NOTES

Characterization of 2-Hydroxy-2′-nitrobiphenyl

By J. C. Colbert, Daniel Fox and W. A. Skinner

Received May 24, 1952

2-Hydroxy-2′-nitrobiphenyl[1] has been obtained in the form of an oil through diazotization and hydrolysis of the partial reduction product from 2,2′-dinitrobiphenyl. The methyl ether of 2-hydroxy-2′-nitrobiphenyl[2] has been prepared using a mixed Ullmann reaction. Solid 2-hydroxy-2′-nitrobiphenyl has not been reported. This phenol has now been prepared in crystalline form by repetition and modification of these two methods. The mixed Ullmann reaction, followed by hydrolysis of the resultant 2-methoxy-2′-nitrobiphenyl, gives an over-all yield of 24% of 2-hydroxy-2′-nitrobiphenyl compared with 5% by the first method. This phenol has been characterized by the preparation of a number of derivatives.

Infrared spectra indicate that some association exists in solutions of this phenol. It is probably intermolecular since the phenol is not volatile in steam as would be true of an *o*-nitrophenol such as 2-hydroxy-3-nitrobiphenyl.[3] While the combined radii of the substituents in the *o,o*′-positions are sufficiently great to somewhat restrict rotation about the pivotal bond of biphenyl[4] chelation is probably inhibited since planarity is impossible without straining the bond angle between the rings.

Experimental

Infrared Spectra of 2-Hydroxy-2′-nitrobiphenyl.—Infrared spectra for chloroform solutions of 2-hydroxy-2′-nitrobiphenyl were determined using a Perkin–Elmer recording spectrophotometer.[5] An absorption peak occurs in the -OH region as well as at higher wave lengths where dipole interaction between groups would be indicated.

Table I

O–H and O–H—O Absorption in Chloroform

Molal concn.	2.80 $m\mu$	3.08 $m\mu$
0.15	11.5%	11.5%
.10	5.0	7.0
.05	1.0	2.3

1. **Preparation of 2-Hydroxy-2′-nitrobiphenyl from 2,2′-Dinitrobiphenyl.**—Hydrogen sulfide was passed for 1.5 hours through 600 ml. of 95% ethanol at 60° to which 10 g. (0.04 mole) of 2,2′-dinitrobiphenyl and six molar proportions of ammonium hydroxide had been added. Following acidification with hydrochloric acid unchanged 2,2′-dinitrobiphenyl was extracted with benzene and the aqueous portion filtered through charcoal to remove free sulfur and highly colored impurities. Concentration and cooling gave 5 g. of the light yellow hydrochloride (49%) of 2-amino-2′-nitrophenyl. The neutral equivalent was 249 (calcd. 250.7).

A 3.75-g. portion of the hydrochloride of 2-amino-2′-nitrobiphenyl was diazotized in the usual manner and added to boiling 50% sulfuric acid. The phenol was recovered by making the solution alkaline, extracting with benzene to remove non-phenolic material, acidifying and extracting the aqueous portion with benzene. Evaporation of the benzene extract gave a tarry residue which was taken up with alkali, acidified and permitted to stand. Pale yellow needles, 0.32 g. (10% or 5% if based upon 2,2′-dinitrobiphenyl), m.p. 139–140°, were obtained.

Anal. Calcd. for $C_{12}H_9O_3N$: C, 67.0; H, 4.2; N, 6.5. Found: C, 66.8; H, 4.0; N, 6.4.

2. **Preparation of 2-Hydroxy-2′-nitrobiphenyl by Mixed Ullmann Reaction.**—Twelve grams (0.048 mole) of *o*-iodonitrobenzene, 10 g. of *o*-bromoanisole (0.053 mole) and 10 g. of activated copper bronze,[6] were placed in a long-necked flask fitted with a mechanical stirrer. Efficient stirring was accomplished by entangling copper-wool in the stirring rod. The reactants were held just short of reflux temperature for 1.5 hours, cooled, flushed out with benzene and centrifuged. The benzene was evaporated and the residue steam distilled to remove unreacted *o*-iodoanisole. The undistilled portion was taken up with benzene, dried and evaporated to a thick oil. Twenty-five ml. each of acetic anhydride and 48% hydrobromic acid were added to the oil and the mixture heated for 48 hours. The hydrolysate was diluted to 300 ml. with water, made alkaline with 10% sodium hydroxide and extracted with benzene. The remaining solution was acidified with hydrochloric acid. Pale yellow needles superimposed upon a darker colored matte formed upon standing overnight. The yield of 2-hydroxy-2′-nitrobiphenyl was 2.48 g. (24%). The melting point was 139–140°.

A benzene extract, following hydrolysis of the methyl ether, when evaporated to dryness, gave 2.94 g. (50%) of 2,2′-dinitrobiphenyl. This by-product, melting at 128°, was used in the preparation of 2-hydroxy-2′-nitrobiphenyl by the first method described.

2-Methoxy-2′-nitrobiphenyl.—This substance was prepared by refluxing a reaction mixture from the previously described mixed Ullmann with several 30-ml. portions of benzene, uniting these extracts, filtering through sintered glass to remove cuprous iodide, and concentrating on a water-bath. The addition of petroleum ether (37–45°) caused separation of a dark oil. Upon standing, crystals of 2,2′-dinitrobiphenyl separated. The supernatant liquid was decanted, concentrated on the water-bath and distilled under atmospheric pressure for removal of excess *o*-iodoanisole. The residue was taken up with benzene and petroleum ether added to precipitate the remaining 2,2′-dinitrobiphenyl. The remaining liquid was concentrated and petroleum ether added. Pale yellow crystals weighing 3.2 g. (27%) and melting at 70–72° were obtained. Recrystallization from chloroform and petroleum ether raised the melting point to 82° which agrees with that previously recorded.[2]

Nitration of 2-Hydroxy-2′-nitrobiphenyl.—To 0.5 g. of 2-hydroxy-2′-nitrobiphenyl in 5 ml. of acetic acid, 0.45 ml. of concd. nitric acid was added dropwise. After 15 minutes standing the reaction mixture was refluxed for one hour. Upon addition of water the trinitrophenol precipitated. Two crystallizations from 95% alcohol gave 0.49 g. (70%). The melting point was 123°. 2-Hydroxybiphenyl yields 2-hydroxy-3,5-dinitrobiphenyl,[7] hence it is assumed that the present product is 2-hydroxy-3,5,2′-trinitrobiphenyl.

Anal. Calcd. for $C_{12}H_7O_7N_3$: N, 13.8. Found: N, 13.9.

Bromination of 2-Hydroxy-2′-nitrobiphenyl.—A 100% excess of brominating solution (made by dissolving 15 g. of potassium bromide in 100 ml. of water and adding 10 g. of bromine) was added to 1 g. of 2-hydroxy-2′-nitrobiphenyl in 20 ml. of acetone. After 30 minutes standing with occasional shaking, water was added to precipitate the bro-

---

(1) L. Mascarelli and D. Gatti, *Atti acad. Lincei*, **13**, 887 (1931).

(2) L. Mascarelli and D. Gatti, *Atti IV Cong. naz. chim. pure applicata*, 503 (1933).

(3) Voroscov and Troscenko, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 432 (1938).

(4) Roger Adams and H. C. Yuan, *Chem. Revs.*, **12**, 284 (1933).

(5) Infrared spectra were determined by Ralph S. Shank through the courtesy of the Phillips Petroleum Company, Research Division, Bartlesville, Oklahoma.

(6) E. C. Kleiderer and Roger Adams, This Journal, **55**, 4219 (1933).

(7) Borche, *Ann.*, **312**, 266 (1900).

TABLE II

DERIVATIVES OF 2-HYDROXY-2′-NITROBIPHENYL

Derivative, 2-(2-nitrophenyl)-phenyl-	Formula	Yield, %	M.p., °C.	Analytical data Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Benzoate	$C_{19}H_{13}O_4N$	50	116	71.5	71.3	4.1	3.9	4.4	4.4
4-Nitrobenzoate	$C_{19}H_{12}O_6N_2$	70	116	62.6	62.5	3.3	3.2	7.7	7.8
3,5-Dinitrobenzoate	$C_{19}H_{11}O_8N_3$	70	180					10.3	10.2
4-Nitrobenzene sulfonate	$C_{18}H_{12}O_7N_2S$	90	147					7.0	6.9
3-Nitrobenzene sulfonate	$C_{18}H_{12}O_7N_2S$	50	161	54.0	54.2	3.0	2.8	7.0	7.0
4-Methylbenzene sulfonate	$C_{19}H_{15}O_5NS$	40	100					3.8	3.7
2,4-Dinitrophenyl ether	$C_{18}H_{11}O_7N_3$	10	118					11.0	11.1

minated product. The crystals were filtered, dissolved in chloroform, the solution dried over sodium sulfate, concentrated and precipitated by addition of petroleum ether. The light yellow material melted at 149°. Since 2-hydroxybiphenyl readily yields 3,5-dibromo-2-hydroxybiphenyl[8] the present product is assumed to be 2-hydroxy-3,5-dibromo-2′-nitrobiphenyl. A yield of 1.2 g. (70%) was obtained.

Anal. Calcd. for $C_{12}H_7O_3Br_2N$: Br, 42.9. Found: Br, 42.7.

This procedure was repeated using 1 g. of 2-methoxy-2′-nitrobiphenyl. The dibrominated ether weighed 1.25 g. (70%) and melted at 108° following recrystallization from chloroform and petroleum ether.

Anal. Calcd. for $C_{13}H_9O_3Br_2N$: Br, 41.3. Found: Br, 41.0.

Hydrolysis of the dibrominated ether was accomplished by heating 0.2 g. of the ether for two days at 90° with 2 ml. each of acetic anhydride and hydrobromic acid. Fifteen milligrams of 2-hydroxy-3,5-dibromo-2′-nitrobiphenyl was isolated. This hydrolysis product melted at 149° when mixed with that obtained by bromination of 2-hydroxy-2′-nitrobiphenyl. The dibromoether is assumed to be 2-methoxy-3,5-dibromo-2′-nitrobiphenyl.

Derivatives of 2-Hydroxy-2′-nitrobiphenyl.—Seven derivatives involving the –OH group of 2-hydroxy-2′-nitrobiphenyl were prepared. All were prepared by well known methods. In general, the phenol was dissolved in pyridine and the acid chloride added in slight excess. Refluxing for 30 minutes was followed by pouring the reaction mixture over ice or into cold water. The precipitate was dissolved in a suitable solvent such as chloroform or alcohol and a crystalline product obtained. Table II supplies details.

---

[8] Auwers and Wittig, *J. prakt. Chem.*, **108**, 99 (1924).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OKLAHOMA
NORMAN, OKLAHOMA

Colored Complexes with Inorganic Salts Mounted on Silica Gel

BY HANS A. BENESI

RECEIVED DECEMBER 29, 1952

Jura, Grotz and Hildebrand[1] have reported that mesitylene reacts with the salts of 19 metals on a silica gel surface to form colored complexes, and attributed the color formation to a generalized acid–base interaction between mesitylene and the respective cations. Evidence is listed below, however, which shows that the colors reported by these investigators can be attributed to the presence of an as yet unidentified trace impurity in mesitylene. This evidence does not, of course, exclude the possibility of the existence of genuine mesitylene complexes that have characteristic absorption bands outside of the visible spectrum.

Sulfates of four of the 19 ions reported to give colored mesitylene complexes—Cu^{++}, Zn^{++}, Mg^{++} and Al^{+++}—were mounted on silica gel. When mesitylene from two different sources was added to these salts, two types of reactions were observed. Mesitylene from the first source, which we will denote mesitylene I, produced an intense red-purple color with each of the above four salts. A sample of mesitylene used by Jura, *et al.*,[2] gave a red-purple color that was not as intense as was the case for mesitylene I. However, mesitylene from the second source (denoted as mesitylene II) produced no color change of any kind with these same salts. A mixture of I and II gave the red-purple color reaction. These results were already strong evidence for the presence of a color-producing impurity in mesitylene I that was absent from mesitylene II.

The attempts to isolate and identify the color-producing impurity—henceforth denoted as X—in mesitylene I can be summarized as follows: (1) Simple distillation or chromatographic treatment with silica gel did not remove impurity X. (2) Ten equal fractions were obtained by distillation of mesitylene I through a 60-plate fractionating column at a reflux ratio of *ca.* 60:1. Since impurity X did not appear in the first nine fractions, but was found in the higher boiling residue (fraction 10), a tenfold concentration of impurity X was effected. (3) After learning that mesitylene I was probably synthesized from acetone, two of the possible higher boiling by-products of this synthesis—phorone and isophorone—were added to the mounted salts. No color reaction was observed. (4) Chromatographic treatment using copper sulfate mounted on silica gel as the adsorbent completely removed impurity X, as was evidenced by the appearance of an extremely intense red-purple zone localized at the top of the chromatographic column. Attempts to remove impurity X from the colored adsorbent by sublimation in high vacuum resulted in decomposition of the adsorbed material. In this respect, the adsorption seemed irreversible. (5) Ultraviolet analysis of mesitylene I revealed no absorption peaks other than those characteristic of mesitylene itself. (6) The above-mentioned mesitylene samples were analyzed mass-spectrometrically at each stage of purification and isolation. In making an intercomparison of the mass spectra of these samples, it was assumed (because of the results described in 2) that impurity X had a molecular weight higher than that of mesitylene. Although it was not possible to assign

---

[1] G. Jura, L. Grotz and J. H. Hildebrand, American Chemical Society Meeting Abstracts, September, 1950, p. 56Q.

[2] The writer gratefully acknowledges the coöperation of Professor George Jura, who kindly supplied this sample of mesitylene.

a particular parent peak to impurity X, it was evident that any of the peaks that were likely possibilities arose from impurities that were present at concentrations lower than 0.01% in the original sample of mesitylene I.

Further attempts to identify impurity X were abandoned upon exhaustion of the supply of mesitylene I.

It is interesting to compare the color reactions of impurity X with metal salts to the work of Walling.[3] This investigator has shown that indicators exhibiting color changes at low *p*H's in aqueous solutions give their acid colors when adsorbed on surfaces of iron, magnesium, silver and copper salts, and on other acidic surfaces. Since indicators are a class of substances having huge extinction coefficients and since it is likely that impurity X falls into such a class, it seems reasonable to postulate that impurity X is an indicator that exhibits a red-purple color on highly acidic surfaces.

Experimental

Mounted Salts.—Ten ml. of 0.5 *M* solutions of each of the four salts was added to 10-g. portions of pure silica gel, stirred on a hot-plate until the product seemed dry, and dried overnight in a 200° drying oven. Copper sulfate mounted on silica gel was used to follow the course of impurity (X) during the purification steps.

Mesitylene.—Both mesitylene I and mesitylene II were Eastman Kodak White Label products. Through the kind coöperation of the Eastman Kodak Company, it was learned that mesitylene I, which was distributed before about 1950, was most likely synthesized from acetone. Mesitylene II, the current Eastman Kodak product, probably was made from a coal tar distillate.

Color Tests.—The intense red-purple color could be brought about by the addition of a few drops of mesitylene I to *ca.* 0.1 g. of mounted salt on a spot plate. The full intensity developed in 5–10 minutes at room temperature, but could be greatly accelerated by warming 1–2 minutes at *ca.* 100°.

(3) C. Walling, THIS JOURNAL, **72**, 1164 (1950).

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

Polar Effects in N-Bromosuccinimide Brominations

BY ELIAS J. COREY

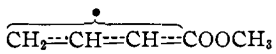
RECEIVED DECEMBER 22, 1952

The reaction between N-bromosuccinimide and unsaturated compounds which results in the substitution of bromine for hydrogen is generally considered as involving free radical intermediates.[1] The allylic bromination of an olefin, for example, has been postulated to occur by dissociation of N-bromosuccinimide into bromine atoms and succinimide radicals, radical displacement on hydrogen by the succinimide radical to give a mesomeric radical and, finally, reaction of this radical with the reagent to give a succinimide radical and the allylic bromide.

According to this interpretation the reaction of N-bromosuccinimide with two isomeric substances which are converted by radical displacement on an allylic hydrogen to the same free radical should lead to the same product (or products).[2]

Methyl crotonate (I) and methyl vinylacetate (II) are such a pair of isomeric substances and their study seemed especially advantageous since only two allylic substitution products are possible and since, as Ziegler and co-workers have already reported, the reaction of methyl crotonate with N-bromosuccinimide produces methyl γ-bromocrotonate in good yield.[3] One might anticipate that methyl γ-bromocrotonate would also be formed from methyl vinylacetate.

$$\underset{\text{I}}{CH_3CH{=}CHCOOCH_3} \qquad \underset{\text{II}}{CH_2{=}CHCH_2COOCH_3}$$



$$\overbrace{CH_2\cdots CH\cdots CH\cdots COOCH_3}^{\bullet}$$

III

We have found that under the same conditions which are favorable for the conversion of methyl crotonate to methyl γ-bromocrotonate, methyl vinylacetate reacts *more slowly* and yields chiefly methyl β,γ-dibromobutyrate (IV) along with an insignificant amount of monobrominated product. Some tarry material is also formed. The structure of IV was proved by debromination to methyl vinylacetate and by synthesis from methyl vinylacetate and bromine.

We and, very recently, others[4] have also observed that a similar situation exists with the corresponding nitriles, crotononitrile and vinylacetonitrile.

Regardless of what the mechanism of formation of dibromide is,[5] the relative inertness of the α-methylene group in methyl vinylacetate and vinylacetonitrile in succinimide radical displacements must still be explained. Since significant steric effects can hardly be operative in the case of vinylacetonitrile, it seems reasonable to suppose that the impediment to radical attack associated with the proximity of the cyano function (or in the case of II, the carbomethoxy group) is primarily electrical in nature.

Experimental

Reaction of Methyl Vinylacetate (II) with N-Bromosuccinimide.—Methyl vinylacetate, b.p. 107° (742 mm.), $n^{25}D$ 1.4060, was prepared by the action of diazomethane on pure vinylacetic acid,[6] b.p. 72.5–73.5° (14 mm.), $n^{25}D$ 1.4210. A mixture 10.0 g. (0.10 mole) of methyl vinylacetate, 17.8 g. (0.10 mole) of N-bromosuccinimide, 0.01 g. of benzoyl peroxide and 50 ml. of pure carbon tetrachloride was heated at reflux for 8 hours, after which time all of the N-bromosuccinimide had disappeared and a brown oil had settled out. The layers were separated by decantation and the oil extracted with two 10-ml. portions of carbon tetrachloride. The carbon tetrachloride solution (plus washings) was cooled to 0°, filtered to remove the precipitate of succinimide (7.2 g.) and concentrated. Distillation of the residual liquid through a semi-micro column yielded 6.14 g. (68.4% based on N-bromosuccinimide) of methyl β,γ-dibromobutyrate (IV), b.p. 70.5° (0.8 mm.), $n^{25}D$ 1.5114 and a small amount (0.48 g.) of a low-boiling fraction, b.p. 48–70°, which probably contained monobromide.

Anal. Calcd. for $C_5H_8O_2Br_2$: C, 23.10; H, 3.10; Br, 61.49. Found: C, 23.28; H, 3.28; Br, 61.78.

Debromination of IV.—A mixture of 3.30 g. of the dibromoester IV and 2 g. of zinc dust in 10 ml. of ether containing a few drops of methanol was heated to reflux for one hour. The resulting mixture was filtered and the filtrate

---

(1) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944).

(2) This point had apparently not been considered in connection with the reaction of N-bromosuccinimide with ketene dimer, A. T. Blomquist and F. H. Baldwin, THIS JOURNAL, **70**, 29 (1948).

(3) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 118 (1942).

(4) P. Couvreur and A. Bruylants, *Bull. soc. chim. Belg.*, **61**, 253 (1952).

(5) See E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952).

(6) *Org. Syntheses*, **24**, 95 (1944).

was distilled carefully through a semi-micro column. The yield of the debromination product (II) was 0.98 g. (77%), b.p. 107° (746 mm.), $n^{25}\mathrm{D}$ 1.4058.

The reaction of bromine (3 g.) with II (2.0 g.) in 10 ml. of carbon tetrachloride at $-10°$ proceeded rapidly and afforded 4.85 g. (93.5%) of the dibromoester (IV), b.p. 70.5° (0.8 mm.), $n^{25}\mathrm{D}$ 1.5112, which was identical with the product obtained by the action of N-bromosuccinimide on II.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

2,2,4-Trimethyl-1,2-dihydroquinoline

BY DAVID CRAIG AND EARL C. GREGG, JR.

RECEIVED NOVEMBER 19, 1952

Recently Johnson and Buell[1] prepared 1,2-dihydroquinoline. On the basis that its ultraviolet absorption spectrum, which had three peaks, was strikingly similar to that of the so-called "acetone anil," they opined that a 1,4-dihydro structure for the latter compound is eliminated. Incidentally, they also stated that 1,4-dihydroquinoline, unlike the 1,2-dihydroquinoline, should have a spectrum similar to that of 1,2,3,4-tetrahydroquinoline. On the contrary, the 1,4-dihydro derivative as a vinylamine has a double bond conjugated with the nitrogen atom[2] and hence its spectrum would not be like that of the 1,2,3,4-tetrahydroquinoline. Nevertheless, their assignment of structure is correct for the dihydroquinolines, in our opinion, not for other reasons given by them but for reasons set forth in the present note.

The spectrum of the trimethyldihydroquinoline[3] (0.00625 g./l.) in methanol, 1,2 N in HCl, is shown in Fig. 1. The doublet at 259 and 255 mμ and E 53 (log ϵ 13.96) can be compared to the single band observed for α-methylstyrene at 242 mμ and log ϵ 4.03 or better still, since the open-chain methyl group here inhibits resonance, to the peak for the cyclic analog 1-methyl-3,4-dihydronaphthalene which Ramart-Lucas and Hoch[4] found to be at 259 mμ, log ϵ 3.8. Morton and de Gouveia[5] found 1,2-dihydronaphthalene to have a maximum at 262 mμ, log ϵ 4.0, and 1,4-dihydronaphthalene was found to have a doublet at 267 and 274 mμ, log ϵ 2.9. It is thus apparent that the spectrum of the trimethyldihydroquinoline in acid solution (the acid is present in order to remove any ability of the nitrogen atom to conjugate with the benzene ring or double bond) requires that a double bond must be conjugated with the benzene ring, thus finally proving the structure of 2,2,4-trimethyl-1,2-dihydroquinoline.

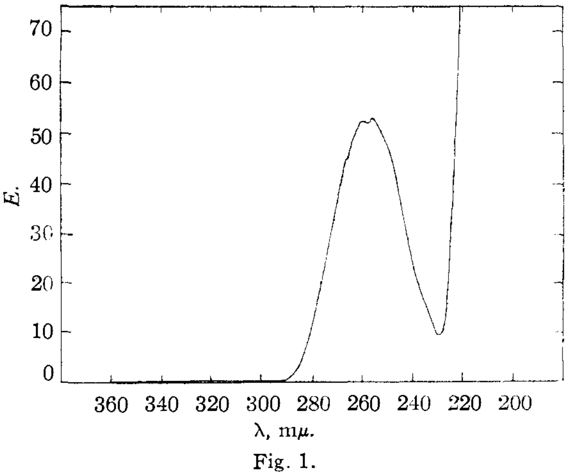


Fig. 1.

Since first submitting the present note, Dr. Paul Downey pointed out to us that Bohlmann[6] has recently reported 1,2-dihydroquinoline, m.p. 40–41° to result from the reaction of $LiAlH_4$ with quinoline. In our hands Bohlmann's directions gave a 90% yield of product which, if purified by extraction with cyclohexane, melted at 72–74°, and which had nearly the same absorption spectrum and other properties reported by Johnson and Buell for their dihydroquinoline. It was unstable in air and in acid solutions so that the absorption spectra in such solutions apparently could not be applied to the elucidation of the structure of the dihydroquinolines. Dr. Franz Widmer found in our laboratory that this compound, like N-phenyl-3,5-diethyl-2-propyl-1,4-dihydroquinoline,[2] evolves hydrogen (about one-third mole) when first contacted with reduced PtO_2 in acetic acid. Subsequently, hydrogen (a net amount of four moles) is absorbed by the acetic acid solution. This confirms Johnson and Buell's finding that their dihydroquinoline, which obviously is the same as Bohlmann's, readily undergoes dehydrogenation.

---

(1) W. S. Johnson and B. G. Buell. THIS JOURNAL, **74**, 4518 (1952).

(2) Compare the spectrum of an N-phenyl-1,2-dihydropyridine. D. Craig, L. Schaefgen and W. P. Tyler, *ibid.*, **70**, 1626 (1952); see also the spectra for eneamines quoted by Johnson and Buell.

(3) D. Craig, *ibid.*, **60**, 1458 (1938).

(4) P. Ramart-Lucas and N. J. Hoch, *Bull. soc. chim.*, [5] **5**, 848 1938).

(5) R. A. Morton and A. J. A. de Gouveia, *J. Chem. Soc.*, 916 (1934).

(6) F. Bohlmann, *Ber.*, **85**, 390 (1952).

THE B. F. GOODRICH RESEARCH CENTER
BRECKSVILLE, OHIO

On the Origin of the Carboxyl Group of Histidine in Yeast[1,2]

BY J. WENDELL DAVIS, VERNON H. CHELDELIN, BERT E. CHRISTENSEN AND CHIH H. WANG

RECEIVED JANUARY 6, 1953

Recently Ehrensvärd, *et al.*,[3,4] have shown by isotopic studies in *Torulopsis utilis*, and Cutinelli, *et al.*,[5] by similar studies in *Escherichia coli*, that when $C^{13}H_3C^{14}OOH$ is administered as a substrate, the carboxyl group of histidine arises exclusively from the methyl carbon atom. This is in contrast to the high C^{14} (acetate carboxyl) incorporation into the carboxyl groups of the other amino acids.

---

(1) This research was supported by contract number AT (45-1)-301 from the Atomic Energy Commission. Published with the approval of the Monographs Publications Committee, Research paper number 220, School of Science, Department of Chemistry. Presented before the Northwest Regional Meeting of the American Chemical Society, Corvallis, June, 1952.

(2) Taken from a thesis presented by J. W. D. for the M.S. degree, Oregon State College, 1952.

(3) G. Ehrensvärd, L. Reio and E. Saluste, *Acta Chem. Scand.*, **3**, 645 (1949).

(4) G. Ehrensvärd, L. Reio, E. Saluste and R. Stjernholm, *J. Biol. Chem.*, **189**, 93 (1951).

(5) C. Cutinelli, G. Ehrensvärd, L. Reio, E. Saluste and R. Stjernholm, *Acta Chem. Scand.*, **5**, 353 (1951).

TABLE I

RADIOACTIVITIES OF HISTIDINE AND ASPARTIC ACID FRACTIONS FROM YEAST

	Histidine							Aspartic acid[8]			
	Content in yeast, %			Radioactivity,[a] counts/min. × 10^3			Ratio[b] $\frac{Py/N_2}{Py/O_2}$	Radioactivity,[a] counts/min. × 10^3			Ratio[b] $\frac{Py/N_2}{Py/O_2}$
	Py/O_2	Py/N_2	Ac/O_2	Py/O_2	Py/N_2	Ac/O_2		Py/O_2	Py/N_2	Ac/O_2	
Whole molecule	1.2	1.3	1.1	8.7	6.1	1.8	0.70	25.4	20.6	15.0	0.81
Carboxyl (histidine)				0.48	0.66	0	1.38				
C_3 (aspartic acid)								1.80	2.15	0	1.19

[a] Expressed as counts/minute/mmole amino acid/mmole substrate utilized. [b] Obtained by dividing the specific activity of the whole molecule or particular atom derived from pyruvate anaerobically (under nitrogen) by the corresponding aerobically derived value.

In this Laboratory, radioactive histidine samples were isolated from bakers' yeast (*Saccharomyces cerevisiae*) grown on $CH_3C^{14}OOH$ aerobically and $CH_3C^{14}OCOOH$ both aerobically and anaerobically.[6] The isolations were carried out through ion-exchange resin column operations according to the method of Winters and Kunin.[7] The histidine samples were purified as a new derivative, the monoöxalate, which is readily recrystallized from aqueous ethanol and gives a definite decomposition point.

In the present work, preliminary degradation of the histidine samples has confirmed Ehrensvärd's observation using acetate; however a significant amount of C^{14} has been observed in the carboxyl group in histidine derived from pyruvate.

The specific radioactivities of histidine derived from each of the three experiments and the activities of the respective carboxyl groups are given in Table I.

From acetate, the histidine carboxyl is seen to be completely inactive, as shown previously.[3] The non-incorporation of acetate carboxyl into histidine carboxyl thus rules out the possibility of union of an imidazole ring with a C_3-unit (such as pyruvate) which might be produced through condensation of a C_2-compound with (radioactive) metabolic CO_2.

Among other possible intermediates in histidine biosynthesis, the C_4-acids deserve consideration. The pattern of labeling in oxalacetate, for example, may be presumed to be similar to the corresponding pattern in aspartic acid in this yeast.[8] In turn, the radioactivity of the methylene carbon (C_3) of aspartic acid furnished an index of histidine carboxyl (C_1) activity. Thus, from pyruvate, incorporation of C^{14} into both these atoms was similarly higher in the *anaerobic* sample (anaerobic/aerobic ratio = 1.38 in aspartate C_3, and 1.19 in histidine C_1) in spite of the fact that these amino acids as a whole showed greater specific radioactivity after *aerobic* growth. Finally, from acetate, both C_3 of aspartate and C_1 of histidine were unlabeled.

Experimental

Isolation of Histidine.—Histidine was isolated from hydrolyzed yeast protein previously freed from arginine, glutamic acid, aspartic acid, tyrosine and lysine.[9] The histidine, after a fivefold dilution with non-radioactive histidine, was adsorbed on an IRC-50 ion-exchange resin column (Rohm and Haas), buffered at *p*H 4.7 with sodium acetate, from which it was eluted with 4% hydrochloric acid solution. The eluate was repeatedly evaporated to dryness by distillation under reduced pressure to remove free hydrochloric acid and dissolved in water. An excess of silver nitrate was then added. The silver chloride was removed by centrifugation and the *p*H of the centrifugate adjusted to *p*H 7.4 to precipitate the silver salt of histidine. The washed silver salt was suspended in water and decomposed with hydrogen sulfide. Removal of the silver sulfide and evaporation of the filtrate under reduced pressure yielded crude histidine which was purified as the monoöxalate.

Purification of Histidine.—The histidine from the foregoing procedure (80–100 mg.) was dissolved in 2 to 4 ml. of water and mixed with a 100% excess of oxalic acid as a saturated solution. Alcohol was added to a concentration of approximately 80%. The white solid that formed was allowed to stand for 12 hours at 0°, then filtered and recrystallized by dissolving in water and reprecipitating with alcohol. The recrystallized material had a decomposition point beginning sharply at 223° (Fischer block, corrected). Over-all yields of 50 to 80% were experienced in this operation on a 100-mg. scale.

Anal. Calcd. for histidine monoöxalate: C, 39.2; H, 4.5; equiv. wt. of oxalate, 122.60; histidine, 63.4. Found: C, 39.9; H, 4.8; equiv. wt. of oxalate ($KMnO_4$), 122.5; histidine (microbiological assay), 67.

Radioactivity Measurements.—The specific radioactivities of histidine oxalate samples were determined by direct plating, using appropriate counting times for samples and backgrounds to maintain an over-all precision of 5%.[10] The carboxyl group specific radioactivities were determined by ninhydrin decarboxylation[11] after preliminary "cold" runs had established that satisfactory yields of barium carbonate could be obtained[4] and that oxalic acid gave no CO_2 with ninhydrin. The $BaC^{14}O_3$ thus obtained was plated and counted in the conventional manner with the usual correction for self-absorption applied.

DEPARTMENT OF CHEMISTRY AND THE
SCIENCE RESEARCH INSTITUTE
OREGON STATE COLLEGE
CORVALLIS, OREGON

---

[6] C. H. Wang, R. F. Labbe, B. E. Christensen and V. H. Cheldelin, *J. Biol. Chem.*, **197**, 645 (1952).

[7] J. C. Winters and R. Kunin, *Ind. Eng. Chem.*, **41**, 460 (1949).

[8] C. H. Wang, R. C. Thomas, V. H. Cheldelin and B. E. Christensen, *J. Biol. Chem.*, **197**, 663 (1952).

[9] R. F. Labbe, R. C. Thomas, V. H. Cheldelin, B. E. Christensen and C. H. Wang, *ibid.*, **197**, 655 (1952).

[10] M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. F. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 288.

[11] *Ibid.*, pp. 260–261.

Freezing Point and Vapor Pressure Data for Solutions of Carbon Dioxide with Some Halogen Substituted Methanes

BY THOMAS DE VRIES AND WILLIAM N. VANDERKOOI

RECEIVED JANUARY 12, 1953

Vapor pressure–composition data were desired for liquid mixtures of carbon dioxide with bromochloromethane, dibromodifluoromethane and bromotrifluoromethane. The solutions were prepared by condensing successive measured volumes of carbon dioxide gas into the liquid organic compound which was in a bulb attached to a closed system and cooled by immersion in a *n*-propyl alcohol-bath. The temperature was adjusted to the desired temperature by means of liquid nitrogen introduced into a coil of copper tubing immersed in the bath liquid. The solution in the bulb was stirred by a helix of wire whose up and down motion was magnetically controlled. The pressure in the system was measured with a mercury manometer. The volume of the system was known in order to apply a correction for uncondensed gases. The temperature when crystals first appeared in the solution upon cooling was measured with a single junction copper–constantan thermocouple and a Rubicon, type B, precision potentiometer.

TABLE I

FREEZING POINTS OF BROMOCHLOROMETHANE-CARBON DIOXIDE SYSTEM

Mole % CO_2	F.p., °C.	Eutectic	Press., cm.
0	−87.9		0.2
4.6	−89.9		14.8
6.0	−90.5		19.8
8.4	−91.3		21.9
10.6	−92.1	−92.1	23.6
12.1	−90.4	−92.1	31.1
15.0	−85.5	−92.1	48.0
21.6	−80.0		79.3
29.2	−73.8		122.6
38.8	−69.7	−92.1	160.7
60[a]	−64.2		242
80[a]	−60.3		316
100[b]	−56.6		388.5

[a] Estimated from smooth curve. [b] "International Critical Tables," Vol. III, McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p. 235.

TABLE II

FREEZING POINTS OF DIBROMODIFLUOROMETHANE-CARBON DIOXIDE SYSTEM

Mole % CO_2	F.p., °C.	Eutectic	Press., cm.
0	−141.6		0.5
0.7	−141.4	−142.5	.4
2.3	−127.7	−142.7	.4
5.0	−114.8	−142.7	2.8
9.7	−104.0		11.4
16.2	− 93.2		27.7
20.1	− 88.2		38.1
28.2	− 80.7		78.9
41.7	− 74.6	−142.6	111.00
47.2	− 71.7		145.0
60[a]	− 67.3		193
80[a]	− 61.4		289
100[b]	− 56.6		388.3

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I.

TABLE III

FREEZING POINTS OF BROMOTRIFLUOROMETHANE-CARBON DIOXIDE SYSTEM

Mole % CO_2	F.p., °C.	Press., cm.	°C. for 76 cm.
0	−168	5	−64.7
0.8	−154.2	4.5	
1.1	−150.9		
2.0	−137.0		
4.9	−121.8	8.4	
10.0	−107.6	21.0	−74.7
22.2	− 92.7	49.2	−81.7
33.8	− 83.7	79.0	−84.1
46.7	− 76.9	121.7	
60[a]	− 71.0	187	−84.0
80[a]	− 62.9	285	−81.7
100[b]	− 56.6	388.5	−78.5

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I.

Materials.—The bromochloromethane was purified by distillation in a multiple plate fractionating column; b.p. 68.0° at 76 cm.; f.p. −87.9°. The dibromodifluoromethane after several distillations had a freezing point of −141.6°. The bromotrifluoromethane as procured contained about 10% carbon dioxide as impurity. After purification a solidification temperature of −168 ± 2° was obtained.

Results.—The data are presented in Tables I-III. For the system $CH_2BrCl-CO_2$, the eutectic temperature is −92.1° at 10.6 mole per cent. CO_2; for the system $CBr_2F_2-CO_2$, −142.6° at 0.5 mole per cent. CO_2; and for the system $CBrF_3-CO_2$, at −170° at a concentration less than 0.5 mole per cent. CO_2.

Acknowledgment.—The work was done under the auspices of the Purdue Research Foundation and Wright Air Development Center, Dayton, Ohio.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

Terpenoids. I. The Triterpenes of the Cactus *Lemaireocereus Thurberi*

BY CARL DJERASSI, L. E. GELLER AND A. J. LEMIN[1]

RECEIVED DECEMBER 22, 1952

In connection with a study now under way in this Laboratory[2] on the alkaloids of certain cacti, it appeared of interest also to investigate the non-basic constituents of certain members of the *Cactaceae* family. The present note is concerned with such an examination of the cactus *Lemaireocereus Thurberi*, the only species of the genus *Lemaireocereus*, the natural habitat of which extends as far north as Arizona.[3] This cactus, reaching up to 21 feet in height, is particularly abundant in northern Mexico in the states of Sonora, Nayarit, Sinaloa and Baja California where it is known as "pitahaya dulce"[4] and it is often used by the natives for natural fences. The specimens employed in the present study were obtained through the cooperation of Dr. R. R. Humphrey, University of Arizona, who collected them near Hermosillo, Sonora.

A chemical study of the alcoholic extract of the dried and pulverized plant indicated the total absence of alkaloids, in marked contrast to the abundance of alkaloids in some related genera.[2] Similarly, the neutral portion yielded only negligible amounts of crystalline material, but there was an appreciable, water-soluble, glycosidic fraction. Acid hydrolysis of this material yielded a neutral and an acidic component. The former appears to be an unknown triterpene ($C_{30}H_{46}O_3$), the infrared spectrum (Fig. 1) of which showed bands at 2.80 and 5.65 μ characteristic of a free hydroxyl group and a five-membered lactone ring. The substance formed a monoacetate with infrared carbonyl

---

[1] Syntex Post-doctorate Fellow, 1952–1953.

[2] C. Djerassi, *et al.*, to be published.

[3] N. L. Britton and J. N. Rose, "The Cactaceae," Vol. II, p. 98, Carnegie Institution of Washington, Washington, D. C., 1920.

[4] H. Bravo, "Las Cactaceas de Mexico," Mexico, D. F., 1937, p. 269.

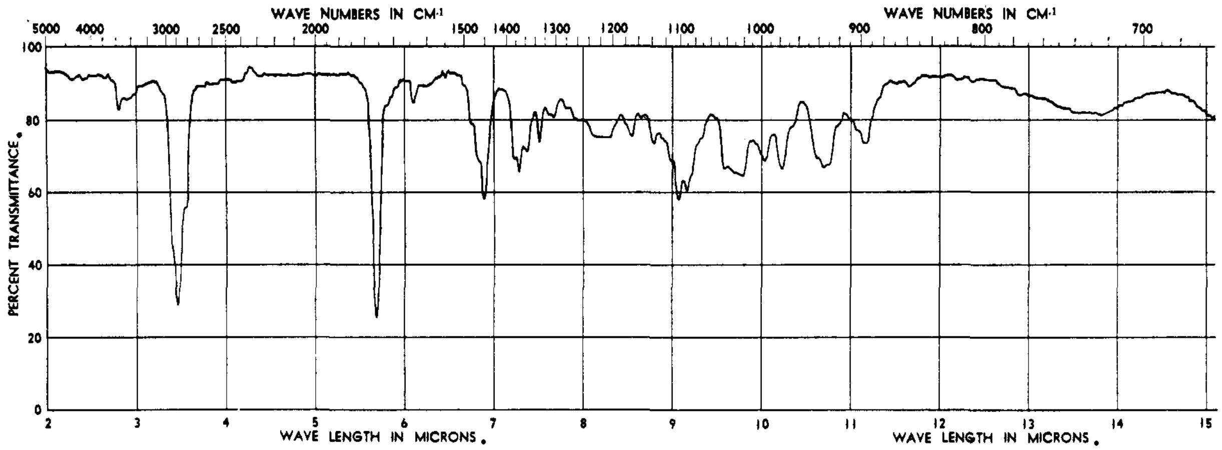


Fig. 1.—Infrared spectrum of thurberogenin in chloroform solution (0.1 mm. sodium chloride cell).

bands at 5.66 and 5.80 μ and was unsaturated to tetranitromethane, but showed no selective absorption in the ultraviolet. Further work on the structure of this compound, which we have named provisionally "thurberogenin," is contemplated when additional supplies of plant become available.

The acidic sapogenin was readily identified as the known oleanolic acid and was further characterized as the methyl ester, acetate and methyl ester acetate. Oleanolic acid has been isolated from over twenty different plant sources in the free state and as the glycoside[5] but it has never been encountered in a cactus. In fact, this appears to be the first report of the isolation of triterpenes from the *Cactaceae* family and it has prompted us to undertake a chemical investigation of representatives of the sub-tribe *Cereanae* to which belong all of the giant cacti indigenous to this continent. Preliminary results indicate that the occurrence of triterpenes is the rule rather than exception in these plants and that a number of new triterpenes will be found; these will form the subjects of future communications.

Experimental[6]

Isolation of Thurberogenin.—Two kilos of the cactus *Lemaireocereus thurberi* (collected in August, 1952, by Dr. R. R. Humphrey 10 miles north of Hermosillo on the road to Nogales) was cut into small pieces, dried for 2 days at 80–90°, passed through a meat grinder and the dry material (303 g.) was extracted continuously in a soxhlet extractor with 2 l. of ethanol until the extract was colorless (2 days). The dark green solution was evaporated to dryness under reduced pressure and the residue (65 g.) was extracted repeatedly with ether. The ether extract gave no precipitate with Mayer reagent and yielded only traces of oily material when processed in the usual manner for alkaloids. The ether-insoluble, semi-crystalline glycosidic portion (36 g.) was refluxed for 3.5 hours with 125 cc. of methanol and 31 cc. of concd. hydrochloric acid. After addition of excess 10% sodium hydroxide solution, the mixture was extracted thoroughly with ether. Evaporation of the dried ether extract followed by crystallization from methanol–chloroform afforded 1.4 g. (0.46%) of colorless needles of *thurberogenin*[7] with m.p. 283–285° (293–295° Kofler), $[\alpha]^{22}\text{D}$ +11°, $\lambda_{\max}^{\text{CHCl}_3}$ 2.80 and 5.65 μ (*cf.* Fig. 1), no selective ultraviolet absorption above 215 mμ, light yellow color with tetranitromethane.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.21; H, 10.23.

Infrared evidence was adduced for the presence of the hydroxyl function as a secondary hydroxyl group attached to a a six-membered (or larger) ring. Thus, oxidation of a small sample of thurberogenin with chromium trioxide–sulfuric acid in acetone solution followed by crystallization from methanol–chloroform afforded crystals with m.p. 233–236°, the infrared spectrum of which showed no more hydroxyl band, but in addition to the 5.65 μ lactone band there was present a second carbonyl band of equal intensity at 5.90 μ, indicative of a six-membered (or higher) ketone. No selective absorption was found in the ultraviolet region.

Thurberogenin acetate, prepared by the acetic anhydride–pyridine method (room temperature), crystallized from methanol–chloroform as needles with m.p. 249–252°, $[\alpha]^{22}\text{D}$ +45°, $\lambda_{\max}^{\text{CHCl}_3}$ 5.66, 5.80 and 8.00 μ, yellow color with tetranitromethane.

Anal. Calcd. for $C_{32}H_{48}O_4$: C, 77.37; H, 9.74. Found: C, 77.14; H, 9.50.

Isolation of Oleanolic Acid.—The alkaline solution from the above described hydrolysis deposited a crystalline sodium salt, which was filtered, dissolved in ethanol and acidified with dilute hydrochloric acid. The solution was extracted with ether, washed, dried and evaporated and the residue was crystallized from methanol–chloroform to yield 5.5 g. (1.8%) of oleanolic acid with m.p. 308–310°,[8] $\lambda_{\max}^{\text{Nujol}}$ 2.88 and 5.88 μ. A sample was sublimed in high vacuum before analysis.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.51; H, 10.43.

Oleanolic acid acetate was obtained as needles after crystallization from methanol–chloroform; m.p. 264–267°,[9] undepressed upon admixture with an authentic specimen

---

[5] In addition to the plant sources enumerated by E. Hardegger and F. G. Robinet (*Helv. Chim. Acta*, **33**, 1871 (1950)), oleanolic acid has also been encountered in *Clematis* root (K. Ishiwatari, K. Nakano and F. Shinkawa, *J. Pharm. Soc., Japan*, **64**, 34 (1944)), in *Thymus vulgaris* (E. J. Rowe, J. E. Orr, A. H. Uhl and L. M. Parks, *J. Am. Pharm. Assoc.*, **38**, 122 (1949)), in *Prunus mume* (Y. Takizima, *J. Agr. Chem. Soc., Japan*, **23**, 8 (1949)), in *Crataegus oxyacanthal* (T. Bersin and A. Müller, *Helv. Chim. Acta*, **35**, 1891 (1952)), in *Randia* (J. Gedeon, *Arch. Pharm.*, **285**, 127 (1952)), and in a number of Western Australian plants (D. E. White, *et al.*, *J. Chem. Soc.*, 4065 (1952)). The most convenient source still appears to be spent cloves (L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **19**, 114 (1936)).

[6] Melting points are uncorrected and were obtained on the Fisher–Johns block. The infrared spectra were measured on a Baird Associates double beam recording spectrometer. All rotations were determined in chloroform solution.

[7] The physical constants of thurberogenin (though not of its acetate) are quite similar to those reported for authentic oleanolic acid lactone which has been synthesized recently by D. H. R. Barton and N. J. Holness (*J. Chem. Soc.*, 78 (1952)). However, a mixture melting point with a sample kindly supplied by Dr. Barton showed a marked depression.

[8] *Inter al.*: A. W. van der Haar, *Rec. trav. chim.*, **46**, 775 (1927), m.p. 307–308°.

[9] E. Wedekind and W. Schicke, *Z. physiol. Chem.*, **195**, 132 (1931), report m.p. 268°, $[\alpha]\text{D}$ +74.5° (chloroform).

obtained from spent cloves,[5,10] $[\alpha]^{22}\text{D}$ +70°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.80, 5.90 and 7.98 μ. The infrared spectra of the two specimens were identical.

Oleanolic acid methyl ester, prepared by diazomethane treatment in ether–methanol solution, crystallized from methanol–chloroform as colorless crystals with m.p. 198–199°, $[\alpha]^{22}\text{D}$ +69°.[11]

Oleanolic acid acetate methyl ester, obtained by diazomethane treatment of the acetate, exhibited m.p. 217–219°, $[\alpha]^{22}\text{D}$ +65°,[12] after crystallization from chloroform–methanol.

Acknowledgment.—The presently used plant specimens were obtained during a collection trip for related cacti under a grant from the American Heart Association.

[10] We are indebted to Dr. T. G. Halsall of the University of Manchester, England, for this sample.

[11] W. A. Jacobs and E. E. Fleck, *J. Biol. Chem.*, **96**, 341 (1932), report m.p. 197–198°, $[\alpha]\text{D}$ +75° (chloroform).

[12] A. Winterstein and G. Stein, *Z. physiol. Chem.*, **199**, 64 (1931), give m.p. 218–220°, $[\alpha]\text{D}$ +66.7°, +70.4°.

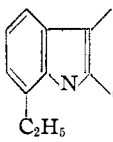
DEPARTMENT OF CHEMISTRY
WAYNE UNIVERSITY
DETROIT 1, MICHIGAN

Heterocyclic Compounds from Ethylanilines

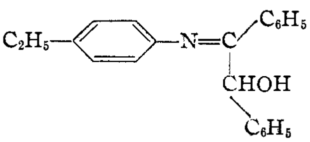
BY WILLIAM S. EMERSON, ROBERT A. HEIMSCH AND TRACY M. PATRICK, JR.

RECEIVED JANUARY 5, 1953

With the ready availability of *o*- and *p*-ethylnitrobenzene, it seemed desirable to hydrogenate them to the corresponding anilines and utilize these in organic syntheses. *o*-Ethylaniline reacted with benzoin in the presence of fused zinc chloride at 130° to give 49% of 2,3-diphenyl-7-ethylindole (I), a method used previously for the preparation of 2,3-diphenylindole itself.[1] Under the same conditions *p*-ethylaniline yielded only the Schiff base N-(1,2-diphenyl-2-hydroxyethylidene)-*p*-ethylaniline (II) in 20% yield.



I



II

o-Ethylaniline and *p*-ethylaniline gave 8- and 6-ethylquinolines, respectively, in 74 and 45% yields under the conditions of the Skraup reaction. Both quinolines were characterized as their methiodides. 6-Ethylquinoline was oxidized to the corresponding amine oxide by a standard procedure.[2] While the acetate resisted all attempts at purification, the picrate crystallized readily.

Experimental

***o*-Ethylaniline** was prepared by the hydrogenation of *o*-ethylnitrobenzene in the presence of Raney nickel. The yield was 78%, b.p. 99–105° (18 mm.) (210–211°),[3] $n^{25}\text{D}$ 1.5562.

2,3-Diphenyl-7-ethylindole.—A mixture of 60.5 g. of *o*-ethylaniline, 106 g. of benzoin, 75 g. of freshly dehydrated zinc chloride and 150 cc. of benzene was heated at 130° in a rocking autoclave for 3 hours. The resulting clear resin was dissolved in ethanol and diluted with water. The product which precipitated at this point was separated by filtration, washed with water and crystallized first from hexane and then from ethanol to yield 73 g. (49%) of 2,3-diphenyl-7-ethylindole, m.p. 112–114°. An analytical sample was recrystallized from ethanol, m.p. 113–114°.

Anal.[4] Calcd. for $C_{22}H_{19}N$: C, 88.9; H, 6.43; N, 4.72. Found: C, 89.1; H, 6.57; N, 4.94.

8-Ethylquinoline was prepared by a modification of the previously described Skraup reaction[5] in 36% conversion and 74% yield, b.p. 132–135° (20 mm.) (256°),[5] $n^{25}\text{D}$ 1.5993 ($n^{25}\text{D}$ 1.6020).[5]

8-Ethylquinoline methiodide was prepared by heating 9 g. of the quinoline with 28 g. of methyl iodide in a bomb at 100° for 18 hours. The 8 g. (47%) of crude product was crystallized twice from ethyl acetate-methanol, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_{14}NI$: C, 48.2; H, 4.69. Found: C, 47.5; H, 4.67.

***p*-Ethylaniline** was prepared in the same way as the ortho isomer in 93% yield, b.p. 98° (14 mm.)–108° (19 mm.) (95–96° (10 mm.))[6], $n^{25}\text{D}$ 1.5520 ($n^{22}\text{D}$ 1.5529)[7].

N-(1,2-Diphenyl-2-hydroxyethylidene)-*p*-ethylaniline was prepared by heating 60.5 g. of *p*-ethylaniline, 106 g. of benzoin, 75 g. of freshly dehydrated zinc chloride and 150 cc. of benzene in a bomb for 3 hours at 130°. After the reaction mixture had been diluted with ethanol, the crude product was separated by filtration, washed with water and dried. On boiling with hexane 2.0 g. of the zinc chloride salt of *p*-ethylaniline remained insoluble. It was separated by filtration and crystallized twice from ethanol, dec. pt. 244–247°. It was soluble in hot water and gave a flocculent precipitate with aqueous silver nitrate.

Anal. Calcd. for $C_8H_{11}N\cdot{}^1/_2ZnCl_2$: C, 50.8; H, 5.82; N, 7.41. Found: C, 51.4; H, 5.89; N, 7.75.

Cooling of the hexane solution yielded 30 g. (20%) of crude N-(1,2-diphenyl-2-hydroxyethylidene)-*p*-ethylaniline, m.p. 102–103°. This product was recrystallized twice for analysis, m.p. 103–104°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.8; H, 6.67; N, 4.40. Found: C, 83.3; H, 6.71; N, 4.43.

6-Ethylquinoline was prepared in the same way as the 8-isomer in 23% conversion and 45% yield, b.p. 132–140° (17 mm.), $n^{25}\text{D}$ 1.6017. Redistillation yielded pure 6-ethylquinoline, b.p. 135–136° (14 mm.), $n^{25}\text{D}$ 1.6009, $d^{25}{}_{25}$ 1.043, $M^{25}\text{D}$ calcd. 51.73, $M^{25}\text{D}$ found 51.55.

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.1; H, 7.01; N, 8.92. Found: C, 83.9; H, 6.92; N, 9.08.

6-Ethylquinoline picrate melted at 205.0–205.5°.

Anal. Calcd. for $C_{17}H_{14}O_7N_4$: C, 52.9; H, 3.63; N, 14.5. Found: C, 53.0; H, 3.59; N, 14.1.

6-Ethylquinoline methiodide was prepared by warming 8 g. of 6-ethylquinoline with 25 g. of methyl iodide. The crude product (15 g., 99%) was separated by filtration and crystallized twice from methanol, m.p. 194.0–194.5°.

Anal. Calcd. for $C_{12}H_{14}NI$: C, 48.2; H, 4.69. Found: C, 48.5; H, 4.83

6-Ethylquinoline-N-oxide Acetate.—A mixture of 73 g. of 6-ethylquinoline, 175 cc. of glacial acetic acid and 175 cc. of 30% hydrogen peroxide was held at 50° for 24 hours. Distillation at 25 mm. to a pot temperature of 110° left as a residue 87 g. (78%) of crude oxide. This material was crystallized three times from benzene with previous treatment of the solution with Norite, but the product always separated as an oil before crystallizing, m.p. 66–67°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.9; H, 6.44. Found: C, 64.3; H, 6.54.

6-Ethylquinoline-N-oxide picrate melted at 156–157°.

Anal. Calcd. for $C_{17}H_{14}O_8N_4$: C, 50.7; H, 3.48; N, 13.9. Found: C, 51.1; H, 3.55; N, 13.8.

---

[1] F. R. Japp and T. S. Murray, *J. Chem. Soc.*, **65**, 889 (1894).

[2] H. J. Den Hertog and W. P. Combe, *Rec. trav. chim.*, **70**, 581 (1951).

[3] F. Beilstein and A. Kuhlberg, *Ann.*, **156**, 206 (1870).

[4] All of the analyses are microanalyses performed by Mr. Donald Stoltz, Miss Winifred Harden and Mrs. Helen LeMay of these laboratories.

[5] R. A. Glenn and J. R. Bailey, THIS JOURNAL, **63**, 639 (1941).

[6] G. Vavon and V. M. Mitchovitch, *Bull. soc. chim.*, [4] **45**, 961 (1929).

[7] R. Schreiner, *J. prakt. Chem.*, [2] **81**, 599 (1910).

A mixture of this picrate with that of 6-ethylquinoline melted at 147–150°.

CENTRAL RESEARCH DEPT.
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

Metathetical Reactions of Silver Salts in Solution. II. The Synthesis of Alkyl Sulfonates[1]

BY WILLIAM D. EMMONS AND ARTHUR F. FERRIS

RECEIVED JANUARY 2, 1953

Alkyl sulfonates have normally been prepared by the base-catalyzed action of a sulfonyl chloride upon an alcohol.[2] This method is dependent on the availability of the appropriate alcohol and is limited to the preparation of those esters which are not sensitive to base. A less useful method has been the heating of a silver sulfonate with an alkyl iodide.[2] This procedure is severely limited by the

$$RSO_3Ag + R'I \longrightarrow RSO_3R' + AgI$$

heterogeneous reaction conditions employed and the relatively high temperatures frequently necessary to effect complete reaction.

We have been able to make a significant improvement in the preparation of alkyl sulfonates by the silver salt method using acetonitrile as a solvent for the reaction. The silver salts of methanesulfonic acid, *p*-toluenesulfonic acid and benzenesulfonic acid are all extremely soluble in acetonitrile at room temperature. Accordingly, the metathetical reaction between these silver salts and primary alkyl halides may be carried out smoothly under mild conditions and with nearly quantitative yields of esters. The following mesylates were all prepared from silver methanesulfonate and the corresponding alkyl iodides except where noted: methyl mesylate (97% yield), ethyl mesylate (94% yield), butyl mesylate (97% yield), allyl mesylate (96% yield from allyl bromide), methallyl mesylate (81% yield from methallyl chloride), methylene bismesylate (72% yield from methylene iodide) and benzyl mesylate (92% yield from benzyl bromide). Tosylates were prepared by essentially the same procedure: methyl tosylate (77% yield), ethyl tosylate (76% yield), ethylene bis-tosylate (65% yield from ethylene bromide), methylene bistosylate (88% yield from methylene iodide) and benzyl tosylate (52% yield from benzyl chloride). Methyl benzenesulfonate was also prepared in 69% yield from methyl iodide and silver benzenesulfonate.

The reaction of silver sulfonates in solution with secondary and tertiary halides was, as might be expected, of no synthetic value for the preparation of sulfonates. Under these conditions dehydrohalogenation takes place; indeed, from *t*-butyl bromide and silver tosylate the only product isolated was *p*-toluenesulfonic acid.

Experimental[3]

The procedures described herein for allyl mesylate and methylene bis-mesylate are typical of those used for preparation of all the other esters. Physical constants and analytical data are given for those esters which have not been described previously in the literature. The yields reported in the discussion refer in most cases to the distilled product. The silver salts were conveniently prepared by addition of a slight excess of silver oxide to an acetonitrile solution of the sulfonic acid. Evaporation of the solvent gave the silver salts in excellent yield and purity. All melting points and boiling points are uncorrected.

Allyl Mesylate.—To a solution of 10.2 g. (0.05 mole) of silver methanesulfonate in 50 ml. of dry acetonitrile was added 7.3 g. (0.06 mole) of allyl bromide. The mixture was allowed to stand one hour and was then filtered. The solvent was removed at reduced pressure and the liquid residue distilled. There was obtained 6.5 g. (96%) of colorless allyl mesylate, b.p. 45–47° (0.05 mm.), n^{20}_D 1.4435.

Anal. Calcd. for $C_4H_8O_3S$: C, 35.28; H, 5.92; sapn. equiv., 136.2. Found: C, 35.04; H, 5.66; sapn. equiv., 133.0.

Methylene Bis-mesylate.—To a hot solution of 22.3 g. (0.11 mole) of silver methanesulfonate in 100 ml. of acetonitrile was added 26.8 (0.1 mole) of methylene iodide. The solution was stirred at reflux for 20 hours. It was then filtered and the volatile solvent removed at reduced pressure. The solid product was dissolved in 150 ml. of warm ethylene dichloride and then filtered to remove the excess silver methanesulfonate. The solvent was removed by distillation yielding the crystalline product which was recrystallized from ethanol; yield 7.4 g. (72%), m.p. 75–76°.

Anal. Calcd. for $C_3H_8S_2O_6$: C, 17.64; H, 3.95; sapn. equiv., 102.1. Found: C, 17.83; H, 3.87; sapn. equiv., 103.6.

Methallyl Mesylate.—This compound was prepared by heating 10.2 g. (0.05 mole) of silver methanesulfonate and 6.4 g. (0.07 mole) of methallyl chloride in 50 ml. of acetonitrile for one hour; yield 6.1 g. (81%), n^{20}_D 1.4468, b.p. 54–56° (0.02 mm.).

Anal. Calcd. for $C_5H_{10}O_3S$: C, 39.98; H, 6.71; S, 21.35; sapn. equiv., 150.2. Found: C, 40.39; H, 6.60; S, 20.95; sapn. equiv., 151.5.

Benzyl Mesylate.—This ester was prepared from 11.2 g. (0.055 mole) of silver methanesulfonate and 8.5 g. (0.05 mole) of benzyl bromide. The product decomposed on attempted distillation, and the data reported here were obtained from the crude sample; yield 8.6 g. (92%), n^{20}_D 1.5199.

Anal. Calcd. for $C_8H_{10}O_3S$: C, 51.59; H, 5.41; S, 17.22; sapn. equiv., 186.2. Found: C, 52.42; H, 5.51; S, 17.32; sapn. equiv., 183.9.

Methylene Bis-tosylate.—A solution of 14.0 g. (0.05 mole) of silver *p*-toluenesulfonate and 6.0 g. (0.023 mole) of methylene iodide in 50 ml. of acetonitrile was heated under reflux for 24 hours. The product was worked up in the same manner as methylene bis-mesylate. The crystalline solid was recrystallized from absolute ethanol, yield 7.0 g. (87%), m.p. 116–117°.

Anal. Calcd. for $C_{15}H_{16}O_6S_2$: C, 50.55; H, 4.53; S, 17.99; sapn. equiv., 178.2. Found: C, 50.27; H, 4.44; S, 17.61; sapn. equiv., 182.1.

ROHM AND HAAS COMPANY
JOSIAH GORGAS LABORATORY
REDSTONE ARSENAL RESEARCH DIVISION
HUNTSVILLE, ALABAMA

---

[1] This work was carried out under Army Ordnance Contract W-01-021-ORD-334.

[2] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 514.

[3] We are indebted to Mr. Al Kennedy and Miss Annie Smelley for analytical data.

Estimation of Entropy

BY GEORGE HOOD

RECEIVED SEPTEMBER 30, 1952

Various methods furnish estimates of the standard entropy of a compound with an uncertainty of a few entropy units. A better estimate can be obtained for the members of a substitution series such as CH_4, CH_3Cl, . . . , CCl_4 if the standard entropies of two members are known.

Figure 1 shows that the translational and vibra-

TABLE I

ESTIMATION OF STANDARD ENTROPIES[a] $S^0_{298(g)}$

	σ	X = H S^0(obsd.)	Y = F S^0(calcd.)	X = H S^0(obsd.)	Y = Cl S^0(calcd.)	X = H S^0(obsd.)	Y = Br S^0(calcd.)	X = F S^0(obsd.)	Y = Cl S^0(calcd.)
CX_4	12	44.50	. . .	44.50	. . .	44.50	. . .	62.7	. . .
CX_3Y	3	53.30	53.43	55.97	56.23	58.74	59.14	. . .	69.89
CX_2Y_2	2	. . .	58.17	64.68	63.80	70.16	69.62	. . .	72.90
CXY_3	3	. . .	62.53	70.86	70.95	79.18	79.68	74.06	75.51
CY_4	12	62.7	. . .	73.95	. . .	85.6	. . .	73.95	. . .

[a] All of the observed entropy values were taken from the National Bureau of Standards, Circular 500, Washington, D. C., 1952.

tional contributions when added together become an approximately linear function of the composition of the compound. The rotational entropy contribution, however, deviates considerably from linearity since it depends on the symmetry number σ, of the various molecules. The symmetry number arises through the term $- R \ln \sigma$ in the equations for the evaluation of the rotational entropy by statistical thermodynamics.

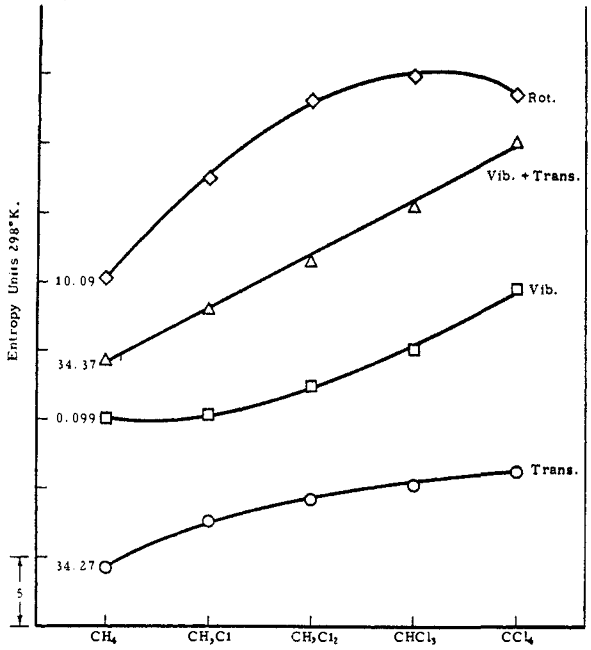


Fig. 1.—Contributions to the standard entropy $S^\circ_{298}(g)$.

Consequently, linear interpolation of $S^0(g) + R \ln \sigma$ leads to satisfactory agreement with observed values for the type of series herein considered (Table I). The average deviation between observed and calculated values for the compounds in Table I is 0.5 entropy unit.

SHELL DEVELOPMENT CO.
EMERYVILLE, CALIFORNIA

Distribution of 8-Quinolinol between Water and Chloroform as a Function of *p*H

BY THERALD MOELLER AND FRED L. PUNDSACK

RECEIVED DECEMBER 20, 1952

The extensive use of 8-quinolinol as an analytical reagent is dependent upon its ability to form with many metal ions water-insoluble chelates which are applicable to both gravimetric and colorimetric determinations. For determinations of the latter type, a number of procedures based upon extraction of metal ions from aqueous solutions into chloroform solutions of 8-quinolinol and subsequent spectrophotometric examinations of the extracts have been proposed.[1-6] These extractions are dependent upon the *p*H of the aqueous phase, and their usefulness is limited somewhat by the concentration of free 8-quinolinol in the chloroform phase, a large excess of free 8-quinolinol interfering markedly with spectrophotometric determinations of the metal chelate concentrations. Inasmuch as the quantity of 8-quinolinol in the chloroform phase is itself *p*H dependent, it would help in establishing optimum conditions for quantitative extraction of metal chelates to evaluate the distribution of the reagent between water and chloroform as a function of *p*H.

From concentration measurements at 18°, Lacroix[2] has calculated a distribution coefficient

$$c_{CHCl_3}/c_{H_2O} = 720 \qquad (1)$$

for molecular 8-quinolinol. In addition, he has evaluated a theoretical distribution curve, based upon data for two extractions, which shows extraction into chloroform to be complete in the *p*H range *ca.* 4–11, but has offered only limited experimental support. No equilibrium studies on this distribution appear to have been made.

Experimental

Reagents.—The 8-quinolinol was an Eastman Kodak Co. product which had been recrystallized from ethanol. Other chemicals were of reagent quality.

Apparatus.—Spectrophotometric measurements were made with a Beckman model DU spectrophotometer. A Beckman model G *p*H meter, the glass electrodes of which were calibrated frequently against suitable buffers, was used for all *p*H measurements.

Procedure.—Twenty-five ml. portions of a chloroform solution of accurately known 8-quinolinol concentration were agitated with 25-ml. volumes of aqueous solutions of known *p*H values in a constant temperature bath at 25.0 ± 0.1°. The concentration of the original chloroform solution was determined spectrophotometrically, using the 3154 Å. absorption peak of 8-quinolinol in this solvent.[7] The *p*H of the aqueous phase was adjusted by using sulfuric acid, sodium acetate and sodium hydroxide as required.

Contact between aqueous and chloroform phases for 24 hours was shown to be sufficient to ensure complete concentration equilibration. After a 24-hour contact period in each instance, the total 8-quinolinol content of the aqueous phase was determined spectrophotometrically on an aliquot, using the light absorption at 2505 Å. for acidic solu-

---

(1) T. Moeller, *Ind. Eng. Chem., Anal. Ed.*, **15**, 346 (1943).

(2) S. Lacroix, *Anal. Chim. Acta*, **1**, 260 (1947).

(3) T. D. Parks and L. Lykken, *Anal. Chem.*, **20**, 1102 (1948).

(4) C. H. R. Gentry and L. G. Sherrington, *Analyst*, **75**, 17 (1950).

(5) T. Moeller and A. J. Cohen, *Anal. Chem.*, **22**, 686 (1950).

(6) J. L. Kassner and M. A. Ozier, *ibid.*, **23**, 1453 (1951).

(7) F. L. Pundsack, Doctoral Dissertation, University of Illinois (1952).

tions and that at 2525 Å. for alkaline solutions.[7] Neutral and nearly neutral solutions were acidified with sulfuric acid and the absorption determined at 2505 Å. Concentration of residual 8-quinolinol in the chloroform phase was determined by difference in each case. The distribution coefficient was then evaluated as the ratio of the molar concentration of 8-quinolinol in the chloroform phase to the total molar concentration of all 8-quinolinol species in the aqueous phase. Substitution of concentrations for activities was permissible because of the low concentration levels employed.

Discussion

Variation in distribution coefficients with *p*H, as indicated in Table I, are easily understood in terms of the amphoteric character of 8-quinolinol. The basic and acidic properties of the compound are described by the equilibria

TABLE I

DISTRIBUTION OF 8-QUINOLINOL BETWEEN CHLOROFORM AND WATER AT 25°

*p*H	$\Sigma c_{\mathrm{H_2O}}$[a] mole/liter. × 10^5	$c_{\mathrm{CHCl_3}}$[b] mole/liter, × 10^3	$c_{\mathrm{CHCl_3}}/c_{\mathrm{H_2O}}$	Molecular HOn in aqueous layer, %
2.06	9.90	0.0575	0.58	0.12
2.65	4.28	0.0792	1.85	0.44
3.75	4.40	1.17	26.4	5.32
4.43	1.51	1.36	89.9	21.2
6.05	0.489	1.72	352	92
7.00	.351	1.21	350	99
7.05	.475	1.71	360	99
8.21	.489	1.72	352	98
9.24	.055	0.121	221	80.5
10.50	2.06	1.36	65.8	18.4
12.00	4.82	0.105	2.18	0.71

[a] Sum of concentrations of molecular, cationic and anionic species. [b] Concentration of molecular species.

$$\mathrm{HOn} + \mathrm{H}^+ \rightleftarrows \mathrm{HOn{\cdot}H}^+ \tag{2}$$

$$\mathrm{HOn} \rightleftarrows \mathrm{H}^+ + \mathrm{On}^- \tag{3}$$

where HOn represents molecular 8-quinolinol. The basic and acidic dissociation constants have been determined[2,8-10] and permit evaluation of the concentrations of all three species at any *p*H. Since the only species existent in chloroform is the molecular one, it follows that essentially complete concentration of 8-quinolinol in the chloroform phase can be expected only over that *p*H range in which the quantity of the molecular species is maximum in the aqueous phase. As shown in Table I, *ca.* 99% of the 8-quinolinol in the latter phase is in the molecular form in the *p*H range 7.0–8.2, with more than 90% being molecular at as low a *p*H as 6.0. In this *p*H range, the average experimental distribution coefficient of 353 closely approximates that calculated for molecular 8-quinolinol.

On the other hand, in either more acidic or more alkaline aqueous solutions, only a small fraction of the 8-quinolinol present is in the molecular form. The experimentally determined distribution coefficients, as based upon the total 8-quinolinol concentration in the aqueous phase, decrease correspondingly. Thus, although the distribution coefficients given in Table I are really theoretical values for only the 6.0–8.2 *p*H range, they are of practical importance in determining optimum *p*H conditions for 8-quinolinol extractions.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

---

[8] K. Stone and L. Friedman, THIS JOURNAL, **69**, 209 (1947).

[9] J. P. Phillips and L. L. Merritt, *ibid.*, **70**, 410 (1948).

[10] H. Irving, J. A. D. Ewart and J. T. Wilson, *J. Chem. Soc.*, 2672 (1949).

Isolation of Methylchrysene from Petroleum

BY R. J. MOORE, R. E. THORPE AND C. L. MAHONEY

RECEIVED JANUARY 15, 1953

In the course of examining a Mid-continent medium petroleum distillate by silica gel chromatography, a white crystalline material has been isolated which is identified as 1-methylchrysene. After recrystallization from ethanol, the melting point was 253° (compared with 251° found by Brode and Pattersen[1]). The ultraviolet absorption spectrum was identical to that reported for synthetic 1-methylchrysene and the parent mass found with a high temperature mass spectrometer was 242, corresponding to $C_{19}H_{14}$. Excepting the *n*-paraffins, we believe that this is the highest molecular weight pure hydrocarbon thus far isolated from native petroleum.

[1] W. R. Brode and J. W. Pattersen, THIS JOURNAL, **63**, 3252 (1941).

SHELL DEVELOPMENT CO.
EMERYVILLE, CALIF.

Carbazic Acid Esters as Carbonyl Reagents

BY NORMAN RABJOHN AND H. D. BARNSTORFF[1]

RECEIVED JANUARY 5, 1953

The common derivatives of aldehydes and ketones such as phenylhydrazones, substituted phenylhydrazones, oximes and semicarbazones, as well as a rather large number of lesser known condensation products, are described extensively in the literature and textbooks for qualitative organic analysis. However, it appears that little use[2] has been made of the esters of carbazic acid as carbonyl reagents. These materials are stable, crystalline solids which can be synthesized readily from hydrazine and an organic carbonate.

The present work describes the preparation of a number of carbonyl derivatives of methyl and ethyl carbazates which have not been reported previously. The data obtained for a series of carbomethoxyhydrazones are given in Table I. The properties of the carboethoxyhydrazones are listed in Table II.

Formaldehyde, benzalacetophenone and benzil gave mixtures of products with both methyl and

[1] From a thesis submitted by Henry D. Barnstorff to the Graduate School of the University of Missouri, 1949, in partial fulfillment of the requirements for the degree of Master of Arts.

[2] A relatively few derivatives are recorded in the following leading references: K. v. Auwers and Th. Breyhan, *J. prakt. Chem.*, **143**, 259 (1935); H. J. Backer and W. Meyer, *Rec. trav. chim.*, **45**, 82 (1926); H. DeGraff, Diss. Leiden (1930), *C. A.*, **24**, 5723 (1930); O. Diels and P. Fritzsche, *Ber.*, **44**, 3018 (1911); D. N. Majumdar and P. C. Guha, *J. Indian Chem. Soc.*, **10**, 685 (1933); and R. B. Woodward, T. P. Kohman and G. C. Harris, THIS JOURNAL, **63**, 120 (1941).

TABLE I

CARBOMETHOXYHYDRAZONES, $RCH(R){=}NNHCO_2CH_3$

Carbonyl compd.	Corrected m.p., °C.	Formula	Analyses, %			
			Carbon		Hydrogen	
			Calcd.	Found	Calcd.	Found
o-Chlorobenzaldehyde	149–150	$C_9H_9O_2N_2Cl$	50.83	50.93	4.27	4.32
m-Chlorobenzaldehyde	120–121	$C_9H_9O_2N_2Cl$	50.83	50.64	4.27	4.53
Cinnamaldehyde	171–172	$C_{11}H_{12}O_2N_2$	64.69	64.43	5.92	5.89
p-Dimethylaminobenzaldehyde	167–168	$C_{11}H_{15}O_2N_3$	59.71	59.68	6.83	6.75
2-Ethylhexaldehyde	82–83	$C_{10}H_{20}O_2N_2$	59.97	59.77	10.07	10.17
Furfural	142–143	$C_7H_8O_3N_2$	50.00	50.02	4.80	4.70
p-Hydroxybenzaldehyde	193–194	$C_9H_{10}O_3N_2$	55.66	55.75	5.19	5.14
Isobutyraldehyde	98–99	$C_6H_{12}O_2N_2$	49.98	49.77	8.39	8.45
o-Methoxybenzaldehyde	154–155	$C_{10}H_{12}O_3N_2$	57.68	57.67	5.81	5.85
m-Nitrobenzaldehyde	202–203	$C_9H_9O_4N_3$	48.43	48.17	4.06	4.31
Salicylaldehyde	165–166	$C_9H_{10}O_3N_2$	55.66	55.78	5.19	5.25
o-Tolualdehyde	127–128	$C_{10}H_{12}O_2N_2$	62.48	62.32	6.29	6.58
m-Tolualdehyde	113–114	$C_{10}H_{12}O_2N_2$	62.48	62.73	6.29	6.50
p-Tolualdehyde	154–155	$C_{10}H_{12}O_2N_2$	62.48	62.72	6.29	6.21
Vanillin	185–186	$C_{10}H_{12}O_4N_2$	53.57	53.34	5.39	5.54
Acetophenone	127–128	$C_{10}H_{12}O_2N_2$	62.48	62.42	6.29	6.60
Benzophenone	120–121	$C_{15}H_{14}O_2N_2$	70.85	70.66	5.55	5.64
p-Bromoacetophenone	147–148	$C_{10}H_{11}O_2N_2Br$	44.30	44.45	4.09	4.28
Cyclopentanone	78–79	$C_7H_{12}O_2N_2$	53.83	53.59	7.74	7.92
Desoxybenzoin	126–127	$C_{16}H_{16}O_2N_2$	71.62	71.58	6.01	5.97
Dibenzyl ketone	146–147	$C_{17}H_{18}O_2N_2$	72.32	72.23	6.43	6.52
Diethyl ketone	65–66	$C_7H_{14}O_2N_2$	53.14	52.99	8.92	9.17
Fluorenone	167–168	$C_{15}H_{12}O_2N_2$	71.41	71.43	4.80	4.91
o-Hydroxyacetophenone	172–173	$C_{10}H_{12}O_3N_2$	57.68	57.48	5.81	6.00
Isophorone	174–175	$C_{11}H_{18}O_2N_2$	62.83	62.56	8.63	8.87
Methyl *n*-amyl ketone	69–70	$C_9H_{18}O_2N_2$	58.03	57.83	9.74	9.91
Methyl *n*-propyl ketone	76–77	$C_7H_{14}O_2N_2$	53.14	52.95	8.92	9.17
Methyl *p*-tolyl ketone	139–140	$C_{11}H_{14}O_2N_2$	64.06	63.85	6.84	6.82
Pinacolone	67–68	$C_8H_{16}O_2N_2$	55.79	55.49	9.36	9.52
Propiophenone	161–162	$C_{11}H_{14}O_2N_2$	64.06	63.98	6.84	6.98

TABLE II

CARBOETHOXYHYDRAZONES, $RCH(R){=}NNHCO_2C_2H_5$

Carbonyl compd.	Corrected m.p., °C.	Formula	Analyses, %			
			Carbon		Hydrogen	
			Calcd.	Found	Calcd.	Found
o-Chlorobenzaldehyde	99–100	$C_{10}H_{11}O_2N_2Cl$	52.98	53.05	4.89	4.94
m-Chlorobenzaldehyde	98–99	$C_{10}H_{11}O_2N_2Cl$	52.98	52.90	4.89	5.03
p-Dimethylaminobenzaldehyde	154–155	$C_{12}H_{17}O_2N_3$	61.25	61.15	7.28	7.44
2-Ethylhexaldehyde	53–54	$C_{11}H_{22}O_2N_2$	61.65	61.34	10.35	10.46
p-Hydroxybenzaldehyde	217–218	$C_{10}H_{12}O_3N_2$	57.68	57.54	5.81	5.94
Isobutyraldehyde	68–69	$C_7H_{14}O_2N_2$	53.14	52.89	8.92	9.14
o-Methoxybenzaldehyde	120–121	$C_{11}H_{14}O_3N_2$	59.45	59.18	6.35	6.28
m-Nitrobenzaldehyde	165–166	$C_{10}H_{11}O_4N_3$	50.63	50.84	4.67	4.94
o-Tolualdehyde	124–125	$C_{11}H_{14}O_2N_2$	64.06	64.25	6.84	7.09
m-Tolualdehyde	102–103	$C_{11}H_{14}O_2N_2$	64.06	64.05	6.84	6.85
Benzalacetone	156–157	$C_{13}H_{16}O_2N_2$	67.22	67.31	6.94	7.15
Benzophenone	112–113	$C_{16}H_{16}O_2N_2$	71.62	71.45	6.01	6.04
p-Bromoacetophenone	150–151	$C_{11}H_{13}O_2N_2Br$	46.33	46.16	4.59	4.51
Cyclopentanone	103–104	$C_8H_{14}O_2N_2$	56.45	56.21	8.29	8.44
Desoxybenzoin	104–105	$C_{17}H_{18}O_2N_2$	72.32	72.04	6.43	6.51
Dibenzyl ketone	98–99	$C_{18}H_{20}O_2N_2$	72.95	73.10	6.80	6.84
Fluorenone	126–127	$C_{16}H_{14}O_2N_2$	72.16	72.45	5.30	5.33
o-Hydroxyacetophenone	134–135	$C_{11}H_{14}O_3N_2$	59.45	59.32	6.35	6.32
Isophorone	128–129	$C_{12}H_{20}O_2N_2$	64.25	64.00	8.99	9.28
Methyl *p*-tolyl ketone	110–111	$C_{12}H_{16}O_2N_2$	65.43	65.66	7.32	7.31
Pinacolone	84–85	$C_9H_{18}O_2N_2$	58.03	58.04	9.74	9.97
Propiophenone	144–145	$C_{12}H_{16}O_2N_2$	65.43	65.30	7.32	7.45

ethyl carbazates. Low melting solids or oils resulted from the condensation of methyl carbazate with *n*-butyraldehyde, methyl ethyl ketone, mesityl oxide and cyclohexanone. Similar results were obtained with ethyl carbazate and *n*-butyraldehyde, methyl ethyl ketone, methyl *n*-propyl ketone, diethyl ketone, mesityl oxide, methyl *n*-amyl ketone and cyclohexanone.

Experimental

Methyl and Ethyl Carbazates.—These esters were prepared in about 90% yields from 85% hydrazine hydrate and dimethyl and diethyl carbonates, respectively, by the procedure of Diels.[3]

Preparation of the Carbomethoxy- and Carboethoxyhydrazones.—Approximately 1 g. of the aldehyde or ketone was dissolved in 3–4 ml. of alcohol and sufficient water was added to cause a faint turbidity. This was removed by means of a few drops of alcohol, and then 3 drops of acetic acid and 1 g. of the carbazate were added. The mixture was shaken and allowed to stand for a few minutes. If crystallization did not result, the reaction mixture was heated to reflux for one hour and cooled. The precipitate was removed by filtration, weighed and crystallized. In those cases where a solid was not obtained readily, the reaction was carried out without the addition of water, and after refluxing for one hour, the solvent was evaporated and the residue recrystallized.

In practically all of the condensations, the yields of the derivatives were high. The products were purified by recrystallization from dilute alcohol or a mixture of benzene and petroleum ether.

---

[3] O. Diels, *Ber.*, **47**, 2183 (1914).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI

Streptohydrazid

BY FRANK C. PENNINGTON, PETER A. GUERCIO AND I. A. SOLOMONS

RECEIVED JANUARY 19, 1953

Previous investigators[1] have demonstrated the condensation of streptomycin with a wide variety of amino compounds. Since isoniazid and streptomycin are both used in the chemotherapy of tuberculosis and have been proposed for combined therapy,[2] it was of interest to prepare and characterize an analogous condensation product, Streptohydrazid.[3]

The condensation of streptomycin with isoniazid was found to occur readily, and it was possible to isolate Streptohydrazid sulfate and hydrochloride as white crystalline products. Whereas isoniazid exhibits an absorption maximum in water at 262 mμ (ε 4,360), Streptohydrazid absorbs at 260 mμ (ε 14,700). The latter value was obtained in the presence of a large molar excess of streptomycin to prevent hydrolysis. It was found that by utilizing the difference in absorption at 260 mμ the extent of reaction could be estimated. It was also observed that in concentrated aqueous solutions Streptohydrazid hydrolyzes very little, but in very dilute solution it dissociates into its component parts.

In tuberculosis protection studies in animals Streptohydrazid has been found at least as effective as combined therapy utilizing streptomycin and isoniazid.[2]

Streptomyclideneisonicotinylhydrazine Trihydrochloride.—A mixture of 30 g. of streptomycin hydrochloride and 6 g. of isoniazid in 300 ml. of absolute methanol was boiled under reflux for 15 minutes. The solution was allowed to stand several days in a refrigerator, and large crystals slowly formed. The supernatant solution was decanted and the product filtered, washed with cold methanol and dried; yield 19.0 g. (54%), decomposes *ca.* 200°.

The infrared spectrum exhibits broad strong absorption at 1650 cm.$^{-1}$ and at longer wave lengths is very similar to isoniazid. Weak absorption is evident near 1350, 1300, 1210, 1140, 1110, 1060 and 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{47}N_{10}O_{12}Cl_3$: C, 40.03; H, 5.85; N, 17.29; Cl, 13.13. Found: C, 39.94; H, 5.90; N, 17.23; Cl, 13.18.

Streptomycylideneisonicotinylhydrazine Sesquisulfate.—Streptomycin trihydrochloride calcium chloride double salt (50 g.) assaying about 660 mcg. per mg., was dissolved in 160 ml. of water containing 8.5 g. of isoniazid. Over a period of 0.5 hour, 85 ml. of methanolic triethylamine sulfate solution (1.98 *M* in $SO_4^{=}$, *p*H 5) was introduced with stirring, followed by the addition of 255 ml. of methanol during the succeeding hour. The precipitated $CaSO_4$ was collected and washed with a mixture of one part methanolic triethylamine sulfate solution, two parts of water, and three parts of methanol.

Methanol (about 100 ml.) was added until a haze persisted and the mixture was then allowed to crystallize. Methanol (2000 ml.) was added dropwise with stirring and the white crystalline product was collected, washed with methanol, and dried *in vacuo;* yield 36.0 g. (75%), decomposes *ca.* 230°.

Anal. Calcd. for $C_{27}H_{44}N_{10}O_{12}\cdot 3/2H_2SO_4$: C, 38.25; H, 5.59; N, 16.52; S, 5.67. Found: C, 38.04; H, 5.74; N, 16.22; S, 5.63.

Streptohydrazid trihydrochloride and sesquisulfate are extremely soluble in water. The former is partially soluble in methanol, whereas the latter is insoluble. Both salts are insoluble in less polar solvents.

RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
BROOKLYN 6, N. Y.

---

[1] W. A. Winsten, C. I. Jarowski, F. X. Murphy and W. A. Lazier, THIS JOURNAL, **72**, 3969 (1950).

[2] G. L. Hobby and T. F. Lenert, "The Action of Isoniazid and Streptomycin Alone and in Combination," Annual Meeting Public Health Association, Cleveland, Ohio, October 24, 1952.

[3] Chas. Pfizer and Co., Inc., trade name for streptomyclideneisonicotinylhydrazine.

Hypotensive Agents. III.[1] Dialkylaminoalkyl Pyrrolidine Derivatives[2a,b]

BY LEONARD M. RICE, CHARLES H. GROGAN AND E. EMMET REID[3]

RECEIVED DECEMBER 19, 1952

In the course of a continuing study of potential hypotensive compounds we investigated the reduction of various N-dialkylaminoalkyl succinimides. The various substituted succinimides were obtained in good yields by the reaction of equimolecular amounts of the appropriate dialkylaminoalkylamine with succinic anhydride. After the exothermic reaction had subsided, the resulting mixture was heated at 160–170° for two hours to complete the reaction. Ohki[4] had prepared this type of imide and studied its electrolytic reduction. He isolated the corresponding pyrrolidone by this means.

The reduction of N-phenylsuccinimide to yield N-phenylpyrrolidine with lithium aluminum hydride has been reported by Spitzmueller.[5] Wojcik and Atkins[6] obtained N-amylpyrrolidine by reduction of amylsuccinimide by means of copper chromite catalyst in excellent yields. In our past experi-

---

[1] For the first paper in this series see L. M. Rice, A. Popovici, M. Rubin, C. F. Geschickter and E. E. Reid, THIS JOURNAL, **74**, 3025 (1952).

[2] (a) Supported (in part) by a research grant from the Geschickter Fund for Medical Research, Inc. (b) Presented at the Meeting of the American Chemical Society at Atlantic City, N. J., Sept., 1952.

[3] Professor Emeritus, Johns Hopkins University, Baltimore, Md.

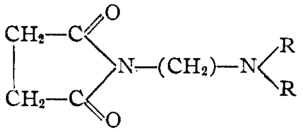
[4] Sadao Ohki, *J. Pharm. Soc. Japan*, **70**, 92 (1950).

[5] Weldon G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 492.

[6] B. Wojcik and H. Adkins, THIS JOURNAL, **56**, 2419 (1934).

TABLE I

N-ALKYLAMINOALKYL SUCCINIMIDES

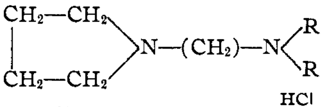


R	n	Formula	B.p., °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Hydrochloride M.p., °C.
CH_3	2	$C_8H_{14}N_2O_2$[b]	93-97	2	56.45	56.51	8.29	8.03	16.46	16.53	198-199
C_2H_5	2	$C_{10}H_{18}N_2O_2$	122-124	3	60.58	60.44	9.15	8.97	14.13	13.94	208-209
CH_3	3	$C_9H_{16}N_2O_2$	105-107	2	58.67	58.41	8.75	8.59	15.21	14.91	196-197
C_4H_8O[a]	2	$C_{10}H_{16}N_2O_3$	140-144	2	56.59	56.85	7.60	7.53	13.20	13.03	217-218

[a] Morpholino. [b] M.p. 40-41°.

TABLE II

N-ALKYLAMINOALKYL PYRROLIDINES



R	n	Formula	B.p., °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	HCl M.p., °C.	Dimethiodide analysis Nitrogen, % Calcd.	Dimethiodide analysis Nitrogen, % Found	Dimethiodide analysis M.p., °C.
CH_3	2	$C_8H_{18}N_2$	92-94	48	67.55	67.52	12.76	12.64	19.69	19.58	294-295	6.57	6.60	261-262
C_2H_5	2	$C_{10}H_{22}N_2$	56-58	3	70.53	70.68	13.02	12.75	16.45	16.89	245-246	6.16	6.37	228-229
CH_3	3	$C_9H_{20}N_2$	50-55	3	69.17	69.06	12.90	12.72	17.93	17.65	264-265	6.36	6.20	295-297
C_4H_8O[a]	2	$C_{10}H_{20}N_2O$	78-80	2	65.17	65.00	10.94	10.73	15.20	15.39	295-296	5.98	6.02	245-246

[a] Morpholino.

ence the reduction of imides with lithium aluminum hydride had proved to give excellent yields in other series. When applied to this series of imides the yields were 90-95%. Phillips[7] had reported that the reaction of ethanolamine with succinic anhydride yielded no imide but only the bis-amide under any of the conditions that he employed. We have prepared diethylaminoethylpyrrolidine by the reaction of β-diethylaminoethyl chloride and pyrrolidine and found that the product obtained was identical with that produced by the reduction of diethylaminoethylsuccinimide.

The various imides prepared and the corresponding pyrrolidine reduction products are listed in Tables I and II, respectively. When tested on dogs for hypotensive activity the dimethiodides of these dialkylaminoalkyl pyrrolidines were found to possess a moderate hypotensive effect.

Experimental

General Procedure for the Preparation and Reduction of Dialkylaminoalkyl Succinimides.—To 0.3 mole of succinic anhydride was slowly added with cooling 0.3 mole of the appropriate dialkylaminoalkyl amine. When the reaction had subsided the mixture was heated in an oil-bath at 175° for two hours. After the product had cooled to room temperature it was fractionated in vacuum to yield the imide as a colorless oil or low melting solid.

The imide (50 g.) was dissolved in twice its volume of anhydrous ether and slowly added with stirring to a solution of 19 g. of lithium aluminum hydride in 1 liter of anhydrous ether. The rate of addition was such as to cause gentle refluxing. After all the imide had been added the reaction mixture was allowed to stand overnight. Decomposition was effected by the slow addition of water and the mixture stirred an additional hour. The suspension was filtered, dried over sodium sulfate, and the ether stripped off. The products were obtained by vacuum distillation as colorless liquids.

The hydrochlorides were prepared in the usual way by means of alcoholic hydrogen chloride.

The dimethiodides were made in the usual manner by adding methyl iodide to an alcohol solution of the amine.

Diethylaminoethylpyrrolidine was obtained in the usual way by reaction of diethylaminoethyl chloride (0.2 mole) with pyrrolidine (0.4 mole) in benzene solution. The boiling point of the base and melting point of the hydrochloride corresponded to those of the product obtained by reduction. A mixed melting point of the hydrochloride gave no depression.

GEORGETOWN UNIVERSITY MEDICAL CENTER
WASHINGTON 7, D. C.

---

[7] A. P. Phillips, THIS JOURNAL, **73**, 5557 (1951).

Isolation of Fructose from Beef Serum[1]

BY FREDERICK A. H. RICE

RECEIVED SEPTEMBER 12, 1952

The isolation of additional amounts of the recently reported TPS (*Treponema pallidum* survival) factor,[2] for the purpose of chemical investigations necessitated the processing of considerable quantities (approximately 100 liters) of beef serum. In order to isolate the TPS factor, protein is removed from the serum by means of tungstic acid, the factor is adsorbed from the protein-free filtrate on charcoal (Darco G-60) and eluted with acetone; the acetone-soluble material after having been extracted with ether, is condensed with acetone in the presence of sulfuric acid. The isopropylidene derivative of the TPS factor which is ether-soluble is now precipitated from ether with petroleum ether (b.p. 30-60°) and recrystallized from ethyl acetate.[2] The material soluble in ether-petroleum ether from individual lots of serum (in all approximately 100 liters) was pooled and concentrated to dryness. The thick brown sirup which resulted gave a strong positive test for carbohydrate by the conventional Molisch and Anthrone[3] tests. It was thought to be of interest particularly in view of the major role played by carbohydrates in metabolism, to attempt to separate, and identify

---

[1] Supported by a grant from the Whitehall Foundation, New York, N. Y.

[2] F. A. H. Rice and Robert A. Nelson, Jr., *J. Biol. Chem.*, **191**, 35 (1951).

[3] R. Dreywood, *Ind. Eng. Chem., Anal. Ed.*, **18**, 499 (1946); L. Sattler and F. W. Zerban, THIS JOURNAL, **72**, 3814 (1950).

if possible, these carbohydrates. Chromatographic adsorption[4] on a silicic acid[5]–Celite[6] mixture led to the isolation of 15 mg. of a compound (m.p. 97°, $[\alpha]_D$ $-32.9°$ Me_2CO *ca.* 0.2) which analyzed for $C_{12}H_{20}O_6$; the physical constants are those of diisopropylidene-β-D-fructose.[7] The compound showed no depression of melting point when mixed with an authentic sample of diisopropylidene-D-fructose.

Although fructose has been shown to be a normal constituent of seminal plasma[8] it does not appear to have been isolated heretofore from blood.

It should be noted that the procedure used in the isolation of the fructose prevents even speculation as to the normal concentration of this sugar in blood, or to the form in which it occurs since the acid used in acetonation may have hydrolyzed a fructose derivative.

Experimental

The sirup obtained by concentrating the ether–petroleum ether soluble material (as indicated above[2]) was thoroughly extracted with petroleum ether (b.p. 30–60°) and the petroleum ether soluble material concentrated to dryness under reduced pressure at room temperature. The material was then separated into two fractions in the following manner: the sirup was dissolved in 10 ml. of benzene and filtered through a column (16 cm. × 2 cm.) packed with a mixture of silicic acid and Celite (3:1 by weight). The column was then washed with 150 ml. of benzene, extracted and the entire column eluted with acetone (250 ml.). The acetone eluate (representing the material adsorbed from benzene solution by silicic acid–Celite) was concentrated to dryness under reduced pressure at room temperature, redissolved in benzene and rechromatographed under the same conditions with the exception that in place of the benzene wash the column was developed with 100 ml. of benzene containing 1% (by volume) of *t*-butyl alcohol. The column was extruded and streaked with alkaline permanganate.[9] The zone at approximately the center of the column was cut and eluted with acetone, concentrated to dryness under reduced pressure at room temperature. The material crystallized after standing several days at 4°. After recrystallization from petroleum ether (b.p. 30–60°) the compound melted at 95–96°, $[\alpha]_D$ $-32.9°$ (Me_2CO *ca.* 0.2).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.43; H, 7.74. Found: C, 55.45; H, 7.53.

The compound showed no depression of melting point when mixed with an authentic sample of diisopropylidene-fructose.

---

[4] W. H. McNeely, W. W. Binkley and M. L. Wolfrom, *ibid.*, **67**, 527 (1945).

[5] Baker and Adamson, Silicic Acid Powder (Reagent) Lot No. 6123.

[6] No. 535 obtained from Johns-Manville, New York.

[7] E. Fischer, *Ber.*, **28**, 1165 (1895); H. Ohle and I. Koller, *ibid.*, **57**, 1573 (1924).

[8] J. Mann, *Biochem. J.*, **40**, 481 (1946).

[9] L. Zechmeister and W. H. McNeely, THIS JOURNAL, **64**, 1919 (1942); B. W. Lew, M. L. Wolfrom and R. M. Goepp, Jr., *ibid.*, **67**, 1865 (1945); **68**, 1449 (1946).

DEPARTMENT OF MICROBIOLOGY
THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH
BALTIMORE, MARYLAND

Reactions of Toluic Acids with Sulfur. I. Stilbenedicarboxylic Acids

BY WILLIAM G. TOLAND, JR., JOHN B. WILKES AND FREDERICK J. BRUTSCHY

RECEIVED NOVEMBER 1, 1952

Previous methods for the preparation of 4,4′-stilbenedicarboxylic acid have involved a number of steps, such as conversion of stilbene to the dibromide, to the dinitrile, and finally to the diester,[1] or by the decarboxylation of more complex acids.[2] The preparation of 3,3′-stilbenedicarboxylic acid does not appear to have been reported. We have found that a shorter, more economical route to both these acids is provided by the reaction of the corresponding toluic acid with sulfur. Spectroscopic evidence indicates that the 4,4′-stilbenedicarboxylic acid thus formed is the *trans* isomer. The reaction of sulfur with amine and hydroxyl-substituted aromatic compounds leads to attachment of sulfur to the aromatic ring, but the dehydrodimerizing action of sulfur has been demonstrated in the conversion of toluene to stilbene and tetraphenylthiophene, of *m*- and *p*-xylenes to the corresponding dimethylstilbenes,[3] and in the dehydropolymerization of 4-picoline.[4] The mechanism of some of these reactions has been discussed.[5] Previously reported dehydrodimerization reactions, however, do not involve compounds containing reactive functional groups such as the carboxyl group.

With *p*-toluic acid, 50–70% yields of 4,4′-stilbenedicarboxylic acid are obtained by reaction with sulfur. Other products are hydrogen sulfide, a large amount of a sulfur-containing acid of higher molecular weight, believed to be tetra-(*p*-carboxyphenyl)-thiophene, and a small amount of an unidentified compound of lower molecular weight. Sulfur reacts with *m*-toluic acid to give lower yields of 3,3′-stilbenedicarboxylic acid, but no stilbene derivatives were obtained from the reaction of sulfur with *o*-toluic acid under the conditions studied.

Several variables of the reaction of sulfur with *p*-toluic acid to yield 4,4′-stilbenedicarboxylic acid were investigated, and the optimum reaction conditions are shown in Table I. The rate of reaction increases rapidly with temperature, but the yield decreases simultaneously. Impurities in the toluic acid prolong the reaction time, and increased reaction time decreases the yield. The higher the toluic acid:sulfur ratio, the higher is the yield, based on *p*-toluic acid reacted. More than 90% of the theoretical amount of sulfur cannot be used in the absence of solvent, or the reaction mixture solidifies before the reaction is complete.

Experimental

Materials.—The isomeric toluic acids were made by the air oxidation of the corresponding xylenes, using a soluble cobalt salt catalyst, and purified by filtering and washing the residue with xylene, followed by distillation through a 90-cm. glass helices-packed column. Isomer content was determined by ultraviolet spectrography. Sublimed flowers of sulfur, U.S.P., were used.

Reaction of *p*-Toluic Acid with Sulfur.—A mixture of *p*-toluic acid and sulfur was heated in a three-neck flask equipped with an air-cooled condenser, stirrer and thermowell. At reaction temperature, the mixture darkened and hydrogen sulfide was evolved. After partial reaction had occurred, a yellow solid, consisting largely of 4,4′-stilbenedicarboxylic acid, began to separate. The threshold tem-

---

[1] G. P. Hager, A. M. VanArendonk and H. A. Shonle, THIS JOURNAL, **66**, 1982 (1944).

[2] F. Bell and D. H. Waring, *J. Chem. Soc.*, 1024 (1948).

[3] L. Aronstein and A. S. Van Nierop, *Rec. trav. chim.*, **21**, 448 (1902).

[4] H. I. Thayer and B. B. Corson, THIS JOURNAL, **70**, 2330 (1948).

[5] A. W. Horton, *J. Org. Chem.*, **14**, 761 (1949).

perature for the reaction is about 245°, but it was found advantageous to work close to a reflux temperature (270–275°). When evolution of hydrogen sulfide ceased, the mixture was cooled to 140°, and about 5 ml. of hot xylene was added for each gram of *p*-toluic acid. The solution was refluxed 30 minutes, filtered hot, and the cake washed with hot xylene. Evaporation of the xylene yielded any unreacted *p*-toluic acid and sulfur and some of the acids of higher molecular weight. The toluic acid could be distilled off and reused. The filter cake was extracted with hot dioxane, which dissolves more than 20 g. of higher polymer acids per 100 ml. The remaining cake consisted largely of 4,4′-stilbenedicarboxylic acid, with a small amount of an unidentified, yellow polymeric acid. The stilbenedicarboxylic acid was dissolved in a slight excess of boiling aqueous KOH, allowing about 4 g. of stilbenedicarboxylic acid per 100 ml. of solution, and the potassium salt of the stilbenedicarboxylic acid crystallized from the solution. The free acid was precipitated from the hot salt solution by addition of an excess of HCl and digestion of the hot solution to ensure the absence of the insoluble half-acid salt and to coagulate the otherwise colloidal precipitate. Purification of 4,4′-stilbenedicarboxylic acid can also be effected through the ammonium or guanidine salts.

TABLE I

REACTION OF *p*-TOLUIC ACID WITH SULFUR

Run	Reactants, mole		*p*-Toluic acid purity, %	*T*, °C.	Hr.	*p*-Toluic acid reacted, %	SDCA[a] Yield, %
	Toluic	S					
1	1.0	0.5	97.8	260	4.5	51.7	60.6
2	1.0	0.05	92.6	260	4.0	5.7	70.6
3	1.0	1.0	Pure	271	2.0	79.5	57.3
4	1.0	0.5	97.8	275–280	3.0	55.0	53.6

[a] SDCA = 4,4′-stilbenedicarboxylic acid, yield based on *p*-toluic acid reacted.

4,4′-Stilbenedicarboxylic Acid.—Repeated recrystallization of the potassium salt of stilbenedicarboxylic acid gives a white, sulfur-free product. The free acid, m.p. 460° (sealed tube), has a neutral equivalent of 134.1. Permanganate oxidation gave terephthalic acid almost quantitatively. The acid chloride was prepared by reaction of thionyl chloride in the presence of pyridine, m.p. 228–232°. The diethyl ester, b.p. 195–203° (0.1–0.09 mm.), m.p. 129.9–130.0°, was prepared from the acid chloride. Previous workers report for the acid chloride, m.p. 223–224°[2] and 227–228°.[6] For the diethyl ester, a m.p. of 130–131° is reported.[1] The absorption spectrum of an aqueous solution of the potassium salt shows broad peaks at 3425, 3275 3150 and approximately 2300 Å. The configuration of the spectrum closely resembles the spectra of *p*-toluic acid and dimethyl terephthalate, but is displaced to longer wave lengths. It closely resembles published spectra[7,8] of *trans*-*p*,*p*′-stilbene derivatives but not those of *cis*-stilbene derivatives. The acid and its solution show intense blue fluorescence when irradiated with ultraviolet light of the appropriate wave length, which is not a characteristic of *cis*-stilbene.[7] Irradiation of stilbenedicarboxylic acid with 2537 Å. light causes a change in the spectrum similar to *trans* to *cis* isomerization of stilbene. Hence, the available evidence points to the conclusion that the product is the *trans* isomer of 4,4′-stilbenedicarboxylic acid.

The solubility of 4,4′-stilbenedicarboxylic acid in most neutral solvents is less than 20 mg./100 ml. It is moderately soluble in dimethyl formamide, acetic anhydride and molten toluic acid, and somewhat soluble in ethylene glycol and diethylene glycol. Solubility in boiling sulfolane is about 2.5 g./100 ml., and the acid can be recrystallized from this solvent.

Tetra-(*p*-carboxyphenyl)-thiophene.—The dioxane-soluble, xylene-insoluble products could not be crystallized from dioxane. A brown to orange, finely divided solid was obtained by pouring the solution slowly into a large excess of xylene or water. Sulfur analyses of this crude material gave values varying from 5.10 to 5.41%, compared to 5.67% for tetra-(*p*-carboxyphenyl)-thiophene. Oxidation of the compound with permanganate gave terephthalic acid. The molecular weight of the crude compound, determined ebulliometrically in acetone, was 520 ± 30 (theoretical for tetra-(*p*-carboxyphenyl)-thiophene, 564.62). As sulfur reacts with stilbene and its analogs to form thiophene derivatives[3-5] it seems probable that the main by-product is impure tetra-(*p*-carboxyphenyl)-thiophene, which has not yet been isolated in pure form due to contamination with low polymers of the type reported by Thayer and Corson.[4]

3,3′-Stilbenedicarboxylic Acid.—Refluxing 104 g. (0.765 mole) of *m*-toluic acid with 12.2 g. (0.383 mole) of sulfur at 262–267° until evolution of hydrogen sulfide ceased (5 hours), followed by extraction with two 150-ml. portions of hot xylene and washing with acetone gave 5.0 g. of dimer acid cake. Evaporation of the xylene, and extraction of the solid with 250 ml. of acetone containing 25 ml. of water, followed by xylene extraction to remove sulfur, gave an additional gram of dimer acid. Crystallization of the ammonium salt, acidification and digestion with hydrochloric acid gave 4.5 g. of acid, neutral equivalent 135.6 (theory 134.1). Oxidation with permanganate gave isophthalic acid.

The dimethyl ester was formed by refluxing 2 g. of acid with 50 ml. of methanol and 5 ml. of concentrated sulfuric acid. The ester was dissolved by addition of chloroform, the solution washed with water and sodium carbonate solution, and the ester crystallized twice from mixed chloroform and methanol to give 1.0 g. of ester, m.p. 145.5–146°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.95; H, 5.44; sapn. equiv., 148.15. Found: C, 72.65; H, 5.35; sapn. equiv., 147.7.

Purified 3,3′-stilbenedicarboxylic acid, prepared by saponifying the dimethyl ester and precipitating the free acid, melted at 352–354°. Titration with 0.1 *N* permanganate solution in boiling 0.05 *N* sodium hydroxide solution to give an end-point stable for more than 30 seconds took 95% of the theoretical permanganate.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.53; H, 4.60.

Acknowledgments.—We wish to thank Mr. R. D. Clark for spectroscopic analysis and interpretation, Dr. B. J. Fontana for molecular weight determinations, and Dr. J. A. Spence for preparation of the acid chloride and diethyl ester.

CALIFORNIA RESEARCH CORPORATION
RICHMOND, CALIFORNIA

---

(6) G. P. Hager and H. A. Shonle, THIS JOURNAL, **68**, 2167 (1946).

(7) G. N. Lewis, T. T. Magel and D. Lipkin, *ibid.*, **62**, 2973 (1940).

(8) M. Calvin and R. E. Buckles, *ibid.*, **62**, 3324 (1940).

The Dielectric Properties of Supercooled Liquids[1]

BY G. N. ROBERTS[2]

RECEIVED JANUARY 15, 1953

Viscosity measurements on phenyl ether[3] indicate the existence of a structural change occurring in the supercooled liquid at the melting point; the points obtained by plotting $\log \eta$ against $1/T$, where η is the viscosity at absolute temperature T, fall into two groups corresponding to measurements made above and below the melting point, the points of each group lying on a straight line but the line for the supercooled liquid being steeper than that for the liquid above the melting point. A similar effect has been observed for *m*-chloronitrobenzene, menthol and salol[4] and Greenwood and Martin[5] have observed corresponding discontinuities at the

---

(1) This note represents part of the work submitted by Dr. G. N. Roberts to the University of London in fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Frick Chemical Laboratory, Princeton University, Princeton, N. J.

(3) C. Dodd and Hu Pak Mi, *Proc. Phys. Soc.* (*London*), **B62**, 454 (1949).

(4) Hu Pak Mi, Thesis, University of London, 1950.

(5) N. N. Greenwood and R. L. Martin, *J. Chem. Soc.*, 1795 (1951).

melting points while examining the conductivities of a number of ionic complexes formed from boron trifluoride. Preliminary measurements on phenyl ether, menthol, salol and azoxybenzene[6] have revealed discontinuities in the temperature variation of the static dielectric constant ϵ_0 of these substances and this note reports further measurements carried out on both polar and non-polar liquids.

Experimental

Measurements of the static dielectric constant ϵ_0 were carried out using an oscillator loosely coupled to a parallel resonance circuit which had the test cell containing the specimen liquid and the variable condensers C_m and C_p which could be adjusted to tune the circuit to resonance. Resonance was indicated by a maximum reading on a valve voltmeter. The oscillator was crystal controlled at a frequency of 80.86 kc./s. C_m was a low-loss micrometer air condenser similar to that described by Ward and Pratt.[7] It had a linear response up to a capacitance value of 8 $\mu\mu$F., corresponding to 2500 scale divisions. C_p consisted of a low-loss air condenser variable between 10-50 $\mu\mu$F. The test cell was of the concentric cylinder type, of low-loss and small stray capacitance. The cell was immersed in a constant temperature bath maintained to within 0.01° for tests above room temperature and to within 0.05° for tests below this temperature. For the empty cell, the capacitance of that portion of the cell normally containing the dielectric was 9.9 $\mu\mu$F. and the stray capacitance 3.02 $\mu\mu$F. The variation of the empty cell capacitance with temperature was approximately linear, changing by only 0.0331 $\mu\mu$F. for a temperature change of 40°.

Experimental Results

(a) **Polar Liquids.**—In Fig. 1, micrometer condenser settings for resonance and values of ϵ_0 deduced from these settings are shown plotted against temperature for liquid methyl *n*-nonyl ketone. The line drawn through the experimental points is the quadratic calculated by the method of least squares to fit best the points corresponding to the liquid above its melting point (12.1°). The points for the supercooled liquid also lie on a line which is, however, inclined to the line for the normal liquid. This discontinuity is brought out more strikingly by the inset to the graph, where deviations of *all* points from the quadratic for the liquid above the melting point are plotted against temperature. Above the melting point the deviations are small and both positive and negative about the zero line, but in the supercooled region the deviations are all positive and increase progressively as the temperature is lowered. A similar discontinuity in the ϵ_0-temperature curve has been observed for *p*-bromotoluene (m.p. 27.5°). It may be mentioned that repeated measurements on salol carried out at the Frick Chemical Laboratory, Princeton University, using a heterodyne beat apparatus[8] and also an impedance bridge,[9] gave results similar to those previously reported.[5]

(b) **Non-polar Liquids.**—Attempts to supercool benzene (m.p. 5.5°) and cyclohexane (m.p. 6.4°) were unsuccessful. The symmetry of the molecules of these substances probably enables them to set into crystal lattices with little rearrangement or re-orientation when the temperature is lowered below their respective melting points. On the other hand, moderately asymmetrical molecules have been shown to supercool readily.[10] Suitable liquids, therefore, appeared to be those with molecules whose attached groups caused sufficient asymmetry to prevent premature crystallization but whose arrangement of groups was such as to make the whole molecule effectively non-polar.

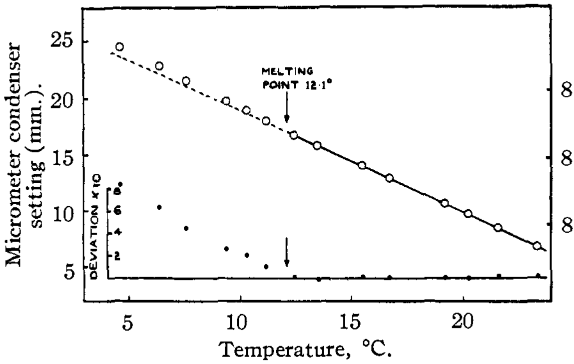


Fig. 1.—Micrometer condenser setting and ϵ_0 *vs.* temperature for methyl *n*-nonyl ketone.

TABLE I

	M.p., °C.	Dipole moment, $\mu \times 10^{18}$ Literature	This work
Diphenylmethane	25.5	0.30, 0.23, 0.37, 0	<0.3
p-Xylene	13.2	0.06, 0.12, 0	< .2
Bibenzyl	50.7	0.36, 0.02, 0	< .3

Table I lists the dipole moments given in the literature[11,12] for the three liquids tested, together with the moments estimated from measurement of ϵ'' over a range of temperature at 3 cm. wave length using a H_{01} cavity resonator. The very small moment observed for *p*-xylene is probably due to impurity. In Fig. 2, the micrometer condenser setting for resonance is plotted against temperature for both normal and supercooled diphenylmethane and the inset to the graph shows the deviations of all points from the best quadratic through the points in the normal region. Over the whole temperature range these deviations are small

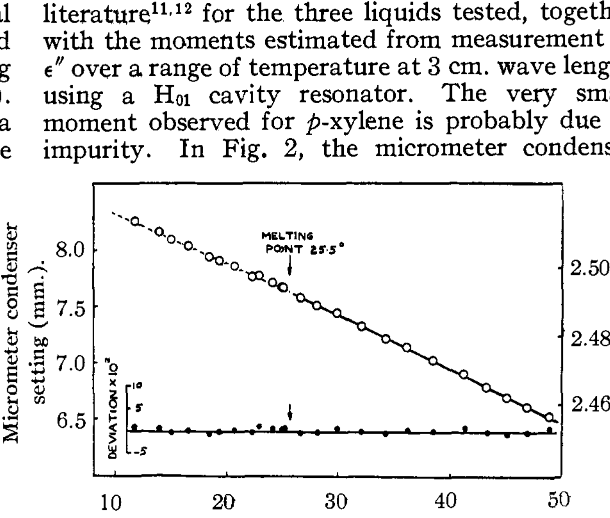


Fig. 2.—Micrometer condenser setting and ϵ_0 *vs.* temperature for diphenylmethane.

---

[6] C. Dodd and G. N. Roberts, *Proc. Phys. Soc.* (*London*), **B63**, 814 (1950).

[7] W. Ward and E. Pratt, *J. Sci. Instruments*, **16**, 192 (1939).

[8] L. M. Kushner and C. P. Smyth, THIS JOURNAL, **71**, 1401 (1949).

[9] C. P. Smyth and C. S. Hitchcock, *ibid.*, **54**, 4631 (1932); **55**, 1830 (1933).

[10] W. O. Baker and C. P. Smyth, *ibid.*, **61**, 2063 (1939).

[11] Table of Dipole Moments, *Trans. Faraday Soc.*, **30**, 1193 (1934).

[12] C. P. Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co. (Reinhold Publ. Corp.), New York, N. Y., 1931

and unsystematic. Similar results have been obtained for *p*-xylene and bibenzyl.

Discussion

For the six polar liquids so far tested, a significant discontinuity in the slope of the static dielectric constant–temperature curve has been found in the neighborhood of the melting point in each case. On the other hand, no such effect has been observed with any non-polar or slightly polar liquids, suggesting that the *magnitude* of the change in slope may be related—at least in a qualitative way—to the permanent dipole moment. In Table II are listed the differences in slope between the lines for the normal and supercooled liquids, together with the respective dipole moments and values of ϵ_0 at the melting point. Examination of the table does reveal a qualitative relationship between the change in slope $d\epsilon_0/dT$ and the dipole moment for the four liquids of smallest dipole moment. This relationship does not hold, however, for azoxybenzene and salol, and one reason for this disagreement may be the existence of dipolar interaction or association which would be expected to have a strong influence on any process that might occur at the melting point. Thus it seems more legitimate to compare the magnitude of the change in slope (change in $d\epsilon_0/dT$) with ϵ_0 itself, since ϵ_0 is a macroscopic measure of the polarization produced in the pure liquid, which includes the effects of dipolar interaction. If n^2 is regarded as the contribution toward the dielectric constant from electronic and atomic polarization, n being the index of refraction, then $(\epsilon_0 - n^2)$ is that part arising only from the orientation of permanent molecular dipoles. In Fig. 3, change in $d\epsilon_0/dT$ is shown plotted against $(\epsilon_0 - n^2)$ for each liquid tested and now the points are seen to lie reasonably well on a line through the origin.

Table II

	Change in slope $d\epsilon_0/dT$	Dipole moment, $\mu \times 10^{18}$	ϵ_0	$\epsilon_0 - n^2$
Azoxybenzene	0.0010	3.39	5.2	2.4
Salol	.0019	3.15	6.4	3.6
Methyl *n*-nonyl ketone	.0036	2.69	8.3	6.3
p-Bromotoluene	.0031	1.90	6.0	3.6
Menthol	.0009	1.58	4.0	1.8
Phenyl ether	.0006	1.15	3.6	1.1
Diphenylmethane	.0	<0.3	2.49	0.01
Bibenzyl	.0	< .3	2.42	.05
p-Xylene	.0	< .2	2.23	.00

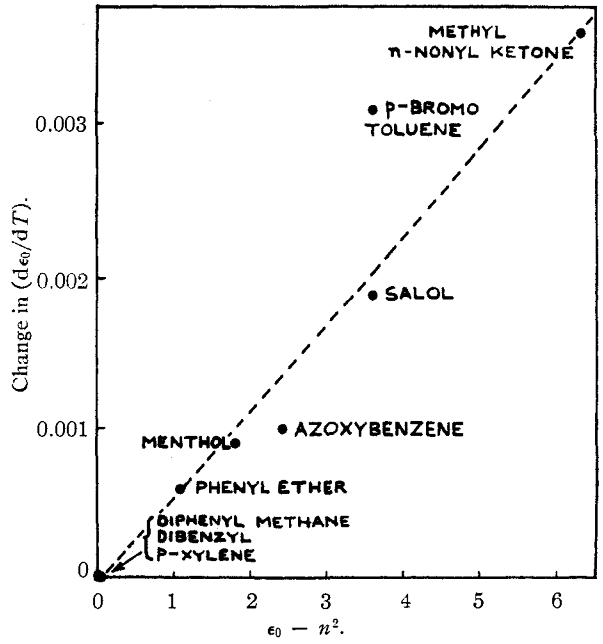


Fig. 3.—Correlation of change in $d\epsilon_0/dT$ with $(\epsilon_0 - n^2)$.

Department of Electrical Engineering
Queen Mary College
University of London
London, England

N-Trifluoroacetyl Derivatives of Carcinogenic Amines[1]

By Eugene Sawicki and F. E. Ray

Received January 12, 1953

N-Acetyl derivatives of 2-aminofluorene,[2] 2,7-diaminofluorene,[3] 2-naphthylamine,[4] 4-aminobiphenyl,[5] 3-aminodibenzofuran[6] and 3-aminodibenzothiophene[7] have been shown to have carcinogenic properties. The free amines, 2-anthramine,[7] benzidine[8] and 2′,3-dimethyl-4-aminoazobenzene,[9] have also been shown to be active.

In the fluorene series it has been shown that 2-aminofluorene is carcinogenic in the rat.[10] The carcinogenic N-acetyl derivative is easily hydrolyzed *in vivo*.[11] On the other hand, 2-benzoylaminofluorene has little activity[12] and cannot be hydrolyzed readily.[13] Similarly the non-carcinogenic[12] 2-*p*-tosylaminofluorene is stated to be very slightly hydrolyzed *in vivo*.[14] On the basis of these facts it is probable that the free amines or their metabolites are the primary carcinogens. To test this hypothesis the N-trifluoroacetyl derivatives have been prepared. According to this hypothesis if the trifluoroacetyl derivatives cannot be hydrolyzed *in vivo*, then they should be non-carcinogenic. If these groups are hydrolyzed, then the compounds should be carcinogenic

The physical properties and yields of the compounds are given in Table I.

General Procedure.—To 0.01 mole of the amine (or 0.005 mole of the diamine) in 20 ml. of hot benzene was carefully added through a reflux condenser 0.01 mole of tri-

---

[1] The work described in this paper was supported by a grant from the Sloan-Kettering Institute for Cancer Research.

[2] R. Wilson, F. DeEds and A. Cox, *Cancer Research*, **7**, 453 (1947).

[3] H. P. Morris and C. Dubnik, *ibid.*, **10**, 233 (1950).

[4] G. Bonser, *J. Path. Bact.*, **55**, 1 (1943).

[5] R. Melby, R. Brown and R. Sandin, This Journal, **72**, 1032 (1950).

[6] E. Miller, J. Miller, R. Sandin and R. Brown, *Cancer Research*, **9**, 504 (1949).

[7] F. Bielschowsky, *Brit. J. Exper. Pathology*, **27**, 54 (1946).

[8] S. Spitz, W. Maguigan and K. Dobriner, *Cancer*, **3**, 789 (1950).

[9] H. Crabtree, *Brit. J. Cancer*, **3**, 387 (1949).

[10] H. P. Morris, C. S. Dubnik and J. M. Johnson, *J. Nat. Cancer Inst.*, **10**, 1201 (1950).

[11] H. P. Morris, J. H. Weisburger and E. K. Weisburger, *Cancer Research*, **10**, 620 (1950).

[12] H. P. Morris, private communication.

[13] H. R. Gutmann and J. H. Peters, *Cancer Research*, in press.

[14] F. E. Ray and M. F. Argus, *ibid.*, **11**, 783 (1951).

TABLE I

Compound	M.p.,[a] °C.	Yield, %	Nitrogen, %		Sulfur, %		Fluorine, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
4-TFA[b] biphenyl	200–201	95	5.28	5.42				
4,4′-Di-TFA biphenyl	324–325	98	7.45	7.13				
2-TFA fluorene	200–201	98					20.6	20.1
2,7-Di-TFA fluorene	300–301	92	7.2	7.4				
3-TFA dibenzofuran	204–205	97	5.02	5.10				
3-TFA dibenzothiophene	186–187	98			10.85	10.7		
2-TFA naphthalene	146–147	95	5.86	5.58				
2-TFA anthracene[c]	245–246	87						
4-TFA-2′,3-dimethylazobenzene	158–159	90	13.1	12.8				

[a] All melting points are uncorrected. [b] TFA = Trifluoroacetylamino. [c] *Anal.* Calcd. for $C_{16}H_{10}F_3NO$: C, 66.44; H, 3.46. Found: C, 66.32; H, 3.82.

fluoroacetic anhydride.[15] In the case of 2,7-diaminofluorene 100 ml. of hot xylene was used as the solvent. After the initial reaction had subsided, the mixture was refluxed for half an hour. The cooled mass was filtered and washed with 10 ml. of cold benzene. Further product was obtained by evaporating the mother liquid under reduced pressure at room temperature. The fairly soluble acyl derivative of 2-naphthylamine was obtained by a similar evaporation of the reaction mixture. The diamine derivatives were crystallized from alcohol. The azo dye and the 4-aminobiphenyl derivative were crystallized from heptane. The 2-naphthylamine derivative was crystallized from aqueous alcohol while 2-trifluoroacetylaminofluorene was crystallized from benzene. These derivatives are more soluble than the analogous acetyl derivatives in non-polar solvents, such as heptane, and polar solvents, such as alcohol. The strong electronegative trifluoroacetyl group confers acidic properties on the new molecules for they are all soluble to some extent in aqueous sodium hydroxide solution.

---

[15] Minnesota Mining and Manufacturing Co., St. Paul 6, Minnesota.

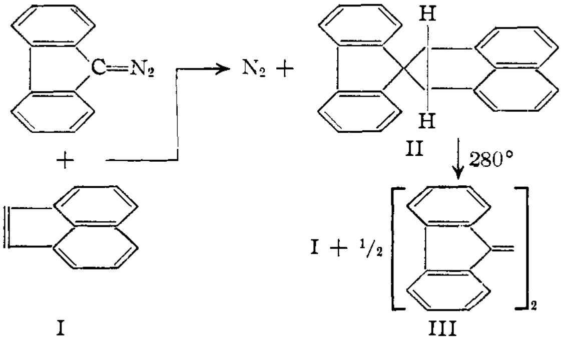
CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

Formation of a Spiro Compound by the Action of Diazofluorene on Acenaphthylene

BY ALEXANDER SCHÖNBERG, AHMED MUSTAFA AND NAZIH LATIF

RECEIVED DECEMBER 22, 1952

Though the action of diazomethanes on ethylenic compounds leading to three-membered rings has been observed frequently,[1] very little seems to be known about the formation of spiro products by this method. When acenaphthylene was treated with diazofluorene, the spiro product (II) was formed in good yield; in contrast with its generators and in agreement with the proposed formula, it is colorless. There seems to be some strain in (II) since it decomposes at 280° into acenaphthylene and $\Delta^{9,9'}$-bifluorene (III).



When acenaphthalene (I) was treated with an ethereal solution of diazomethane, it was recovered.

Experimental

Diazofluorene and Acenaphthylene.—A solution of 0.5 g. of acenaphthylene and 0.7 g. of 9-diazofluorene in 15 ml. of dry benzene was refluxed for 30 minutes. The mixture was allowed to stand overnight, concentrated and a few ml. of acetone was added to the residue. On standing, crystals separated which were recrystallized from benzene. 7,8-9′,-9′-Fluorenyleneacenaphthene (II) is colorless, m.p. 275° (red-brown melt), yield about 80%.

Anal. Calcd. for $C_{25}H_{16}$: C, 94.9; H, 5.0; mol. wt., 316. Found: C, 94.4; H, 5.1; mol. wt. (micro-Rast), 282.

Thermal Decomposition.—A 0.5-g. sample of II was heated for one hour at 280–300° (bath temp.) in a test-tube shaped vessel (Pyrex glass) which was connected during pyrolysis to a working oil vacuum pump. The reaction vessel was then allowed to cool in a vacuum; the oily drops on the upper part of the tube solidified and proved to be acenaphthylene (m.p. and mixed m.p.). The bottom of the reaction vessel contained a red substance which was extracted several times with boiling ether. After concentration of the ethereal extract to about 1 ml., light petroleum (b.p. 40–60°) was added dropwise at room temperature to turbidity. A reddish-brown substance separated and was dissolved in a very small amount of hot benzene. The addition of a saturated benzene solution of picric acid yielded orange crystals overnight; these proved to be the picrate of $\Delta^{9,9'}$-bifluorene (III) (m.p. and mixed m.p.).

Diazomethane and Acenaphthylene.—An ethereal solution containing 1 g. of acenaphthylene and diazomethane[2] (prepared from 10 g. of nitrosomethylurea) was allowed to stand for 24 hours in the ice-chest. Acenaphthylene was recovered unchanged.

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
FOUAD I UNIVERSITY
CAIRO, EGYPT

---

[1] H. Wieland and O. Probst, *Ann.*, **530**, 277 (1937); P. C. Guha and S. Krishnamurthy, *Ber.*, **70**, 2113 (1937); W. Braren and E. Buchner, *ibid.*, **33**, 684, 3453 (1900).

[2] *Org. Syntheses*, **15**, 3 (1935).

σ-Constants of the Carbethoxyl and Hydroxyl Groups

BY JOHN D. ROBERTS AND WALTER T. MORELAND, JR.[1]

RECEIVED SEPTEMBER 2, 1952

As part of another investigation,[2] we have had occasion to determine the σ-constants[3] of the *m*- and *p*-carbethoxyl and *m*-hydroxyl groups. The

---

[1] U. S. Atomic Energy Commission Predoctoral Fellow, 1951–1952.

[2] J. D. Roberts and W. T. Moreland, Jr., THIS JOURNAL, **75**, 2167 (1953).

[3] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII.

TABLE I

σ-CONSTANTS FOR THE CARBETHOXYL AND HYDROXYL GROUPS

Reaction	Solvent	Temp., °C.	log $k^{\circ a}$	ρ^a	σ (m-$CO_2C_2H_5$)	σ (p-$CO_2C_2H_5$)	σ (m-OH)
Ionization of benzoic acids	H_2O	20	-4.234^b	$+1.107^b$	.....	.....	$+0.040^b$
		25	-4.203^a	$+1.000^a$	.....	.....	$+ .124^c$
	50% EtOH	25	-5.71^d	$+1.464^d$	+0.348	+0.437	+ .068
Benzoic acids with diphenyldiazomethane	100% EtOH	30	-0.014^d	$+0.937^d$	+ .313	+ .336	− .123
Alkaline hydrolysis of ethyl benzoates	87.83% EtOH	30	-3.072^a	$+2.498^a$	.....	$+ .443^c$	.....
	56% acetone	25	-2.513^a	$+2.373^a$	$+ .243^{e,f,g}$	$+ .392^{e,f}$	.....
Phenols with acetyl bromide	Ethyl acetate	0	$-1.170^{h,i}$	-1.898^h	$+ .341^i$	.....	.....
Methyl benzoates with aniline	Nitrobenzene	100	-0.898^j	$+0.379^h$	.....	.....	$+ .040^j$
				Mean	+ .334	+ .402	+ .014

[a] Ref. 3. [b] Calculated from data of B. Jones and J. C. Speakman, *J. Chem. Soc.*, 19 (1944). [c] Calculated from the data of J. Shorter and F. J. Stubbs, *ibid.*, 1180 (1949). [d] Ref. 4. [e] Calculated after correcting the observed rate by a statistical factor of two. [f] Calculated from the data of E. Kivinen and E. Tommila, *Suomen Kemistilehti.*, **14B**, 7 (1941). [g] Not used in calculation of the mean. [h] Calculated from the data of H. L. Bassett, *J. Chem. Soc.*, 1313 (1930); 2516 (1931); H. L. Bassett and A. O'Leary, *ibid.*, 2945 (1932). [i] Relative value. [j] Calculated from the data of N. J. Vartak, N. L. Phalnikas and B. V. Bhide, *J. Indian Chem. Soc.*, **24**, 131A (1947).

reactions and procedures have been described previously in detail.[4,5]

The apparent ionization constants in 50% aqueous ethanol (by volume) at 25.0 ± 0.1° were 6.31×10^{-6}, 8.42×10^{-6} and 2.45×10^{-6} for m-carbethoxy, p-carbethoxy and m-hydroxybenzoic acids, respectively. The second-order rate constants with diphenyldiazomethane at 30.0 ± 0.1° in 100% ethanol were 2.16, 2.27 and 0.843, respectively, (all in $\text{l. mole}^{-1}\ \text{min.}^{-1}$) for the same series of substituted benzoic acids. The alkaline saponification rate of diethyl terephthalate in 87.83% ethanol at 30.0 ± 0.1° was 1.28 $\text{l. mole}^{-1}\ \text{min.}^{-1}$. The σ-constants from the available data are summarized in Table I.

The mean σ-values obtained from the data of Table I are: m-carbethoxyl, +0.334, r (the median deviation) equal to 0.014; p-carbethoxyl, +0.402, r equal to 0.038; and m-hydroxyl, +0.014, r equal to 0.076. A σ-value of −0.34 has been obtained previously[4] for the p-hydroxyl group.

(4) J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2923 (1949).

(5) K. Kindler, *Ann.*, **450**, 1 (1926).

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

The Solubility of Indium in Mercury

BY WILLIAM M. SPICER AND CYRIL J. BANICK

RECEIVED DECEMBER 20, 1952

In spite of the recent interest in alloys that are liquid at room temperature, the system mercury–indium has received little attention. Richards and Wilson[1] dissolved indium in mercury to the extent of 1.92% and found that the resulting amalgams are liquid at both 30 and 0°. Hildebrand[2] made amalgams containing up to 2.1% indium at 30°. Williams[3] in a study of the conductivity of liquid amalgams made an amalgam containing 3% indium. More dilute indium amalgams were used by Davies and Keeping.[4] None of these investigators attempted to determine the limit of the solubility of indium in mercury. Parks and Moran[5] investigated the solubility of indium in mercury over the temperature range 0–50°. They reported an increase in solubility from 1.23 weight % at 0° to 1.31 weight % at 50°.

It was in view of the paucity of the above data and their disagreement that this investigation was undertaken.

Preliminary tests indicated indium to be much more soluble than reported by Parks and Moran. It was therefore decided to investigate the entire range of compositions by means of cooling curves.

Experimental

The mercury used in this investigation was purified in the following manner. Air was bubbled through it for several hours to oxidize metallic impurities. It was filtered to remove the coarser particles of oxide and dirt, sprayed through a column of 3 N HNO_3, washed with distilled water to remove the acid and dried with filter paper. It was then vacuum distilled.

The indium used had a guaranteed purity of better than 99.97%. This high purity was confirmed by qualitative spectrographic analysis which showed only small amounts of cadmium and zinc. Its melting point was determined as 156.2°. There is considerable disagreement in the literature concerning the melting point of indium. Roth and Meyer[6] give 156.4°, Grube and Wolf[7] give 155°, while Denny, Hamilton and Lewis[8] give 156.1°.

An electric furnace for melting the alloys was constructed by modifying a tube furnace as follows. The furnace, which was approximately 15 inches in length with an opening approximately 3/4 inch in diameter, was closed at one end with a plug of magnesia and arranged vertically. The outside wall of the furnace was wrapped with nichrome wire and covered with asbestos. This heating unit was left on while the sample was cooling to retard its rate of cooling. In this way rates of cooling ranging from 0.5 to 2.0° per minute were obtained.

This furnace was used in analyzing melts in the range beginning with those melting near pure indium down to about 60°. From this point, the furnace was replaced by a large tube with an air space to provide slower cooling. This outer tube was surrounded first by ice-water, then with

---

(1) Theodore W. Richards and J. H. Wilson, *Z. physik. Chem.*, **72**, 129 (1910).

(2) Joel H. Hildebrand, THIS JOURNAL, **35**, 501 (1913).

(3) E. J. Williams, *Phil. Mag.*, **50**, 589 (1925).

(4) W. G. Davies and E. S. Keeping, *ibid.*, **7**, 145 (1929).

(5) W. G. Parks and W. G. Moran, *J. Phys. Chem.*, **41**, 343 (1937).

(6) W. M. Roth and I. Meyer, *Z. anorg. allgem. Chem.*, **214**, 315 (1933).

(7) G. Grube and W. Wolf, *Z. Elektrochem.*, **41**, 679 (1935).

(8) J. P. Denny, J. H. Hamilton and J. R. Lewis, *J. Metals*, **4**, 39 (1952).

calcium chloride solution–ice, and finally a Dry Ice–acetone-bath.

Temperature measurements were made with a copper–constantan thermocouple by means of a Leeds and Northrup precision type potentiometer No. 7551. This instrument could be read to one microvolt corresponding to a temperature difference of approximately 0.02°.

The thermocouple was made from No. 32 B and S gage copper and constantan wires. To prevent contamination of the melt and also to provide good thermal contact, the junctions were enclosed in fine glass tubes about 5 mm. long which were collapsed tightly upon the metal.

The thermocouple was calibrated against the following accurately known transition points: melting point of tin (231.85°), boiling point of water, transition temperature of Glauber's salt (32.384°), and melting point of mercury (−38.89°).

Studies were made first on the indium-rich alloys. These were prepared by adding the desired increments of mercury to the previously analyzed alloys in a 15 × 120 mm. test-tube. In a similar manner mercury-rich alloys were prepared. The volume of sample analyzed was limited to about 5 ml. The alloys were covered with mineral oil to protect them from oxidation and wetting the walls of the tube. All samples were cooled from above the melting point of indium to at least −10°.

Results.—The results are given in Table I and are plotted in Fig. 1.

TABLE I

Sample	Weight % indium	Liquidus temp., °C.	Solidus temp., °C.
1	100.00	156.2	156.2
2	97.46	151.3	148.9
3	90.12	135.1	125.8
4	84.07	121.7	90.2
5	79.30	108.2	...
6	74.70	94.2	...
7	69.84	78.1	...
8	64.89	59.2	...
9	60.01	37.6	...
10	54.92	10.3	...
11	49.98	...	...
12	45.01	...	...
13	40.04	...	...
14	32.98	...	...
15	25.01	...	...
16	20.00	...	...
17	14.95	...	...
18	10.06	...	...
19	4.93	...	...
20	0.00	...	...

Between 10° and the melting point of indium, 156.2°, the solubility of indium in mercury is expressed by the equation

$$\log N_2 = (122.13/T) + 0.0027625T - 1.4740$$

where N_2 is the weight fraction indium and T is in °K.

Since these results differ seriously from those reported by Parks and Moran[5] the following supplementary experiment was performed. At room temperature (approximately 25°), weighed portions of indium and mercury were mixed to yield two mixtures, containing 84.4 and 63.2% mercury. In each case, within a few minutes the indium seemed to have dissolved to yield a homogeneous liquid. To ensure that a two-phase system was not formed each mixture was subjected to centrifugation and then separate portions of the alloy were analyzed as follows: A sample was removed from the top of each mixture and another from the bottom. Each was weighed and treated with hot concentrated hydrochloric acid to dissolve the indium. The mercury, which was unattacked by the acid, was dried and weighed. The composition of the upper and lower samples were found to be essentially the same and equal to that of the total mixture. (In the case of the mixture containing 63.2% Hg, the lower sample analyzed 62.9% and the upper 63.0%.)

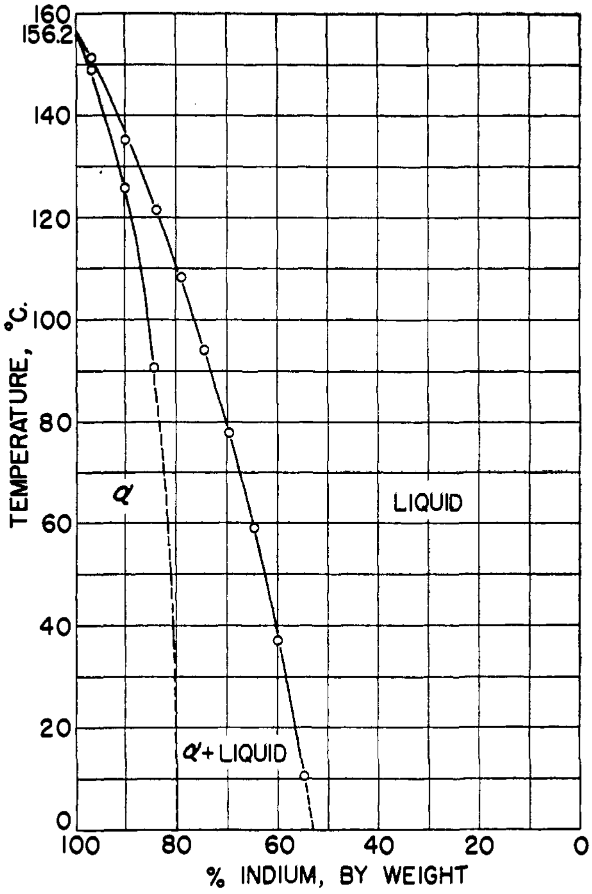


Fig. 1.

The cooling curves indicate that mercury forms a solid solution with indium. The solid solution region is labeled α in Fig. 1.

SCHOOL OF CHEMISTRY
GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GA.

The Logarithmic Growth Law for the Oxidation of Titanium

BY J. T. WABER, G. E. STURDY AND E. N. WISE

RECEIVED JUNE 2, 1952

Two different studies of the oxidation of titanium have led to contradictory interpretations regarding the form of the rate law above and below 350°. Gulbransen and Andrew[1] concluded that a modified parabolic rate law holds throughout the range 250 to 600°, although their Arrhenius plot of the parabolic rate constants shows a change of slope for

---

(1) E. A. Gulbransen and K. Andrew, *J. Metals*, **1**, 741 (1949).

temperatures below 350°. Alexander and Pidgeon[2] obtained a logarithmic growth law in their study throughout the range 25 to 330°. However, above 460° both investigations established that oxidation was controlled by diffusion. The latter investigators state that the parabolic growth law was not applicable to their data.

According to Gulbransen and Andrew the energy of activation for temperatures above 350° is 26.0 kcal./g. mole of activated complex. The author's calculation from the slope at lower temperatures leads to 12.4 kcal./g. mole for this energy of activation. In a study of the oxidation of tantalum, the authors[3] observed a similar change in the energy of activation from 12.57 kcal./g. mole for the logarithmic growth law to 27.2 kcal./g. mole for the parabolic rate.

The present study was undertaken to determine whether the break in the Arrhenius plot of Gulbransen and Andrew's data is due to a change in the rate law. It was found that a logarithmic growth law represents the data up to 316°

$$\lambda = k_L \log(t + 1)$$

where λ is the wave length corresponding to maximum absorption after t hours of exposure. At this temperature, one run was observed to follow a cubic growth law.

Experimental Procedures.—Iodide titanium analyzing 500 p.p.m. of aluminum and 10 p.p.m. each of iron, silicon and magnesium was cold rolled without intervening anneals to 28 mil sheet specimens at Battelle Memorial Institute. These specimens were hand polished through 4/0 aloxite metallographic paper and then finished on dry gamal cloth without added abrasive.

The course of oxidation was followed spectrophotometrically as well as gravimetrically. The details of the two methods and evidence of the reliability of the former method have been presented elsewhere.[3,4]

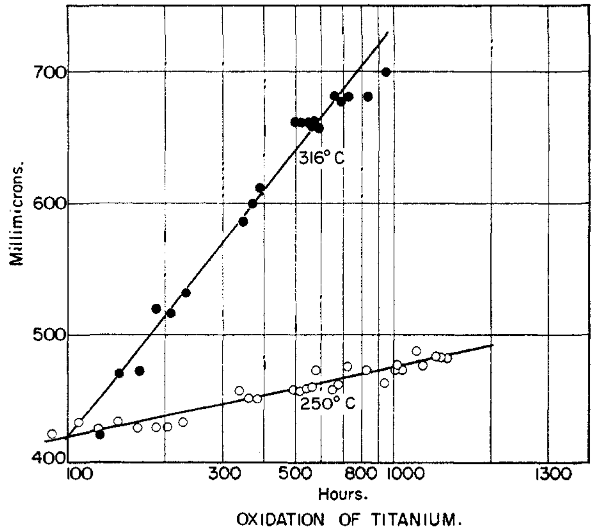


Fig. 1.—A logarithmic plot of the spectrophotometric data obtained in the study of the oxidation of iodine titanium.

The specimens lost weight for about 50 hours, although the interference colors due to the oxide were present. These colors progressed smoothly, changing to those characteristic of greater oxide thicknesses with ensuing time. Repeated heating, followed by polishing to remove the oxide coating, reduced the magnitude and duration of the weight loss.

Alexander and Pidgeon[2] mention that their titanium, made by the Kroll–Dean method, contained about 0.05% hydrogen, which could only be partially removed by outgassing at 311°. The authors believe that the large weight decrease was probably a result of the escape of hydrogen.

Dr. Gulbransen kindly tested one of these samples in his vacuum microbalance. After the sample was outgassed in a high vacuum at 600°, there was a slight decrease in weight prior to oxidation but the behavior of this sample was then no different from that of outgassed specimens which he had discussed earlier in his paper with Andrew.

Experimental Results.—The spectrophotometric data are summarized in Fig. 1. Fairly consistent data were obtained both at 250 and 316°. The ordinate plotted is the wave length of the light which at each time corresponded to the minimum on the reflectance curve. The present data are too few to permit accurate determination of the activation energy, ΔE, in the lower temperature range. However, a preliminary estimate of this quantity based upon the rate constant, k_L, indicates that it is of the order of 13 kcal./g. mole. The values from which it was estimated are given in terms of ångströms in Table I.

TABLE I

VALUES OF THE LOGARITHMIC RATE CONSTANT FROM THE SPECTROPHOTOMETRIC DATA

Temp., °C.	k_L in Å.	
250	507	520
316	3350	5700

Conclusions.—The oxidation of titanium below 350° has been reinvestigated and found to follow the logarithmic growth law, confirming the work of Alexander and Pidgeon. The break in the Arrhenius plot of Gulbransen and Andrew is due to the change from the logarithmic to the parabolic rate law at temperatures increasing above 350°.

Acknowledgments.—The assistance of C. R. Tipton in procuring the cold-rolled specimens is acknowledged. Discussions with F. W. Schonfeld, A. S. Coffinberry and E. R. Jette were helpful and the kind counsel of E. A. Gulbransen was greatly appreciated.

UNIVERSITY OF CALIFORNIA
LOS ALAMOS SCIENTIFIC LABORATORY
LOS ALAMOS, NEW MEXICO

Studies in the Furan Series. Reaction of Some Substituted 2-Furamides with Phenyl Isocyanate

BY JOE R. WILLARD AND CLIFF S. HAMILTON

RECEIVED DECEMBER 13, 1952

In conjunction with other studies in the furan series, some 5-substituted-2-furamides were treated with phenyl isocyanate according to the procedure of Wiley[1] to give the corresponding 1-(5-substituted-2-furoyl)-3-phenylureas. To show that normal addition had occurred, 1-(2-furoyl)- and 1-(5-bromo-2-furoyl)-3-phenylurea were prepared by reaction of phenylurea with the corresponding furoyl chloride according to the method of Stoughton.[2] In accord with the observations of Wiley,[1b]

---

[2] W. A. Alexander and L. M. Pidgeon, *Can. J. Research*, **28B**, (1949).

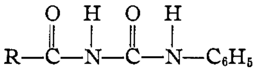
[3] J. T. Waber, E. N. Wise, G. E. Sturdy and C. R. Tipton, *J. Electrochem. Soc.*, **99**, 121 (1952).

[4] It should be pointed out that small thicknesses of lower oxides may increase the phase shift in terms of equivalent oxide thickness although the fundamental equations of the spectrophotometric method are not changed. It has been assumed that lower oxides of titanium were not present in significant amounts.

[1] (a) P. F. Wiley, THIS JOURNAL, **71**, 1310 (1949); (b) **71**, 3746 (1949).

[2] R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

TABLE I



$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}C_6H_5}$

R-	M. p., °C.	Solvent	Color	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
2-Furyl	186–188	EtOH	White	50	62.60	62.75	4.38	4.55	12.27	12.18
5-Bromo-2-furyl-	198–200	HOAc	White	98	46.59	46.91	2.93	2.95	9.06	9.35
5-Methyl-2-furyl-	162–163	EtOH	White	45	63.91	63.98	4.95	4.99	11.47	11.58
5-*t*-Butyl-2-furyl	186–188	EtOH	White	64	67.49	67.66	6.34	6.32	9.79	9.96
5-Nitro-2-furyl-	249–251	HOAc	Yellow	79	52.37	52.57	3.30	3.53	15.27	15.27
β-(2-Furyl)-vinyl-	198–201	EtOH	Tan	73	65.61	65.64	4.77	4.99	10.94	11.03

N-substituted furamides did not add normally to phenyl isocyanate and no characterizable product could be isolated from the reaction mixture.

Experimental

Starting Materials.—Details of the preparation of the substituted 2-furamides will appear in a later paper in this series.

Addition of Amides to Phenyl Isocyanate.—A mixture of the amide with a slight excess of phenyl isocyanate was heated under gentle reflux until entirely liquid (5–10 minutes). Ten milliliters of absolute ethanol was added cautiously to react with excess phenyl isocyanate and the solution was chilled. The solid which separated was isolated on a filter, washed with cold ethanol and recrystallized to constant melting point. The properties of the resulting 1-acyl-3-phenylureas are given in Table I.

Acylation of Phenylurea.—A solution of 6.75 g. (0.05 mole) of phenylurea in 20 ml. of benzene was heated to the reflux temperature and to the hot mixture was added slowly a solution of 6.5 g. (0.05 mole) of 2-furoyl chloride in 10 ml. of dry benzene. The mixture was heated under reflux while stirring vigorously for 6 hours.

The solution was cooled to room temperature and the solid which separated was isolated and recrystallized from hot ethanol to give 0.8 g. (7%) of 1-(2-furoyl)-3-phenylurea which melted at 187–188°. Mixing with the product from addition of 2-furamide to phenyl isocyanate did not depress the melting point of this product.

1-(5-Bromo-2-furoyl)-3-phenylurea was prepared similarly in 1% yield by acylation of a toluene solution of phenylurea with 5-bromo-2-furoyl chloride.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NEBRASKA
LINCOLN 8, NEBRASKA

COMMUNICATIONS TO THE EDITOR

ENZYMATIC PHOSPHORYLATION OF *l*-ASPARTATE

Sir:

The biological incorporation of amino acids into more complex compounds is known in certain instances[1] to utilize energy from ATP.[2] However, phosphorylated intermediates have not been demonstrated in these processes, and the mechanisms of energy transfer are obscure. The enzymatic formation of an "energy-rich" amino acid-phosphate compound, β-aspartyl phosphate, is described here. Suggestive evidence that this substance is a precursor of asparagine is the presence in the enzyme preparation of a very active asparagine "transferase" similar to the enzymes found by Waelsch and co-workers[3] in certain bacteria.

The enzyme was obtained from an extract of baker's yeast and purified about 10-fold with weak acid and ammonium sulfate. It appears to catalyze the reaction

$$\text{ATP} + l\text{-aspartate} \rightleftarrows \text{ADP} + \beta\text{-aspartyl phosphate}$$

Though its equilibrium is unfavorable to accumulation of the new compound, the reaction may be followed readily if hydroxylamine is used to trap the aspartyl phosphate, forming a hydroxamic acid, as has been done with acetyl phosphate.[4] In Table I are shown the essential components of the system and the effect on hydroxamate formation of omitting each. Substitution of *d*-aspartate or *l*-glutamate reduced hydroxamic acid formation to 2 and 6%, respectively, of the value with *l*-aspartate.

TABLE I

All tubes contained 0.4 μM. hydroxylamine hydrochloride brought to *p*H 8.0 with tris. The incubation was at 30° for 30 minutes in a total volume of 1.0 ml.

Component omitted	Hydroxamic acid formed, μM.
None	3.2
25 μM. *l*-aspartate (potassium salt)	0.09
10 μM. ATP (sodium salt)	0.00
10 μM. $MgCl_2$	0.14
Enzyme, 0.1 ml.	0.00

High concentrations of aspartate and ATP favor synthesis of aspartyl phosphate, as shown in Table II. In this experiment hydroxylamine at *p*H 4.0 was added to stop the enzymatic activity after samples had been taken for phosphate analyses. Acyl phosphate was determined as hydroxamic acid,[5] and as the difference between inorganic

---

[1] P. P. Cohen in W. D. McElroy and B. Glass, "Phosphorus Metabolism," The Johns Hopkins Press, Baltimore, Md., 1951, Vol. I, p. 630.

[2] Abbreviations used are ATP (adenosine triphosphate), ADP (adenosine diphosphate), AMP (adenosine-5-phosphate), and tris-[tris-(hydroxymethyl)-methylamine].

[3] H. Waelsch, *Advances in Enzymol.*, **13**, 237 (1952).

[4] F. Lipmann, *ibid.*, **6**, 231 (1946).

[5] F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).