packing and prewashing of the column and the types of developer were identical with those used by Green and Kay[3] for the separation of DNP-amino acids on silicic acid–Celite. The abbreviations used below are also those of Green and Kay.

The choice of a suitable solvent in which to place a DNP-peptide on the chromatographic column is determined to a large extent by the solubility of the individual DNP-peptide. In the present study, the sample solvents ranged in composition from 10 to 40 volume % of acetone in ligroin (60–70°) (abbreviated 10A-L to 40A-L) and from 5 to 10 volume % of acetic acid in benzene (5AA-B to 10AA-B). Of these, 10A-L is the poorest solvent and 10AA-B the best but for some DNP-peptides 10A-L is entirely satisfactory. More recent experience has led to the conclusion that solvents in which at least a little acetic acid is present are to be preferred over those which contain only acetone and ligroin. Most peptides are fairly strongly adsorbed and as a result 5AA-B or 10AA-B may generally be used and 2AA-10A-L certainly can. If the peptide is very insoluble, it is probably also very strongly adsorbed and solvents such as 5AA-5A-B and 10AA-10A-B which are good solvents but also strong developers are altogether satisfactory. In the majority of cases, 5AA-B or 10AA-B is very suitable. When columns about 1 cm. in diameter are used, a sample volume of 2 or 3 ml. is generally adequate. The amount of DNP-peptide which was used in each chromatogram is not known but it was sufficient to produce a nicely visible zone.

All of the chromatograms were run on 9 × 150-mm. columns of silicic acid–Celite. In general, each zone was developed with 7 *V* ml.[7] of developer and the position of the zone was measured at regular intervals throughout the development. Although each compound was chromatographed individually, only a few mixtures were studied. The chromatographic behavior was determined with the following nine developers: 2AA-10A-L, 3AA-15A-L, 4AA-20A-L, 8AA-8A-L, 8AA-4A-L, 12AA-6A-L, 10AA-B, 2AA-10A-B and 3AA-15A-B. Not all DNP-peptides have been developed with all of these developers and, likewise, duplicate chromatograms of a given DNP-peptide with a given developer have not usually been made. In those instances, in which duplicates or replicates have been made either within a short time or even after more than a year, the positions of leading and trailing edges of the zones usually did not differ by more than 5 mm.; this is a normal variation. One serious discrepancy was resolved by further chromatograms.

Results and Discussion

Representative results from several useful developers are recorded in Fig. 1. Only a portion of the available data is presented here, but the general features of the remainder will be correlated with the information of Fig. 1 in the discussion to follow. The bar graphs of Fig. 1 show the position of each zone of DNP-peptide after development with the type and quantity of developer listed.

Correlation between Structure and Chromatographic Behavior.—Even cursory examination of the data demonstrates that there is no correlation between the chromatographic behavior of dissimilar DNP-peptides on silicic acid–Celite and the length of the peptide chain: DNP-dipeptides, DNP-tripeptides, *etc.*, do not fall into distinct groups but rather there is such a wide range of adsorption affinities within each group that some DNP-dipeptides are as strongly adsorbed as DNP-tetrapeptides. Neither is the chromatographic behavior conditioned by the presence of a given

(2) W. A. Schroeder, THIS JOURNAL,, **74**, 5118 (1952).

(3) F. C. Green and L. M. Kay, *Anal. Chem.*, **24**, 726 (1952).

(4) W. A. Schroeder, L. Honnen and F. C. Green, *Proc. Nat. Acad. Sci.*, **39**, 23 (1953).

(5) The abbreviations follow the suggestions of E. Brand (*Ann. N. Y. Acad Sci.*, **47**, 222 (1946)) and F. Sanger (*Adv. Prot. Chem.*, **7**, 5 (1952)).

(6) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(7) *V* ml. is the volume of solvent required to wet the column.

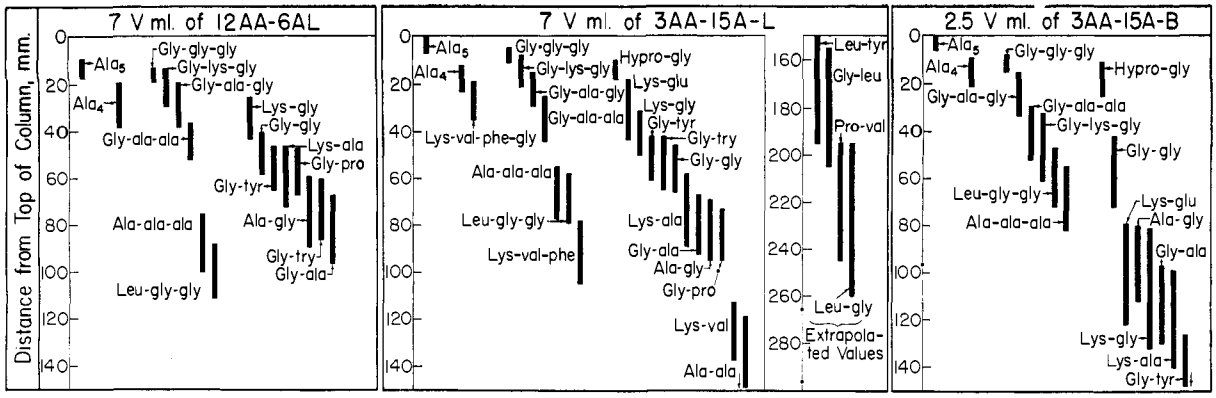

Fig. 1.—Positions of zones of DNP-peptides on columns of silicic acid–Celite after development with the type and quantity of developer listed.

amino acid in a certain position in the peptide, say, N-terminal or C-terminal: if this were so, all glycyl peptides, for example, would have similar affinities.

However, it is possible to establish a very generally applicable correlation between the relative adsorption affinities of DNP-peptides and the type of the constituent amino acids. This correlation may be stated in general form as follows: If the adsorption affinities of the DNP-derivatives of amino acids A, B, C, D, *etc.*, increases in the order listed, then the adsorption affinities of the DNP-derivatives of the peptides XA, XB, XC, XD, *etc.*, or AX, BX, CX, DX, *etc.*, (where X is any given amino acid) also increases in the order listed. Before considering this proposed correlation, attention should be called to Table I in which the relative adsorption affinities of the DNP-amino acids are listed.

TABLE I

RELATIVE ADSORPTION AFFINITIES OF DNP-AMINO ACIDS IN ACETIC ACID–ACETONE–LIGROIN DEVELOPERS

Hydroxyproline	Most strongly adsorbed
Serine	
Aspartic acid, lysine	Group I[a,b]
Threonine, tyrosine	
Glutamic acid	
Tryptophan	Group II
Glycine	
Proline	Group III
Alanine	
Methionine	
Phenylalanine	
Valine	Group IV
Leucine, isoleucine	Least strongly adsorbed

[a] The grouping is that of Green and Kay.[3] The chromatographic properties of DNP-hydroxyproline have been determined since that publication. [b] Within group I, the relative positions are subject to considerable variation or even inversion depending upon the ratio of acetic acid and acetone in the developer.

The chromatographic behavior of the DNP-amino acids with the three developers listed in Fig. 1 is as follows. Even the amino acids of group I would have been washed through the column by 2.5 V ml. of 3AA-15A-B. Only amino acids of group I would remain on the column when 7 V ml. of either 12AA-6A-L or 3AA-15A-L is used and they would be in the lower half of the chromatogram.

Let us consider first only those data which were obtained with 3AA-15A-L as the developer. In accordance with the proposed correlation, the adsorption affinities of di-DNP-lys-val, di-DNP-lys-ala, di-DNP-lys-gly and di-DNP-lys-glu increase in that order which is also the order of increase of DNP-val, DNP-ala, DNP-gly and DNP-glu, Likewise, the relative affinities of DNP-ala-ala and DNP-ala-gly; of DNP-leu-gly and di-DNP-leu-tyr; of DNP-leu-gly, DNP-ala-gly, DNP-gly-gly, di-DNP-lys-gly and DNP-hypro-gly all are in agreement. Among the six glycyl peptides the relative affinities are: DNP-gly-leu < DNP-gly-pro ~ DNP-gly-ala < DNP-gly-gly ~ DNP-gly-try ~ di-DNP-gly-tyr. Now DNP-ala and DNP-pro as well as DNP-gly, DNP-try and DNP-tyr may easily be separated,[3] and one would expect greater differences in the DNP-peptides. However, 3AA-15A-L is much too strong a developer to be used in the scheme for separating the enumerated DNP-amino acids and, in fact, it is probable that if it were tried they would group together much as do the above DNP-glycyl peptides.

If we extend the proposed correlation to the glycyl tripeptides, prediction would place di-DNP-gly-lys-gly above DNP-gly-gly-gly instead of below.

A comparison has not yet been made of such peptides as DNP-AX and DNP-XA. DNP-Ala-gly and DNP-gly-ala have very similar affinities and cannot be separated completely by any developer which has been used. On the other hand, DNP-gly-leu and DNP-leu-gly separate readily if the developer is 2AA-10A-L. Thus, the arrangement of amino acid residues in the peptide influences the chromatographic behavior of the DNP-peptide but the examples are too few to permit any generalizations to be made.

Little can be said about the relative affinities of two peptides which do not have an amino acid residue in common. There seems to be general validity, however, to the idea that the chromatographic behavior of a DNP-peptide is related to the chromatographic behavior of the DNP-derivatives of the constituent amino acids of the peptide. For example, DNP-gly is more strongly adsorbed than DNP-ala so that one would anticipate the observed result that DNP-gly-gly is more strongly adsorbed than DNP-ala-ala. Consider also di-DNP-lys-val

and DNP-ala-ala. Di-DNP-lys falls in group I and is rather strongly adsorbed whereas DNP-val in group IV is rather weakly adsorbed while DNP-ala in group III is intermediate; it is not surprising then to find that di-DNP-lys-val and DNP-ala-ala have similar affinity. Such examples could be multiplied.

With only one exception it has been found that a DNP-peptide is more strongly adsorbed than the DNP-derivative of any of the constituent amino acids. DNP-Leu-gly is coincident with DNP-gly when the developer is 2AA-10A-L. Leucine in the N-terminal position may have a somewhat anomalous effect on the adsorption affinity and this may be responsible for the ready separation of DNP-leu-gly and DNP-gly-leu which has already been mentioned. Note also that DNP-leu-gly-gly is very much less strongly adsorbed than DNP-gly-gly-gly and, in fact, is less strongly adsorbed than DNP-gly-gly.

Not all of the DNP-peptides have been developed with 12AA-6A-L or 3AA-15A-B but their number is sufficient to give some idea as to whether the above generalizations apply. Broadly considered, the generalizations still apply although in certain particulars the results may seem to be discrepant. Thus, when 12AA-6A-L is used as contrasted to 3AA-15A-L, DNP-ala-ala-ala and DNP-leu-gly-gly are less strongly adsorbed than DNP-gly-ala instead of more strongly adsorbed. Likewise, the sequences of DNP-gly-gly, di-DNP-gly-try, di-DNP-lys-ala, DNP-gly-pro, DNP-ala-gly, DNP-gly-try and DNP-gly-ala differ in the two developers, Furthermore, note that when 3AA-15A-B is the developer, peptides which contain lysine or tyrosine are relatively less strongly adsorbed, These apparent inconsistencies are related to the fact that the ratio of acetic acid to acetone in the developer as well as the interchange of ligroin and benzene has such marked effects on the chromatographic behavior of DNP-amino acids as was very clearly pointed out by Green and Kay.[3] In this same way the changes in the developer must alter the behavior of the DNP-peptides. Because these developers are much too strong for most of the DNP-amino acids and, hence, their chromatographic properties have not been studied with them, it cannot be stated whether the differences between 12AA-6A-L and 3AA-15A-L are exactly what would be expected. However, the lesser affinity of lysine- and tyrosine-containing peptides in 3AA-15A-B is to be anticipated because it is known that di-DNP-lys and di-DNP-tyr are much less strongly adsorbed relative to the other DNP-amino acids of group I if benzene developers rather than ligroin developers are used.

It is of interest to compare the present results briefly with the chromatography of peptides on paper and as an example, the data of Knight[8] will be used. Inspection of Knight's data shows that a peptide on paper may either have an affinity intermediate between that of the constituent amino acids or it may have an affinity greater or less than that of the constituent amino acids even if the peptide is rather long. This behavior is in great contrast to that of the DNP-peptides. Pardee[9] has made a mathematical analysis of Knight's data and has been able with considerable success to predict the R_F value of a peptide on paper from a knowledge of the R_F values of the constituent amino acids. No such analysis has been tried in the present work in the main because most of the DNP-amino acids have not been chromatographed with the developers which are most satisfactory for the DNP-peptides. Furthermore, the strong adsorption of the DNP-peptides (equivalent to small R_F) and the weak adsorption of the DNP-amino acids (equivalent to large R_F) are the two conditions which, as Pardee points out, lead to the greatest errors in such a mathematical analysis,

Comments on Developers.—As has already been mentioned, this study was made to obtain general information and not because of interest in any peptide *per se*. On the other hand, it was of importance to learn which developers would be most likely to separate the DNP-peptides of an unknown mixture. Very much progress has been made toward this goal.

In order to compare the movements of the DNP-peptides with those of the DNP-amino acids, all DNP-peptides have been chromatographed with 8AA-4A-L which was used by Green and Kay[3] for the separation of the DNP-amino acids into groups. As a developer 8AA-4A-L is too weak because all but a few DNP-peptides were distributed throughout the region of group I. Some of the DNP-peptides have been developed with 12AA-6A-L as shown in Fig. 1; this is a stronger developer but the ratio of acetic acid to acetone is unchanged. The movement of the zones is more satisfactory with this stronger developer and many separations which are incomplete as shown in the figure could have been achieved by a greater volume of developer or perhaps by a stronger one such as 16AA-8A-L.

Some of the first chromatograms were made with DNP-gly-leu and DNP-leu-gly which behave much like the DNP-amino acids of group II. Compounds in this group develop well with 2AA-10A-L and, as mentioned above, DNP-gly-leu and DNP-leu-gly separate completely when this developer is used. Indeed, it is a rather satisfactory developer also for DNP-ala-ala and similarly adsorbed DNP-peptides. Because the ratio of acetic acid to acetone in the developer has such a profound influence on the effectiveness of the developer in producing separations, 3AA-15A-L was used as a stronger developer for the more strongly adsorbed DNP-peptides. The results in Fig. 1 again point out that a greater volume or a stronger developer would achieve many separations some better, some worse, some different than when 12AA-6A-L is used. Changing the strength of the developer by increasing the content of acetic acid and acetone while keeping their ratio constant does increase the rate of movement of the zones but it is not entirely without effect on the relative positions. However, the degree of the effect is by no means as great as that produced by changing the ratio. It has sometimes been necessary to use 4AA-20A-L or 5AA-25A-L.

(8) C. A. Knight, *J. Biol. Chem.*, **190**, 753 (1951).

(9) A. B. Pardee, *ibid.*, **190**, 757 (1951).

The movement of many DNP-peptides with 3AA-15A-B is more rapid than is generally desirable. The use of 2AA-10A-B or 1AA-5A-B accordingly is indicated. The usefulness of this type of developer lies in its ability in some instances to invert the relative positions of certain DNP-derivatives.

Applications

We have made extensive use of the above information in the study of peptides from partial hydrolysates of gelatin.[4] The chromatographic behavior of all of the peptides which have been identified has agreed very well with that which would be expected from the generalizations which have been formulated above.

In attempting to separate a mixture of unknown DNP-peptides, it has been found to be beneficial to develop first with 7 *V* ml. of 8AA-4A-L. In this way, any contaminating DNP-amino acids will largely be removed and any weakly adsorbed DNP-peptides will begin to move down the chromatogram. Further development with as much as 7 *V* ml. of 3AA-15A-L will often separate the DNP-peptides into well-defined well-separated zones but depending upon the nature of the peptides it may be necessary to change further to 4AA-20A-L or 5AA-25A-L. Each zone should then be rechromatographed with 1AA-5A-B or stronger developer of the same type. By the use of this procedure it was possible to separate 14 definite DNP-derivatives from one peptide zone which was isolated from a partial hydrolysate of gelatin by means of an initial ion exchange chromatogram of the free peptides.

Acknowledgment.—We wish to thank Miss Lois M. Kay and Dr. F. Charlotte Green for having determined the chromatographic properties of some of the DNP-peptides.

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Ethyl Trithioörthoglyoxylate

BY M. L. WOLFROM AND EARL USDIN

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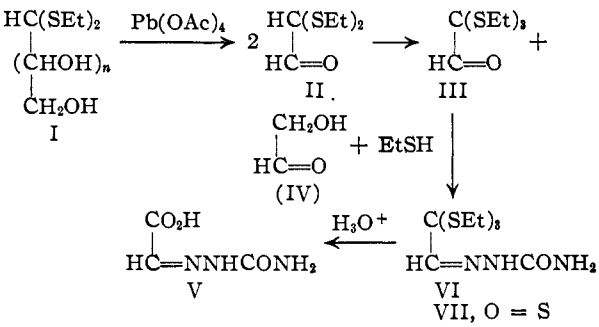
Fischer and Baer[1] synthesized the mono-(diethyl acetal) of glyoxal by subjecting DL-glyceraldehyde diethyl acetal to lead tetraacetate oxidation. The compound was a liquid that polymerized on standing. Schmidt and Wernicke[2] prepared glyoxal mono-(dibenzyl thioacetal) as a crystalline solid by the oxidative scission of 4,5-isopropylidene-D-fucose dibenzyl thioacetal with lead tetraacetate. In attempts to obtain the diethyl analog of this substance by the corresponding scission of aldose (D-galactose, L-arabinose and glyceraldehyde) diethyl thioacetals, the only product isolated (as the semicarbazone VI or thiosemicarbazone VII) was ethyl trithioörthoglyoxylate. Its structure was proved by the partial acid hydrolysis of its semicarbazone to the known glyoxylic acid semicarbazone (V). It is probable that the ethyl trithioorthoglyoxylate (III) arose as a bimolecular disproportionation product of the intermediate glyoxal mono-(diethyl thioacetal) (II). Fischer and Baer[1] demonstrated that two moles of glyoxal mono-(diethyl acetal), on treatment with alkali, underwent such a disproportionation to produce one mole of acid; the presence of glyoxylic acid and of glycolaldehyde were demonstrated in the acidified reaction mixture by these workers. The appearance of the thioörthoester in the glyoxylic acid moiety obtained by us is unexpected.



Experimental

Oxidative Scission of Aldose Thioacetals.—An amount of 2.86 g. (0.01 mole) of D-galactose diethyl thioacetal (mercaptal)[3,4] was dissolved in 500 ml. of dry dioxane in an apparatus protected from moisture. Lead tetraacetate (17.6 g., 0.04 mole) was added portionwise under stirring while maintaining the reaction mixture at 10–20°. After the addition, the cooling bath was removed and stirring was maintained for 2 hr. Lead diacetate was separated by filtration and the solvent was removed, under reduced pressure, from the filtrate, The reaction product was recovered by distillation under reduced pressure, yield 1.1 g., b.p. 100° (1 mm.).

From the product there were isolated, in low yield, the crystalline semicarbazone and thiosemicarbazone described below. These were also obtained: from the reaction mixture before distillation; on similar oxidation in benzene solution or in abs. chloroform–acetic acid solution; and on oxidation of the diethyl thioacetals (mercaptals) of L-arabinose and of glyceraldehyde.[5]

Ethyl Trithioörthoglyoxylate Thiosemicarbazone (VII).—Following Wolfrom and Tanghe,[6] the above distilled oil was dissolved in 100% ethanol, and thiosemicarbazide was dissolved in a 30% solution of acetic acid in ethanol. The two solutions were heated just short of boiling and then mixed. After cooling to room temperature, water was added to incipient turbidity and crystallization was effected at ice-box temperature; m.p. 140.5–141°.

Anal. Calcd. for $C_9H_{19}N_3S_4$: C, 36.33; H, 6.44; N, 14.13; S, 43.10. Found: C, 36.47; H, 6.37; N, 14.14; S, 43.26.

Ethyl Trithioörthoglyoxylate Semicarbazone (VI).—Semicarbazide hydrochloride (1 g.) was dissolved in 10 ml. of *N* potassium hydroxide and then more solid semicarbazide hydrochloride was added until the solution was just acid. The above distilled oxidation product (1 g.), dissolved in 10 ml. of 95% ethanol, was warmed to 90° and the semicarbazide solution was added to it. More water was added to effect complete solution at that temperature and a crystalline product separated on slow cooling. Pure material was obtained on recrystallization from 95% ethanol; m.p. 195°.

Anal. Calcd. for $C_9H_{19}ON_3S_4$: C, 38.41; H, 6.81; N, 14.94; S, 34.18. Found: C, 38.63; H, 6.84; N, 14.92; S, 33.89.

(1) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).
(2) O. T. Schmidt and E. Wernicke, *Ann.*, **556**, 179 (1944).
(3) E. Fischer, *Ber.*, **27**, 673 (1894).
(4) M. L. Wolfrom, THIS JOURNAL, **52**, 2466 (1930).
(5) H. W. Arnold and W. L. Evans, *ibid.*, **58**, 1950 (1936).
(6) M. L. Wolfrom and L. J. Tanghe, *ibid.*, **59**, 1601 (1937).

Hydrolysis of Ethyl Trithioörthoglyoxylate Semicarbazone to Glyoxylic Acid Semicarbazone (V).—The above ethyl trithioörthoglyoxylate (400 mg.) was added to a mixture of 66 ml. of ethanol and 10 ml. of 12 *N* (concd.) hydrochloric acid. A stream of nitrogen gas was passed through the mixture while it was refluxed under a condenser containing water at 40°. The reaction was stopped when no more ethanethiol was evolved as detected by odor. Solvent removal under reduced pressure yielded a product that was obtained crystalline from 50% aqueous ethanol; m.p. 220–224° dec. An authentic sample of glyoxylic acid semicarbazone showed no melting point depression on admixture with the above product and the following X-ray powder diffraction measurements were identical when made on the two preparations: 6.48,[7] 1[8]; 4.53, 3; 4.25, 7; 3.58, 2; 3.13, 1; 2.81, 6; 2.46, 4; 2.26, 9; 1.89, 10.

(7) Interplanar spacing in Å., CuK_α radiation.

(8) Relative intensity; 1 = highest; estimated visually.

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Di-*t*-butyl Phosphonate

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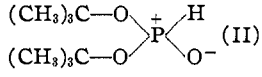
The reaction of *t*-butyl alcohol with phosphorus trichloride has been reported to give tri-*t*-butyl phosphite (I).[1] Previous to this publication, several attempts were made in this Laboratory to prepare I by analogous procedures, but instead di-*t*-butyl phosphonate (II) was obtained; b.p. 62–62.5° at 4 mm.,[2]



(II)

$n^{25}D$ 1.4168, d^{25} 0.975; MD calcd. 50.18,[3] found 50.03. This appears to be the first example of the preparation of a tertiary dialkyl phosphonate from an aliphatic tertiary alcohol.[4]

II is insoluble in water and 3 *N* sodium hydroxide, but it dissolves immediately in 3 *N* hydrochloric acid with the evolution of isobutylene. This gas is also evolved slowly when the compound is heated to 70° at atmospheric pressure. II is relatively stable at room temperature, although evidence of slight decomposition was noted after storage for several weeks. Upon redistillation, the original material was recovered with little loss.

The infrared spectrum exhibits the characteristic strong absorption for the $\overset{+}{P}\text{–}\overset{-}{O}$ stretching vibration[5] at 1270 cm.$^{-1}$ as well as another strong band at 2420 cm.$^{-1}$ corresponding to the P–H bond.[5,6] There is little or no absorption in the 750 cm.$^{-1}$ region where the aliphatic C–P stretching frequency usually appears,[6] an observation which rules out structures which are based on catalytic isomerization of the Arbusov type.[7]

Although repetition of the literature procedure[1] afforded a substance having the reported refractive index, it could not be redistilled without decomposition and concomitant lowering of the refractive index. The infrared spectra showed strong P–H and $\overset{+}{P}\text{–}\overset{-}{O}$ absorption and were not significantly different from the spectrum of pure II. Successive redistillations eventually yielded material having a refractive index and infrared spectrum identical to II. In view of these results, the purity of I is doubtful.

Experimental[8]

A solution of 82.4 g. (0.6 mole) of phosphorus trichloride in 500 cc. of petroleum ether (b.p. 30–60°) was cautiously dropped over a period of one hour into an ice–methanol chilled solution of 267 g. (3.6 moles) of *t*-butyl alcohol and 91.2 g. (1.8 moles) of triethylamine in 3 l. of petroleum ether. Stirring was continued for one hour without external cooling, after which time the suspension was filtered, the cake being washed well with an additional 1 l. of petroleum ether. The solvent was removed on the steam-bath at water aspirator pressure, the resultant yellow residue being rapidly distilled at 0.1 mm. without fractionation. The distillate was distilled slowly (considerable frothing), giving 60 g. (51%), b.p. 72–78° at 10–12 mm., $n^{25}D$ 1.4162. A final distillation gave a single fraction b.p. 70–72° at 10 mm., $n^{25}D$ 1.4168, d^{25} 0.975.

Anal. Calcd. for $C_8H_{19}O_3P$: C, 49.5; H, 9.86; P, 15.9. Found: C, 49.5; H, 9.60; P, 15.8.

A portion of this product was redistilled at 4 mm., b.p. 62–62.5°. In various other preparations, samples of higher refractive index were obtained, but repeated slow distillations at 10–12 mm. eventually produced II of constant refractive index. The high refractive indices observed in some cases are probably due to the presence of some I which is decomposed on successive distillations.

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(1) G. M. Kosolapoff, THIS JOURNAL, **74**, 4953 (1952).

(2) Compare b.p. 65–66° at 4 mm. for I (ref. 1). This b.p. was obtained by rapid distillation without fractionation (G. M. Kosolapoff, private communication).

(3) The value of 4.44 for the atomic refraction of phosphorus in secondary phosphites was used; G. M. Kosolapoff, *ibid.*, **73**, 4989 (1951).

(4) T. Milobedzki and A. Sachnowski, (*Chem. Polski*, **15**, 34 (1917) [*C. A.*, **13**, 2865 (1919)], report both tri- and di-*t*-butyl phosphites. They did not isolate either compound or report any physical properties.

(5) N. B. Colthup, *J. Opt. Soc.*, **40**, 397 (1950).

(6) It is noteworthy that di-*n*-butyl phosphonate has two corresponding bands at 1265 and 2410 cm.$^{-1}$; L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

(7) T. Milobedzki and K. Szulgin, *Chem. Polski*, **15**, 66 (1917), [*C. A.*, **13**, 2866 (1919)], and numerous references given by G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(8) (a) The analysis was performed in these laboratories under the direction of Dr. J. A. Kuck. (b) All operations were performed under an atmosphere of dry nitrogen.