NOTES

Some 5-Substituted Derivatives of Ethyl 2-Methylnicotinate[1]

By Paul E. Fanta

Received October 6, 1952

The reaction of sodium nitromalonaldehyde (I) with ethyl β-aminocrotonate (II) was studied as part of a program of synthesis of new heterocyclic compounds of possible pharmacological interest. The only product isolated from the reaction mixture was ethyl 2-methyl-5-nitronicotinate (III). This is the first reported use of sodium nitromalonaldedehyde for the synthesis of a nitropyridine.[2] The nitro ester was readily hydrolyzed to the carboxylic acid (IV), which unexpectedly was not decarboxylated by heating at its melting point. Catalytic hydrogenation of the nitro ester with platinum catalyst in neutral alcohol gave a large amount of ethyl 5-hydroxamino-2-methylnicotinate (V, 45% yield) in addition to the expected ethyl 5-amino-2-methylnicotinate (VI, 46% yield). Ethyl 5-acetylamino-2-methylnicotinate (VII) was obtained when the catalytic reduction was conducted in a mixture of acetic acid and acetic anhydride.

The amino group of VI reacted in the expected manner upon diazotization. Heating the diazonium sulfate gave the hydroxy derivative (VIII), while reaction with potassium iodide yielded the iodo compound (IX). The diazonium chloride was reduced by treatment with hypophosphorus acid to the previously reported ethyl 2-methylnicotinate (X).[3] The latter compound is an oil which was identified by means of its picrate and the hydrochloride of the corresponding acid (XI).

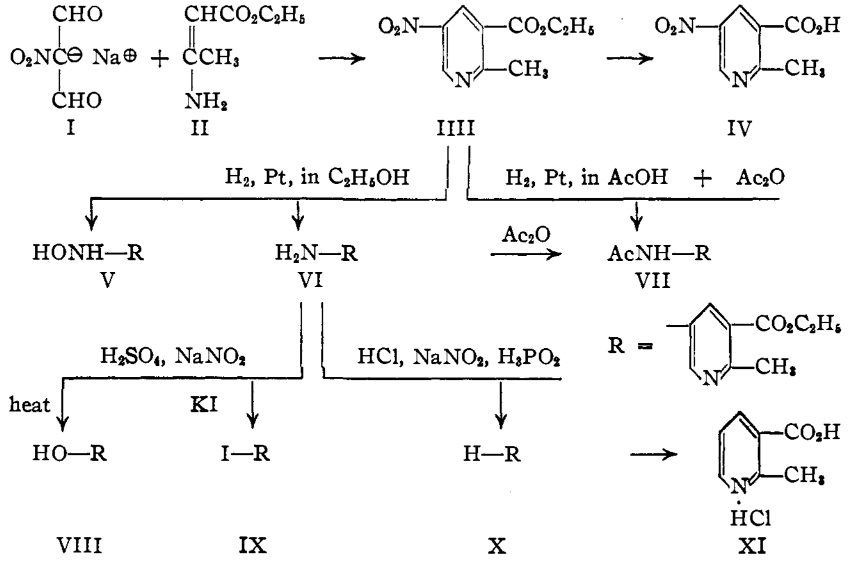

Table I

Wave Lengths of Principal Infrared Bands in the Region 2.50 to 7.40 μ

All determinations on 0.7 to 0.8% solutions in chloroform

Compound	—OH	—NH	Ester	Aromatic ring	$—NO_2$	—NHOH	$—NO_2$
	Probable assignment[4]						
Nitrobenzene	....	....	..	6.23	6.53	..	7.39
N-Phenylhydroxylamine	2.80 (weak)	3.03 (weak)	..	6.23	..	6.67	..
Nitro compound III	....	....	5.80	6.24, 6.32	6.53	..	7.36
Hydroxamino compound V	2.80 (weak)	3.03 (weak)	5.84	6.25, 6.35	..	6.82	..

The hydroxamine V instantaneously reduced Tollens reagent and cold Fehling solution. It was further characterized by comparison of the infrared absorption spectrum with the spectra of several model compounds. From the data summarized in Table I it is evident that the spectra of V and III have the same relationship to each other as N-phenylhydroxylamine has to nitrobenzene.

Experimental[5]

Ethyl 2-Methyl-5-nitronicotinate (III).—Ethyl β-aminocrotonate was prepared by saturating a solution of 26.0 g. (0.20 mole) of ethyl acetoacetate in 200 ml. of absolute ether with ammonia gas at −10°. The granular, white precipitate was quickly collected on a cold buchner funnel and added to a solution of 15.7 g. (0.10 mole) of sodium nitromalonaldehyde[6] in 100 ml. of water. The mixture was heated to 50° with stirring, then cooled to −5°. The precipitated product was collected on a filter and purified by two recrystallizations, using 150 ml. of 50% alcohol each time. The yield of pure product was 7.46 g. (35%, based

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[1] This work was supported by a grant from the Office of Ordnance Research.

[2] For examples of pyridine syntheses utilizing ethyl β-aminocrotonate and other β-dicarbonyl compounds see H. S. Mosher in R. C. Elderfield's "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York. N. Y., 1950, p. 468.

[3] E. Ochiai and Y. Ito. *Ber.*, **74B**, 1111 (1941): P. Baumgarten and A. Dornow. *ibid.*, **72B**, 563 (1939).

[4] With the exception of the —NHOH band, for which no assignment was given, these data agree with the range of values published by H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, facing p. 20.

[5] All melting points are corrected. Analyses are by Micro-Tech Laboratories, Skokie, Illinois.

[6] P. E. Fanta. *Org. Syntheses*, **32**, 95 (1952). The furoic acid used in this preparation was obtained from the Quaker Oats Company through the courtesy of Dr. A. P. Dunlop.

on the amount of sodium nitromalonaldehyde used) of very pale yellow needles, m.p. 64–65°.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.76; H, 4.80; N, 13.40.

2-Methyl-5-nitronicotinic Acid (IV).—A solution of 2.00 g. of the ester III in a mixture of 5 ml. of concentrated hydrochloric acid and 5 ml. of water was refluxed for one hour. The solution was diluted with 30 ml. of water and neutralized by the addition of solid sodium bicarbonate. After cooling, 1.47 g. (85%) of crude acid was obtained. Recrystallization from a mixture of 40 ml. of water and 10 ml. of alcohol gave 1.26 g. (73%) of fine, white needles which melted with decomposition at 215–215.5°, when placed in the melting point bath at 211° with the temperature rising 2° per min.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.43; H, 3.62; N, 15.64.

When a small portion of IV was melted in a test-tube at atmospheric pressure and then sublimed at 60 mm., the fluffy, white sublimate was shown by melting point to be pure starting material.

Catalytic Hydrogenation of III in Alcohol.—A solution of 6.30 g. (0.03 mole) of III in 70 ml. of absolute alcohol was shaken with 0.05 g. of platinum oxide catalyst (American Platinum Works) for five minutes at 32–35° and a hydrogen pressure of 900 lb. After removal of the catalyst by centrifugation, the solvent was distilled on the steam-bath at 60 mm. pressure and the sirupy residue was dissolved in 100 ml. of hot benzene. Cooling gave 2.67 g. (45%) of nearly pure, fine, colorless needles of **ethyl 5-hydroxamino-2-methylnicotinate** (V). The analytical sample, prepared by recrystallization from benzene, melted at 111.5–112.5° and became slightly pink after standing for several weeks.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.11; H, 6.28; N, 14.38.

The benzene solution from the isolation of V was evaporated to a volume of 30 ml. and 60 ml. of 60–70° petroleum ether was added. Cooling to −5° gave 2.50 g. (46%) of crude **ethyl 5-amino-2-methylnicotinate** (VI) which consisted of a yellow powder melting at 60–70°. It was used in subsequent experiments without further purification. A sharply melting, analytically pure sample was not obtained by recrystallization from various solvents. **A picrate** was obtained by mixing an aqueous solution of the amine with saturated aqueous picric acid. After recrystallization from water containing a little alcohol it formed yellow platelets which melted to a dark red liquid at 191–192°.

Anal. Calcd. for $C_{15}H_{15}N_5O_9$: C, 44.01; H, 3.69. Found: C, 44.48; H, 3.82.

An analytically pure sample of VI was obtained by extracting an ether suspension of the pure picrate with strong, aqueous sodium hydroxide solution until the yellow color was discharged. Evaporation of the ether and recrystallization of the residue from benzene–ligroin gave fine, white clusters, m.p. 64–65°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.94; H, 6.74; N, 15.87.

Catalytic Hydrogenation of III in Acetic Acid–Acetic Anhydride.—A solution of 0.50 g. of III in a mixture of 5 ml. of acetic acid and 1 ml. of acetic anhydride was shaken with 0.05 g. of platinum oxide catalyst for five minutes at 30–40° and a hydrogen pressure of 1500 lb. After removal of the catalyst by centrifugation, the solvent was removed on the steam-bath at 60 mm. pressure. The slightly greenish, sirupy residue of crude **ethyl 5-acetylamino-2-methylnicotinate** (VIII) could not be induced to crystallize and was not submitted for analysis. On mixing an aqueous solution of the crude product with a saturated aqueous solution of picric acid, the **picrate** was precipitated. Upon recrystallization from water it was obtained in the form of yellow clusters which sintered at 169–170° and melted to a clear, light red liquid at 170–171°.

Anal. Calcd. for $C_{17}H_{17}N_5O_{10}$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.28; H, 3.81; N, 15.47.

The same picrate was obtained when VI was treated successively with hot acetic anhydride, water and saturated aqueous picric acid.

Ethyl 5-Hydroxy-2-methylnicotinate (VIII).—A solution of 0.36 g. (0.002 mole) of VI in a mixture of 10 ml. of water and 1.0 ml. (0.018 mole) of sulfuric acid was diazotized at 0° by the addition of 0.14 g. (0.002 mole) of sodium nitrate. When the clear, yellow solution was rapidly heated to boiling, gas was evolved and the solution darkened. The reaction mixture was cooled, diluted with 10 ml. of water and neutralized to *p*H 6 by the addition of solid sodium carbonate. The desired product was isolated in low yield by ether extraction, followed by two vacuum sublimations and successive crystallizations from aqueous alcohol and benzene–ligroin, when it formed fine, colorless platelets which melted at 163–164.5°.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.42; H, 6.22; N, 7.63.

Ethyl 5-Iodo-2-methylnicotinate.—A solution of 0.18 g. (0.001 mole) of VI in a mixture of 5 ml. of water and 0.36 ml. of sulfuric acid was diazotized at 0° by the addition of 0.10 g. of solid sodium nitrite. The yellow solution was added to a solution of 0.33 g. (0.002 mole) of potassium iodide in 5 ml. of water at 0° and the reaction was completed by heating to boiling. A light amber colored solution was obtained which was diluted with 10 ml. of water and neutralized by the addition of solid sodium bicarbonate. A tan precipitate was obtained which was recrystallized from 40 ml. of 50% alcohol, giving 0.16 g. (55%) of dark tan needles which melted at 92–92.5°. A colorless analytical sample was obtained by two vacuum sublimations, m.p. 92.5–93.5°.

Anal. Calcd. for $C_9H_{10}NO_2I$: C, 37.13; H, 3.46; N, 4.81. Found: C, 37.12; H, 3.52; N, 4.91.

Hypophosphorous Acid Deamination[7] **of VI.**—A solution of 0.90 g. (0.005 mole) of VI in a mixture of 30 ml. of water and 2.0 ml. (0.025 mole) of concentrated hydrochloric acid was diazotized at 0° by the addition of 0.39 g. (0.0055 mole) of sodium nitrite. After two minutes, 9.9 g. (0.075 mole) of cold 50% hypophosphorous acid was added and the mixture was allowed to stand at 0° for 16 hours. The clear solution was brought to *p*H 8 by the addition of solid sodium carbonate and the brown oil which separated was extracted with two 30-ml. portions of ether. Evaporation of the ether and distillation of the residue at 0.5 mm. gave 0.51 g. (62%) of very light yellow, oily ethyl 2-methylnicotinate (X). The picrate crystallized from water in the form of long, fine, yellow needles which melted at 145.5–146.5° (the value previously reported in the literature[3] is 146–147°). The ester was converted to 2-methylnicotinic acid hydrochloride (XI) according to the published directions.[3] After recrystallizations from ethyl acetate it melted with vigorous decomposition at 230.5–231° (the previously reported values[3] are 225 and 226°).

Infrared absorption spectra were determined with the Model 21 Perkin and Elmer double-beam recording infrared spectrophotometer in 0.1-mm. sodium chloride cells.

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(7) N. Kornblum in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 262.

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Polarography of *p*-Chlorobenzophenone and Xanthone

BY R. A. DAY, JR., AND R. E. BIGGERS

RECEIVED AUGUST 18, 1952

In a recent publication on the polarography of aromatic ketones, several compounds were compared as to their formation of double waves in basic ethanol–water media.[1] It was pointed out that if the aromatic group attached to the carbonyl in a ketone tended to increase the stability of the dimer of a metal ketyl intermediate, double waves were likely to occur. The aromatic groups studied in this work were the 9-fluoryl, benzanthryl, phenyl and α-naphthyl.

It is known that the *p*-chlorophenyl group has less effect in stabilizing a free radical than the

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(1) R. A. Day, Jr., S. R. Milliken and W. D. Shults, THIS JOURNAL, **74**, 2741 (1952).

phenyl group whereas the xanthyl group has a greater effect than two phenyl groups.[2] Thus one would expect that the ketone *p*-chlorobenzophenone would have a greater tendency while xanthone would have a lesser tendency to form double waves in basic media than benzophenone.

These two ketones have been studied in 25% ethanol–water media over a *p*H range of about 1 to 13. The results listed in Table I were in accord with those expected. *p*-Chlorobenzophenone gives the usual two waves in acid media, these merging at a *p*H between 4.7 and 5.6.[3] The potential of this single wave decreases to −1.52 as the *p*H is increased to 12.8. A small second wave of half-wave potential −1.61 was first observed at a *p*H of 7.5. The potential of this wave had decreased to −1.74 v. at a *p*H of 11.2. The wave was not present in 0.1 *M* NaOH (ketone concentration 2.5 × 10^{-4} *M*) but did appear when the base concentration was reduced to 1 × 10^{-3} *M*. Benzophenone at the same concentration gave only one wave in these same basic solutions.[1]

TABLE I

$E_{1/2}$ *vs.* THE SATURATED CALOMEL ELECTRODE (ALL $E_{1/2}$ VALUES ARE NEGATIVE)

*p*H (aq.)	*p*H (alc.)	$E^1_{1/2}$	$E^2_{1/2}$	$E^{12}_{1/2}$[a]	$E^3_{1/2}$	Total curr., μa.
		p-Chlorobenzophenone[b]				
1.1	1.4	0.89	..	..	..	0.75
2.7	3.1	0.93	1.15	..	..	1.39
4.7	5.1	1.07	1.26	..	..	1.57
5.6	6.0	..	..	1.26	..	1.57
7.5	8.0	..	..	1.36	1.61	1.52
8.5	9.1	..	..	1.41	1.70	1.63
9.6	10.2	..	..	1.45	1.74	1.66
11.2	11.5	..	..	1.49	1.77	1.28
12.8	12.8	..	..	1.52	..	1.05
		Xanthone[c]				
1.0	1.3	0.84	..	..	..	0.44
2.7	3.2	0.99	..	..	..	.47
3.7	4.1	1.05	..	..	..	.42
4.7	5.2	..	..	1.21	..	1.12
5.6	6.2	..	..	1.23	..	0.92
6.7	7.2	..	..	1.26	..	.90
7.6	8.0	..	..	1.29	..	.83
8.6	9.0	..	..	1.37	..	.88
9.6	10.1	..	..	1.43	..	.59
12.7	12.7	..	..	1.45	..	.45

[a] Indicates $E_{1/2}$ of wave formed by merging waves 1 and 2. [b] Concentration of ketone 0.000250 *M*. [c] Concentration of ketone 0.000156 *M*.

In the case of xanthone, only one wave was observed over the entire *p*H range. There was a slight indication of separation of the two acid waves at a *p*H of 5.2. Considerably higher currents were observed between a *p*H of about 5 to 9 than at lower or higher *p*H values. A few runs were also made in dilute sodium hydroxide solutions. At a ketone concentration of 1.56 × 10^{-4} *M* and NaOH concentration of 1 × 10^{-4} *M* no indication of a second wave could be seen. Since benzophenone also gave only one wave under these conditions some runs were made at higher ketone concentrations. It was necessary to use 50% ethanol to keep xanthone from precipitating. At ketone concentrations of 8 × 10^{-4} to 1.25 × 10^{-3} *M* in 50% ethanol a second wave could be definitely seen with benzophenone, whereas there was only a slight indication of a second wave with xanthone.

Experimental

The current–voltage curves were determined with a Leeds and Northrup Electro-Chemograph Type E. The instrument was normally operated at a damping of 3, the half-wave potentials being corrected by 0.056 v. for lag at this damping. The electrolysis cell, buffer solution and experimental procedure were the same as previously described.[1]

A single capillary of Corning Marine barometer tubing was used. Its characteristics were: droptime 5.0 sec., *m* = 1.858 mg./sec., determined in 25% ethanol at a *p*H of 5.5 and −1.00 v. The resistance of the cell was measured at several *p*H values and a correction for *IR* drop was made when this amounted to as much as 0.01 v.

All cell solutions were 25% by volume of 95% ethanol unless otherwise indicated. The two ketones were commercial products, purified by recrystallization. Melting points (uncor.) were: *p*-chlorobenzophenone 72–73°, xanthone 173–174°. Cell solutions of *p*-chlorobenzophenone were 2.5 × 10^{-4} *M*, those of xanthone 1.56 × 10^{-4} *M*. More concentrated solutions of the latter ketone gave precipitation when mixed with basic buffers.

Measurements of *p*H were made using a glass electrode and a Beckman model H-2 *p*H meter. A high *p*H glass electrode was used in basic media.

All experiments were run at room temperature, which was normally between 23 and 28°.

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[2] H. Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 591.

[3] All *p*H values herein are of the aqueous buffer.

The Rate of Deuterium Exchange between Ethanol and Water. A Reinvestigation[1]

BY JACK HINE AND CYRUS H. THOMAS

RECEIVED OCTOBER 9, 1952

Orr has reported that the establishment of equilibrium between ethanol and heavy water is a reaction of measurable rate, having a half-time of about four hours at 25°.[2] Orr mixed samples of heavy water (about 10% D) with somewhat smaller volumes of ethanol and after an allotted time added anhydrous calcium sulfate. The calcium sulfate was removed, air-dried of the adherant ethanol and dehydrated at 150° in vacuum. The composition of the resultant mixture (containing light and heavy water and < 0.4% ethanol) was measured by determination of the density and of the refractive index (using an interferometer).

On the other hand, Jungers and Bonhoeffer found that the equilibrium between ethanol and heavy water is established too rapidly to measure.[3] These workers, however, separated their aqueous ethanol solutions by extraction with benzene.

Since the validity of the widely-held belief that all proton transfer reactions between oxygen atoms occur too rapidly to measure (by con-

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[1] This study was carried out as part of a project sponsored by the Atomic Energy Commission.

[2] W. J. C. Orr, *Trans. Faraday Soc.*, **32**, 1033 (1936).

[3] J. C. Jungers and K. F. Bonhoeffer, *Z. physik. Chem.*, **A177**, 460 (1936).

ventional means, at least) is of considerable importance in relation to the theory that in reactions subject to general acid and/or base catalysis the rate-controlling step is a proton transfer,[4] and also in relation to learning what compounds are *primary* acids and bases in the Lewis sense,[5] it was felt that another check of Orr's work, using his method for separating water from ethanol, would be desirable.[6] However, in order that the final concentration of deuterium in the water should differ more significantly from that used originally, a larger amount of ethanol relative to water, and a higher concentration of heavy water were used in our experiments, of which the following procedure is an example:

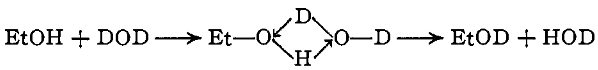
To 3.2 ml. of absolute ethanol at 0° was added 1.0 ml. of water (17.1 atom % deuterium) at about 0.5°. The mixture was shaken until homogeneous (5 seconds), poured onto 10 g. of anhydrous calcium sulfate, shaken for five minutes, and evacuated to 8 mm. pressure for 2.5 hours to remove the ethanol (all at 0°). The water was removed by heating to 197° under 8 mm. pressure, its ethanol content determined by the method of Williams and Reese[7] and its density by the falling drop method of Roseburg and Van Heyningen.[8] From the density and a correction for the 0.0087 g./ml. ethanol (based on the assumption that its partial molal volume is not affected by the deuterium content of the solvent), the water was shown to contain 9.0 atom % deuterium (11.3% would correspond to random distribution).

In another experiment at 0°, 9.4% deuterium (*vs.* 11.3% if random) was found and in a run at room temperature (*ca.* 34°) 10.1% deuterium (*vs.* 11.4% for random distribution) was found.

While we believe we have shown that the prototropic equilibrium between water and the hydroxy group of ethanol is established too rapidly to measure under our conditions, this does not establish any minimum for the rate of reactions such as

$$\mathrm{EtOH} + \mathrm{H_2O} \rightleftarrows \mathrm{H_3O^+} + \mathrm{EtO^-}, \text{ etc.}$$

which accomplish a net proton transfer, since the unshared electron pairs on oxygen make feasible[9] the establishment of this equilibrium by proton-*exchange* reactions by mechanisms of the type shown below in which ions play no part.



It seems possible that the results of Orr are fortuitous. In no case would an error of more than 0.4 mg. in weighing his pycnometer be necessary to make his results correspond to purely random distribution of deuterium between the hydroxy group of the ethanol and water. From the facts that his weights are given to the nearest 0.1 mg., and that no contrary statement is made, it seems likely that he used an ordinary analytical balance on which the error of weighing (plus all of the other errors in the determination, such as that in filling the pycnometer) might reasonably have this magnitude.

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[4] R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, chap. VII; L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 241.

[5] G. N. Lewis, *J. Franklin Inst.*, **226**, 293 (1938); G. N. Lewis, and G. T. Seaborg, THIS JOURNAL, **61**, 1886 (1939).

[6] Since this problem was begun, we have learned from a private communication that Dr. H. Kwart of the University of Delaware has found the deuterium exchange between methanol and water to be too rapid to measure under similar conditions.

[7] M. B. Williams and H. D. Reese, *Anal. Chem.*, **22**, 1556 (1950).

[8] F. Roseburg and W. E. Van Heyningen, *Ind. Eng. Chem., Anal. Ed.*, **14**, 363 (1942).

[9] See A. J. Brodskii and L. V. Sulima, *Doklady Akad. Nauk S. S. S. R.*, **74**, 513 (1950).

Extension of the Willgerodt Reaction

BY RICHARD T. GERRY AND ELLIS V. BROWN

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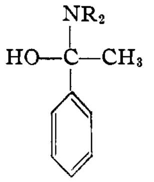
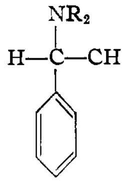
Recent papers have shown that the scope of the Willgerodt reaction is considerably broader than had previously been supposed. Several investigators[1,2] have reported successful Willgerodt reactions with olefins, carbinols, thiols and acetylenes.

We feel that further extensions of the Willgerodt reaction may be of assistance in elucidating the mechanisms of this reaction as proposed by King and McMillan[1] and Carmack and DeTar.[2] The intermediates proposed by these workers are in many cases too reactive to be isolated by the usual preparative methods. However, the behavior of more stable but closely related compounds may be of interest. For example, Carmack and DeTar postulated a hydramine intermediate (I) in their reaction sequence. We have tested three amines (II) of somewhat related structure.



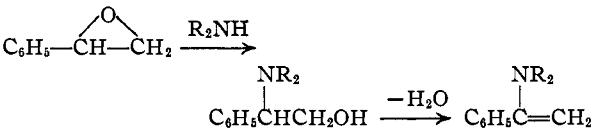
I



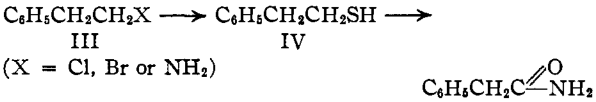
II

(R = CH_3, CH_2CH_2OH or H)

Styrene oxide was also investigated since it could conceivably go through the following steps to yield another intermediate of Carmack and DeTar.



Again, compounds of type III would be expected to follow the sequence of King and McMillan. This is possible since the yields of amides from



$$\underset{\text{III}}{C_6H_5CH_2CH_2X} \longrightarrow \underset{\text{IV}}{C_6H_5CH_2CH_2SH} \longrightarrow C_6H_5CH_2C(=O)NH_2$$

(X = Cl, Br or NH_2)

these compounds are only slightly lower than that reported for 2-phenylethanethiol (IV).

If either mechanism is applied to β-bromostyrene the amides might be formed in fewer steps than from styrene itself. Styrene yielded 71% of phenylacetamide while bromostyrene, under comparable conditions, gave 80% yield of this amide.

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[1] J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 525, 632 (1946).

[2] M. Carmack and D. F. DeTar, *ibid.*, **68**, 2029 (1946).

Experimental

The Willgerodt Reactions.—The method of Fieser and Kilmer[3] was used throughout this study. Usually several tubes were heated in the same furnace so yields would be directly comparable. Identity of the amide obtained was proved by melting point and mixed melting point with an authentic specimen. The amides were all hydrolyzed and the identity of the acid was also proved by melting point and mixed melting point. The results are given in Table I. A typical example of the procedure is given for the reaction of styrene oxide. Styrene oxide (10 g.), 5 g. of sulfur, 50 ml. of yellow ammonium polysulfide and 40 ml. of dioxane were sealed in a Carius tube and heated in an electric furnace for 7 hr. at 170 ± 5°. The contents of the cooled tube were evaporated to dryness and the residue extracted several times with boiling water. The product crystallizes on cooling and a second crop of crystals may be obtained by concentration of the mother liquor. Recrystallization from water gave 9.8 g. (87%) of phenylacetamide melting 156–157°.

TABLE I

PERCENTAGE YIELDS OF PHENYLACETAMIDE FROM WILLGERODT REACTIONS

1-Phenylethylamine	61
1-Phenylethyldimethylamine	31
1-Phenylethyl-(monoethanol)-amine	63
1-Phenylethyl-(diethanol)-amine	66
2-Phenylethylamine	32
1-Phenylethyl bromide	40
2-Phenylethyl bromide	66
Styrene oxide	87
β-Bromostyrene	80
Phenacylpyridinium iodide	53
ω-Morpholinoacetophenone	72

Hydrolysis of the Amide.—Three-gram samples of the amides were refluxed for 5 hours with 100 ml. of 10% aqueous potassium hydroxide, acidified and filtered. Phenylacetic acid crystallized in white plates melting at 76°.

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[3] L. F. Fieser and G. W. Kilmer, THIS JOURNAL, **62**, 1354 (1940).

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The Ternary System $NaVO_3$–Na_2SO_4–H_2O

BY R. TRUJILLO AND E. TEJERA

RECEIVED SEPTEMBER 12, 1952

Continuing our studies in connection with ternary systems involving alkali vanadates,[1] we here report the solubility relations in the system sodium vanadate–sodium sulfate–water at 25°.

The sodium vanadate was recrystallized from B.D.H. "Laboratory Reagent" material. It was analyzed as follows: vanadium was determined by potentiometric titration with Mohr's salt in presence of sulfuric acid, and sodium was determined as the sulfate after elimination of vanadium by precipitation with mercuric nitrate. The results agreed within several tenths per cent. with the composition $NaVO_3 \cdot 2H_2O$. The sodium sulfate, a Merck product, was used without further purification, after satisfactory tests on the limits of impurities.[2]

The ternary mixtures were placed in test-tubes and rotated in a thermostat at 25.0 ± 0.5° for three days. Samples were taken in the usual way, with a pipet provided with a cotton-waste filter, after one day settling in the thermostat. The remaining solution was poured off and samples of wet residues were also weighed. The concentrations of vanadate and sulfate were determined in each sample, the former by the process already described, and the latter as barium sulfate, by precipitation with a solution of barium chloride slightly acidified with acetic acid to prevent precipitation of the slightly soluble barium vanadate.

The results are listed in Table I. The system is simple, the solid phases being $NaVO_3 \cdot 2H_2O$ and $Na_2SO_4 \cdot 10H_2O$, as determined by the Schreinemakers method.[3] The composition of the hydrates was verified through direct analysis.

TABLE I

SYSTEM $NaVO_3$–Na_2SO_4–H_2O AT 25°

Densities	Liquid solution Wt. % Na_2SO_4	Liquid solution Wt. % $NaVO_3$	Wet residue Wt. % Na_2SO_4	Wet residue Wt. % $NaVO_3$	Solid phase[a]
1.084	...	12.80	...	40.15	A
1.088	3.40	9.62	2.65	30.76	A
1.090	5.30	7.50	3.65	30.22	A
1.091	8.88	5.18	6.49	26.54	A
1.108	10.50	4.60	9.09	15.05	A
1.120	12.00	3.76	8.69	25.21	A
1.129	13.15	3.22	10.56	18.25	A
1.138	14.27	3.15	11.70	17.01	A
1.167	16.05	2.65	13.11	16.87	A
1.179	19.28	1.93	15.65	16.62	A
1.185	19.89	1.53	16.14	15.73	A
1.186	20.86	1.48	29.72	17.63	A + B
1.192	21.54	0.53	41.35	0.12	B
1.194	21.72	0.36	41.10	0.15	B
1.196	21.85	...	42.96	...	B

[a] A = $NaVO_3 \cdot 2H_2O$; B = $Na_2SO_4 \cdot 10H_2O$.

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[1] R. Trujillo and E. Tejera, *An. Soc. Españ. Fis. Quim.*, **XLVII** (B), 495 (1951); R. Trujillo and L. Pastor, *ibid.*, 501 (1951).

[2] Rosin, "Reagent Chemicals and Standards," D. Van Nostrand Co., Inc., New York, N. Y., 1946.

[3] Schreinemakers, *Z. physik. Chem.*, **11**, 81 (1893).

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Unsaturated Lactones. III. Absorption Spectra in a Group of α-Benzal-γ-substituted Crotonolactones[1]

BY CALVIN HANNA AND F. W. SCHUELER

RECEIVED SEPTEMBER 27, 1952

The effect of substitution of aromatic groups in the α-position on the absorption spectra in a series of γ-phenylcrotonolactones has been previously reported.[2] We have extended this study to include a series of γ-substituted α-benzalcrotonolactones to determine the effect of substituents on the γ-position on the light absorption.

Out of a group of twelve crotonolactones[3] prepared during this investigation four were pre-

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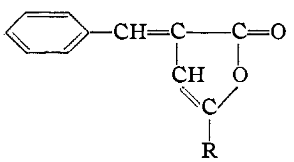
[1] This work was aided by a grant from the U. S. Public Health Service.

[2] F. W. Schueler and C. Hanna, THIS JOURNAL, **73**, 3528 (1951).

[3] These compounds have been studied for cardiac activity; F. W. Schueler and C. Hanna, *Arch. intern. pharmacodynam.*, **86**, 91 (1951).

TABLE I

α-BENZAL-γ-SUBSTITUTED CROTONOLACTONE DERIVATIVES

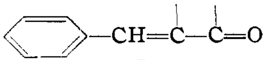


No.	R	M.p.,[b] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Max. 1 mμ	Max. 1 ε × 10⁴	Max. 2 mμ	Max. 2 ε × 10⁴
1	4-CH_3–C_6H_4–[5]		$C_{18}H_{14}O_2$					256	1.67	395	2.94
2	4-Br–C_6H_4–[6]		$C_{17}H_{11}O_2Br$					255	1.48	396	2.39
3	4-CH_3O–C_6H_4– (Y.) or (G.)[a]		$C_{18}H_{14}O_3$					255	1.83	397	3.20
4	4-Cl–C_6H_4–		$C_{17}H_{11}O_2Cl$					255	1.47	394	2.38
5	3,4-di-CH_3–C_6H_3–	146	$C_{19}H_{16}O_2$	82.59	82.52	5.84	5.79	256	1.98	397	3.04
6	2-Tetralyl-	150	$C_{21}H_{18}O_2$	83.41	83.55	6.00	6.10	256	1.78	397	3.50
7	4-C_6H_6–O–C_6H_4–	143	$C_{23}H_{16}O_3$	81.15	81.32	4.74	4.81	250	1.95	397	1.71
8	4-C_6H_5–C_6H_4–	201	$C_{23}H_{16}O_2$	85.16	85.27	4.97	4.85	288	0.34	400	3.08
9	4-CH_3CONH–C_6H_4–	232	$C_{19}H_{15}O_3N$	74.74	74.69	4.94	4.98	288	1.61	409	2.92
10	2-Thienyl- (O.)[a]	131	$C_{15}H_{10}O_2S$	70.85	71.10	3.96	3.87	278	1.49	400	3.44
11	3-Acenaphthyl- (O.)[a]	131	$C_{23}H_{16}O_2$	85.16	85.21	4.97	5.02	246	1.47	410	2.22
12	2-Fluorenyl- (O.)[a]	207	$C_{24}H_{16}O_2$	85.69	85.78	4.80	4.83	298	1.75	410	3.52

[a] All compounds had a yellow color except as otherwise noted, thus O. orange, G. green. [b] Melting points corrected.

viously reported and no spectroscopic data appear to have been reported on any of these materials in which the aromatic group at the α-position is now substituted. The crotonolactones synthesized in this study are detailed in Table I together with their absorption maxima, melting points and analysis.

In regard to the conjugated system in the α-benzal-γ-phenylcrotonolactone molecule, which may be involved in the absorption of light, there appear to be three possibilities



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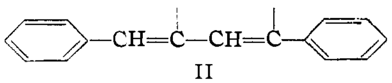

II

and (III) some cross conjugation of the above two systems. The K-bands of a large number of α,β-unsaturated ketones with a conjugated system of type (I) have maxima which fall within the range of 218 to 241 mμ. It would appear that the first possibility (I) in the crotonolactones studied is not the dominant system. An open chain analog of system (II) would be 1,1,3,4-tetraphenylbutadiene but no spectrographic data have been reported on this compound. However, a number of tetraphenylbutadienes have been studied[4] and of these only 1,1,4,4-tetraphenylbutadiene which cannot exist as *cis–trans* isomers is comparable with the α,γ-substituted crotonolactones.

Of the tetraphenylbutadienes studied, only 1,1,4,4-tetraphenylbutadiene exhibits two band spectra with no fine structure as do the crotonolactones. The relationships involved are illustrated in Fig. 1. The positions of the maxima of this butadiene are very similar with respect to shape, position and magnitude, to that of α-benzal-γ-phenylcrotonolactone, indicating that the conjugated system (II) is probably dominant in the crotonolactones.

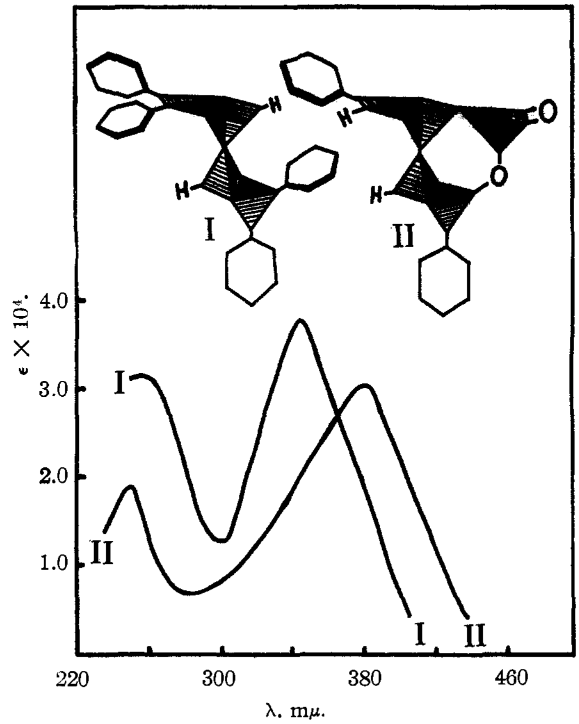

Fig. 1.—I, 1,1,4,4-Tetraphenylbutadiene redrawn from reference 4 in dioxane; II, α-benzal-γ-phenyl crotonolactone in 95% ethanol, absolute ethanol or glacial acetic acid.

Experimental

Absorption Spectra.—All spectra were determined with a model DU Beckman quartz spectrophotometer.

Measurements of the optical densities were made regularly at 2-mμ intervals within the range 220 to 300 mμ, at 5-mμ intervals between 300 and 400 mμ, and at 10-mμ intervals above 400 mμ; except in the neighborhood of maxima and minima where the interval was reduced to 1 mμ. Silica cells of a path length of 1 cm. were employed in the

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[4] Y. Hirshberg, E. Bergmann and F. Bergmann, THIS JOURNAL, **72**, 5120 (1950).

[5] W. Borsche, *Ber.*, **47**, 1108 (1914).

[6] E. P. Kohler, G. A. Hill and L. A. Bigelow, THIS JOURNAL, **39**, 2417 (1917).

determinations in the ultraviolet region and corex cells of the same thickness were used in the visible region. The solvent used for the samples and blank was 95% ethanol. All samples were dissolved in the solvent to a concentration of 10 mg. per l. at 20 to 25°. The results in the measurement of the absorption spectra of the azlactones are expressed as the molar extinction ϵ which was obtained from the optical density readings D and the molecular weights m by the relations $k = D/cl$ and $\epsilon = km$, where c is the concentration of the solution in mg. per ml. and l is the length of the cell.

Preparation of Materials.—The crotonolactones were prepared by the following general procedure: A mixture of 0.05 mole of benzaldehyde, 0.05 mole of the corresponding β-aroylpropionic acid, 0.05 mole of freshly fused sodium acetate and 16 ml. of acetic anhydride was heated in a beaker on a hot-plate until a complete solution was obtained. The beaker was then transferred to a steam-bath and heating was continued until crystals separated. The reaction was next poured into water, the solid product filtered with suction, washed with water and finally recrystallized repeatedly from 95% ethanol until a constant melting point was obtained. The yield, in general, ranged from 50–70%. The crotonolactones No. 6–12 of Table I are relatively insoluble in 95% ethanol (10 mg./100 ml.) and were recrystallized from chloroform.

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1-Nitrofluorenone

BY ERNEST H. HUNTRESS, EDWARD R. ATKINSON,[1] EDWARD A. HAM AND MERRICK S. TIBBETTS

RECEIVED OCTOBER 7, 1952

Recently the first synthesis of 1-nitrofluorenone has been described by Chase and Hey[2] who used the sequence: chloride of 2-methyl hydrogen 3-nitrophthalate → peroxide of this acid → methyl 3-nitrobiphenyl-2-carboxylate → 3-nitrobiphenyl-2-carboxylic acid → 1-nitrofluorenone (m.p. 188.5–189.5°). The substance was obtained later in very small amounts by the action of heat on diazotized 2-amino-6-nitrobenzophenone.[3] The structure of the substance was proved[2] by reduction to the known 1-aminofluorenone.[4]

The purpose of this Note is to describe our synthesis of 1-nitrofluorenone by three routes, two of which involve an intermediate used by Chase and Hey. These syntheses are of interest as practical preparative methods and involve several compounds described here for the first time.

(A).[5]—1-Aminofluorenone was diazotized and converted to the nitro compound by the action of sodium nitrite and mixed copper sulfites.[6]

(B).[5]—2-Aminobiphenyl → 2-acetaminobiphenyl → 3-nitro-2-acetaminobiphenyl → 3-nitro-2-aminobiphenyl → 3-nitro-2-cyanobiphenyl → 3-nitrobiphenyl-2-carboxylic acid → 1-nitrofluorenone.

(C).[7]—3-Nitrophthalimide → 6-nitrophthalamic acid → 6-nitro-2-aminobenzoic acid → methyl 6-nitro-2-aminobenzoate → methyl 3-nitrobiphenyl-2-carboxylate → 1-nitrofluorenone. The last step in this synthesis was carried out directly and avoided the isolation of 3-nitrobiphenyl-2-carboxylic acid.[2]

Experimental Part

All melting points are uncorrected.

1-Nitrofluorenone.—1-Aminofluorenone[4] was diazotized and treated with sodium nitrite and mixed copper sulfites.[6] There was obtained a 34% yield of bright yellow needles, m.p. 190.5–191.5° after recrystallization from glacial acetic acid. Mixed melting points of this product with those from our other syntheses were not depressed.

Anal. Calcd. for $C_{13}H_7O_3N$: C, 69.3; H, 3.14; N, 6.22. Found: C, 69.4; H, 3.37; N, 6.28.

Attempts to replace the diazo group by the cobaltinitrite method[8] or by the action of sodium nitrite on the diazonium fluoborate[9] were unsuccessful.

1-Nitrofluorenone Oxime.—0.91 g. of 1-nitrofluorenone and 1 g. of hydroxylamine hydrochloride were heated at 100° for five hours in 10 cc. of pyridine and 10 cc. of absolute alcohol. The reaction mixture was diluted with 200 cc. of ice-water and the oxime obtained in 97% yield, m.p. 198–199° dec.

Anal. Calcd. for $C_{13}H_8O_3N_2$: C, 65.0; H, 3.36; N, 11.7. Found: C, 65.0; H, 3.48; N, 11.4.

The infrared absorption spectrum of this compound is available.[5] The oxime was soluble in 2 N sodium hydroxide. It was hydrolyzed to the parent ketone by heating in 65% sulfuric acid at 125° for two hours.

3-Nitro-2-cyanobiphenyl.—This was prepared from 3-nitro-2-aminobiphenyl[10] by a procedure similar to that used for the isomeric 5-nitro compound.[11] We obtained a 32% yield of crude material, m.p. 124–130°, which was sublimed to give colorless needles, m.p. 131.5–132.0°.

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.6; H, 3.60; N, 12.5. Found: C, 69.4; H, 3.73; N, 12.6.

3-Nitrobiphenyl-2-carboxylic Acid.—Hydrolysis of the hindered nitrile by the procedure used for the 5-nitro isomer[11] was difficult. The procedure of Sudborough[12] was used to obtain 35% yields of colorless needles, m.p. 200–205°; Chase and Hey[2] record m.p. 200.5–201.5°. The acid was cyclized by heating in concentrated sulfuric acid for ten minutes at 115° and a 93% yield of 1-nitrofluorenone obtained.

Methyl 6-Nitro-2-aminobenzoate.—6-Nitro-2-aminobenzoic acid was prepared from Eastman Kodak Co. 3-nitrophthalimide by way of 6-nitrophthalamic acid.[13,14] 2.4 g. (0.0134 mole) of the acid was dissolved in the minimum amount of dry ether and esterified with diazomethane in ether by the conventional procedure. 2.45 g. (95% yield) of crude product was washed with dilute bicarbonate solution and then recrystallized from methyl alcohol–water to give orange crystals, m.p. 105–108°.

Anal. Calcd. for $C_8H_8O_4N_2$: N, 14.3. Found: N, 14.5, 14.6.

Satisfactory values for the saponification equivalent in aqueous solution were not obtained but the acid was recovered from the partially hydrolyzed samples. We were unable to prepare the methyl ester by the conventional procedure used with isomeric nitroaminobenzoic acids,[15] by the use of methyl alcohol and ethylene dichloride,[16] by the method of Newman[17] or by the use of boron trifluoride.[18] The latter method resulted in decarboxylation.

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[1] Address communications to E. R. Atkinson, Dewey & Almy Chemical Co., 62 Whittemore Avenue, Cambridge 40, Mass.

[2] B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 553 (1952).

[3] A. J. Nunn, K. Schofield and R. S. Theobald, *ibid.*, 2797 (1952).

[4] E. H. Huntress, K. Pfister and K. H. T. Pfister, THIS JOURNAL, **64**, 2845 (1942).

[5] E. A. Ham, Ph.D. Thesis, Massachusetts Institute of Technology, 1951.

[6] H. H. Hodgson, A. P. Mahadevan and E. R. Ward, *J. Chem. Soc.*, 1392 (1947); *Org. Syntheses*, **28**, 52 (1948).

[7] M. S. Tibbetts, M.S. Thesis, University of New Hampshire, 1951.

[8] H. H. Hodgson and E. Marsden, *J. Chem. Soc.*, 22 (1944); H. H. Hodgson and E. R. Ward, *ibid.*, 127 (1947).

[9] E. B. Starkey, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 225.

[10] S. Sako, *Bull. Chem. Soc. Japan*, **9**, 55 (1934).

[11] F. E. Ray and J. G. Barrick, THIS JOURNAL, **70**, 1492 (1948).

[12] J. J. Sudborough, *J. Chem. Soc.*, **67**, 601 (1895).

[13] R. Kahn, *Ber.*, **35**, 3857 (1902).

[14] M. T. Bogert and V. J. Chambers, THIS JOURNAL, **27**, 649 (1905).

[15] J. J. Blanksma and D. Hoegen, *Rec. trav. chim.*, **65**, 335 (1946).

[16] R. O. Clinton and S. C. Laskowski, THIS JOURNAL, **70**, 3135 (1948).

[17] M. S. Newman, *ibid.*, **63**, 2431 (1941).

[18] F. J. Sowa and J. A. Nieuwland, *ibid.*, **58**, 271 (1936).

Methyl 3-Nitrobiphenyl-2-carboxylate.—Methyl 6-nitro-2-aminobenzoate was diazotized and subjected to the Gomberg reaction with benzene as described previously for the analogous case of methyl 5-nitro-2-aminobenzoate.[19] A 7% yield of colorless crystals, m.p. 121°, was obtained; Chase and Hey[2] record m.p. 121.5–122.5°. 0.3 g. of this substance was converted directly to yield 50 mg. of 1-nitrofluorenone by heating in 5 cc. of concentrated sulfuric acid for one hour at 100°.

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[19] I. M. Heilbron, D. H. Hey and R. Wilkinson, *J. Chem. Soc.*, 115 (1938).

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A Novel N-Alkylation Reaction

BY IRVING ALLAN KAYE, CHESTER L. PARRIS AND NATHAN WEINER

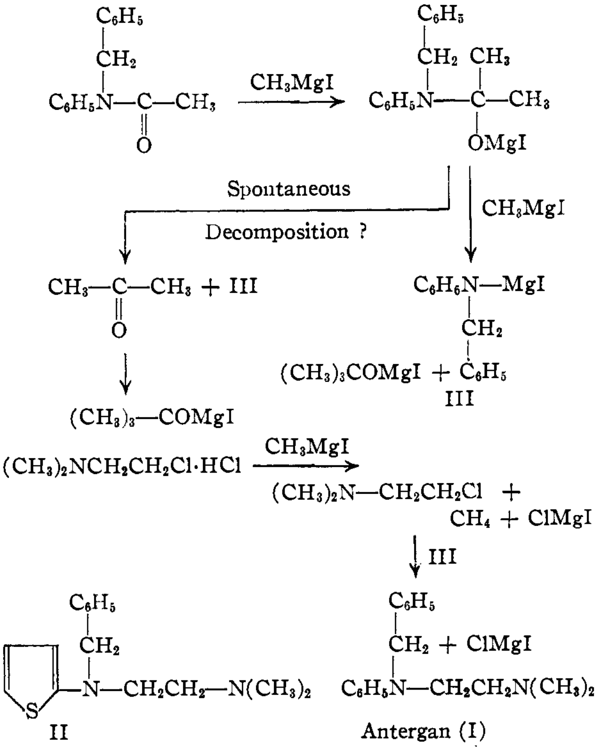
RECEIVED SEPTEMBER 15, 1952

Attempts to prepare the thiophene analog (II) of Antergan (I)[1] by methods which have been successfully employed in the synthesis of its thiazole[2] and pyridine[3] isosteres have not been found practical due to the low reactivity of the halogen in 2-bromothiophene[4] and the extreme air-sensitivity of 2-thienylamines.[5] Stability of the latter in air is enhanced considerably by acetylation and the amides, in the form of N-sodio derivatives, can be alkylated.[5] Since N-benzyl-N-(2-thienyl)-acetamide, obtained in good yield by heating 2-acetamidothiophene and benzyl chloride in toluene solution in the presence of lithium amide, was on hand, a method was sought whereby this amide could be converted directly to the tertiary amine (II) without isolation of the presumably unstable 2-benzylaminothiophene. It appeared possible to accomplish this by interaction of the amide with a Grignard reagent, a method available for the preparation of ketones[6] which yields the corresponding halomagnesium amide (RR'N–MgX) as a by-product. Treatment of the reaction mixture with an alkyl halide should form the desired tertiary amine.

The preparation of Antergan by this method was undertaken as a model experiment. N-Benzyl-N-phenylacetamide was treated with an excess of methylmagnesium iodide followed by dimethylaminoethyl chloride hydrochloride. The quantity of the Grignard reagent employed was sufficient to liberate the aminoalkyl halide from its salt. The product, Antergan (I), was obtained in 53.5% yield. Its picrate was identical with that obtained from a product prepared by the alkylation of N-benzylaniline with dimethylaminoethyl chloride hydrochloride in the presence of lithium amide.

When the reaction was repeated with N-benzyl-N-(2-thienyl)-acetamide in a nitrogen atmosphere, a pale yellow oil was obtained which remained unchanged for weeks when kept at room temperature in an inert atmosphere but which decomposed rapidly when exposed to air. Its elementary analysis revealed that it was not the desired diamine (II) and attempts to establish its structure have been unsuccessful thus far.

The procedure is illustrated as



Experimental[7]

N,N-Dimethyl-N'-benzyl-N'-phenylethylenediamine (I). **Alkylation of N-Benzylaniline.**—A mixture of 9.2 g. (0.05 mole) of N-benzylaniline, 8.7 g. (0.06 mole) of dimethylaminoethyl chloride hydrochloride, 2.8 g. (0.12 mole) of lithium amide (98% purity) and 100 ml. of dry benzene was refluxed for 25 hours. The reaction mixture was then filtered and the residue washed with benzene. The solvent was removed from the filtrate by distillation and the residue distilled *in vacuo*. There was obtained 11.8 g. (92%) of a pale yellow oil distilling at 159–163° (2 mm.). The picrate prepared in ether and recrystallized once from isopropyl alcohol, melted at 149–150°. Huttrer[8] reported a boiling point of 195–196° (0.03 mm.) and a melting point of 149–154° (dec.) for the picrate; Carrara[9] found that his product distilled at 157–158° (1 mm.).

From **N-Benzyl-N-phenylacetamide.**—To 200 ml. of an ether solution of methylmagnesium iodide, prepared from 8.5 g. (0.35 mole) of magnesium turnings and 49.7 g. (0.35 mole) of methyl iodide, 21.3 g. of N-benzyl-N-phenylacet-

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[1] Antergen is the trade mark for N,N-dimethyl-N'-benzyl-N'-phenylethylenediamine, Rhône-Poulenc.

[2] C. W. Sondern and P. J. Breivogel, U. S. Patent 2,440,703 (May 4, 1948), prepared N,N-dimethyl-N'-benzyl-N'-(2-thiazolyl)-ethylenediamine by heating 2-bromothiazole with N,N-dimethyl-N'-benzylethylenediamine.

[3] C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946), prepared Pyribenzamine [N,N-dimethyl-N'-benzyl-N'-(2-pyridyl)-ethylenediamine] and other 2-pyridyl tertiary, as well as secondary, amines by alkylating a 2-pyridylamine with an alkyl halide in the presence of either sodamide or lithium amide.

[4] Employing the same conditions which were used successfully in condensing 2-bromopyridine [N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949)] with ethanolamine, no product could be isolated from a mixture of 2-bromothiophene and the aminoalcohol. The reactants were recovered even after prolonged heating at 250° in the presence of copper powder.

[5] I. W. Steinkopf, "Die Chemie Des Thiophens," reprinted by Edwards Brothers, Inc., Ann Arbor, Mich., 1944, pp. 59–60.

[6] W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1948, p. 276.

[7] Melting points are corrected, boiling points are not.

[8] C. P. Huttrer, *Enzymologia*, **12**, 278 (1947).

[9] G. Carrara, *et al.*, *Chimica e Industria (Milan)*, **28**, 9 (1946); *C. A.*, **40**, 7241 (1946)

amide[10] was added in small portions. The mixture was refluxed, with stirring, for 1.5 hours. After chilling in an ice-bath, 21.6 g. (0.15 mole) of dimethylaminoethyl chloride hydrochloride was added in small quantities to the stirred reaction mixture which was then refluxed for an additional 2 hours. Fifty-five ml. of a saturated aqueous ammonium chloride solution was added to the stirred suspension. The magnesium salts were removed by filtration and washed with ether. The filtrate was dried over anhydrous potassium carbonate and then distilled, initially at atmospheric pressure to remove the ether and afterwards *in vacuo*. The product, collected at 98–107° (0.05 mm.), weighed 13.8 g. (53.5%). The picrate melted at 147.5–149° after two recrystallizations from isopropyl alcohol. Mixed with a sample prepared by alkylating N-benzylaniline, the melting point was not depressed (147.5–149.5°).

N-Benzyl-N-(2-thienyl)-acetamide.[11]—A mixture of 70.6 g. (0.5 mole) of 2-acetamidothiophene,[5] 75.9 g. (0.6 mole) of benzyl chloride and 14.1 g. (0.6 mole) of lithium amide (98% purity) in 500 ml. of dry toluene was refluxed for 24 hours. The suspended solids were removed by filtration and washed with toluene. The filtrate was stripped of solvent and the residue distilled *in vacuo*. The pale yellow distillate, b.p. 137–143° (0.5 mm.), weighed 96.7 g. (84%). On redistillation, the fraction (78.7 g.) distilling at 133–137° (0.4 mm.) was collected and analyzed.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.48; H, 5.66; N, 6.06; S, 13.86. Found: C, 67.60; H, 5.68; N, 6.15; S, 13.82.

Attempts to Prepare N,N-Dimethyl-N'-benzyl-N'-(2-thienyl)-ethylenediamine (II) from N-Benzyl-N-(2-thienyl)-acetamide.—Prepared in exactly the same manner and on the same scale as I, except that the reaction was performed in an atmosphere of nitrogen, the product which was obtained distilled at 129–132° (0.09 mm.) and weighed 12.1 g. On redistillation, the light yellow oil, collected at 118–122° (0.08 mm.), weighed 9.1 g. No salt could be prepared which was stable in air. *Anal.* (under nitrogen). Calcd. for $C_{15}H_{20}N_2S$: C, 69.17; H, 7.74; N, 10.76; S, 12.31; mol. wt., 260.4; neut. equiv., 260.4. Found: C, 72.40, 72.59; H, 8.36, 8.34; N, 5.73, 5.71; S, 13.42, 13.68; mol. wt.,[12] 284; neut. equiv.,[12] 262.0.

Acknowledgment.—The authors wish to thank Endo Products, Inc., for support (in part) of this investigation.

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[10] Prepared by refluxing N-benzylaniline with a 3 molar excess of acetic anhydride for 4 hours. The product was obtained in 91% yield as a colorless oil, b.p. 110–125° (0.04 mm.). On chilling in a bath of solid carbon dioxide and trichloroethylene, the distillate solidified. After washing with cold hexane and air-drying, the solid melted at 57–58°. The m.p. has been given as 58° (N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947, p. 406).

[11] The authors are indebted to Mr. Dave Regenbogen for carrying out the initial preparation of this compound.

[12] The validity of these two results is questionable. In the Rast molecular weight determination darkening occurred on heating which made it difficult for the analyst to determine the melting point. The end-point in the neutralization equivalent titration [method of J. S. Fritz, *Anal. Chem.*, **22**, 1028 (1950)] was similarly obscured.

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Iodine-catalyzed Benzoylations

BY IRVING ALLAN KAYE, HOWARD C. KLEIN AND WILLIAM J. BURLANT[1]

RECEIVED SEPTEMBER 18, 1952

In connection with another investigation[2] involving the condensation of some benzohydryl chlorides with heterocyclic amines, several substituted benzophenones and 2-benzoylthiophenes[3] were prepared, in yields comparable with those obtained by the Friedel–Crafts method, using the iodine-catalyzed acylation procedure of Hartough and Kosak.[4]

N,N-Dimethylaniline and benzoyl chloride, in the presence of iodine, yielded, instead of the expected *p*-benzoylated product, demethylated derivatives of aniline; the extent of demethylation depended upon the amount of condensing agent employed.[5]

In addition to catalyzing acylation reactions, it has been found that iodine can promote the benzylation of anisole.[6] This, however, does not seem to be a very general reaction, for no product was obtained from reactions with thiophene or 2-chlorothiophene, although these compounds are easily benzoylated in the presence of iodine.

Experimental[7]

4-Chloro-4'-methoxybenzophenone. Method A.—A mixture of 10.8 g. (0.10 mole) of anisole, 19.3 g. (0.11 mole) of *p*-chlorobenzoyl chloride[8] and 2.5 g. of iodine was refluxed for 15 hours. Refluxing was continued for 15 minutes longer after the cautious addition of 120 ml. of isopropyl alcohol. The chilled mixture was then filtered and the precipitate washed with the cold solvent and air-dried. One recrystallization of the tan solid, weighing 23.0 g. (93%), from isopropyl alcohol, raised the melting point from 115–119° to 124–125°.[9]

When the reactants were refluxed for 1, 5 and 24 hours, the product was obtained in yields of 43, 84 and 85%, respectively. In the presence of 6.0, 6.4, 12.8, 25.0, 30.0 and 40.0 g. of iodine, a mixture of 1.0 mole of anisole and 0.5 mole of *p*-chlorobenzoyl chloride, heated 15 hours, gave yields of 20, 29, 62, 72, 57 and 56%, respectively.

1-Benzoyl-2-methoxynaphthalene. Method B.—A mixture of 71.1 g. (0.45 mole) of 2-methoxynaphthalene, 42.3 g. (0.30 mole) of benzoyl chloride and 4.5 g. of iodine, was refluxed 7.5 hours and subsequently dissolved in 200 ml. of ether. The brown solution was washed twice with 50-ml. portions of 10% aqueous potassium carbonate solution and twice more with 50 ml. of 10% sodium bisulfite solution. After drying over anhydrous potassium carbonate, the ether was removed and the residual liquid distilled *in vacuo*. The colorless distillate, b.p. 200–205° (2 mm.), weighing 56.5 g. (72%), solidified on cooling. The product melted at 124–125° after two recrystallizations from heptane.[10]

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[1] From the M.A. Thesis of W. J. Burlant submitted to the Graduate Faculty of Brooklyn College, September, 1951.

[2] I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952).

[3] No evidence of ability to retard the growth of sarcoma 180 in mice was shown by 2-(*p*-methoxybenzoyl)-thiophene, 2-(*p*-chlorobenzoyl)-thiophene, 2,4,6-trimethylbenzophenone, 4-chloro-4'-methoxybenzophenone, 4-chlorobenzohydryl chloride, 4-methoxybenzohydryl chloride and 4,4'-dimethoxybenzohydryl chloride. The authors wish to thank Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research for this information.

[4] H. D. Hartough and A. I. Kosak, THIS JOURNAL, **68**, 2639 (1946), acylated thiophene and furan. More recently S. Chodroff and H. C. Klein, *ibid.*, **70**, 1647 (1948), and D. L. Turner, *ibid.*, **71**, 612 (1949), prepared some aromatic ketones by a similar procedure.

[5] Since N,N-dimethylaniline has been found to undergo nuclear iodination with the liberation of hydrogen iodide under conditions similar to those employed in this reaction (*cf.* W. Militzer, E. Smith and E. Evans, *ibid.*, **63**, 436 (1941)), the hydroiodide of some of the unreacted compound may have been formed initially and subsequently undergone thermal decomposition with the formation of methyl iodide and either aniline or N-methylaniline. Our isolation of the methiodide of N,N-dimethylaniline by heating this amine with iodine, in the absence of an acylating agent, would tend to substantiate this inference.

[6] C. D. Nenitzescu, D. A. Isacescu and C. N. Ionescu, *Ann.*, **491**, 210 (1931), have obtained *p*-methoxydiphenylmethane in unstated yield by condensation of benzyl chloride with anisole in the absence of a catalyst.

[7] Melting points are corrected; boiling points are not.

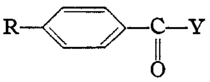
[8] Samples of *p*-chlorobenzoyl chloride and anisoyl chloride were generously supplied by the Heyden Chemical Corporation.

[9] P. P. Peterson, *Am. Chem. J.*, **46**, 325 (1911), obtained an 85% yield using aluminum chloride.

[10] R. R. Galle, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 402 (1938); *C. A.*, **32**, 7910 (1938).

TABLE I

KETONES OF FORMULA



R[a]	Y	Iodine, g.	Reflux time, hr.	Method	Yield,[b] %	M.p., °C.	B.p. °C.	B.p. Mm.
OCH$_3$ (1:2)	*p*-Anisyl	7.7	15	A	84	142–144[c]		
H (0.5:1)	*p*-Xenyl	15.0	14	B	50	102–103[d]	156–158	0.1
Cl (1.1:1)	*p*-Anisyl	25	15	A	93	124–125		
NO$_2$ (1:2)	*p*-Anisyl	40	15	B	57	126–128[e]	192–194	0.9
H (1.1:1)	Veratryl	2	15	[f]	81[g]	102–103[h]	162–170	2.0
H (0.5:1)	2-Mesityl	20	10	B	65		141–143[i]	0.03
H (1:2)	*p*-Ethoxyphenyl	8	15	B	83[j]		129[j]	0.6
H (1:1.5)	2-Methoxynaphthyl	15	7.5	B	72	124–125[k]	200–205	2.0
OCH$_3$ (1:2)	2-Thienyl	2	8	A	76[l]	76–77		
Cl (1:1)	2-Thienyl	6	8	A	50[m]	99.5–100[m]		
H (1:1)	2-(5-Chlorothienyl)	20	9	A	34[n]	63–64[k]		
Cl (1:1)	2-(5-Chlorothienyl)	20	15	A	58	105–106[o]		

[a] Figures in parentheses refer to mole ratios of reactants, the first number representing the moles of acylating agent, *p*-R—C$_6$H$_4$COCl. [b] All compounds were recrystallized from isopropyl alcohol unless otherwise stated. [c] H. Schnackenberg and R. Scholl, *Ber.*, **36**, 654 (1903), using aluminum chloride, reported no yield. [d] L. Long and H. Henze, THIS JOURNAL, **63**, 1939 (1941), obtained a 75% yield with aluminum chloride as condensing agent. [e] *Anal.* Calcd. for C$_{14}$H$_{11}$NO: N, 5.45. Found: N, 5.38. N. Böeseken, *Rec. trav. chim.*, 19, 25 (1900), found a melting point of 121°. [f] At the end of the reflux period, the reaction mixture was distilled *in vacuo*. [g] A small amount (2.3 g.) of a higher boiling fraction, b.p. 207–210° (0.04 mm.), was also obtained. This presumably dibenzoylated veratrole gave a mono-2,4-dinitrophenylhydrazone which melted at 190–191° after recrystallization from ethanol. *Anal.* Calcd. for C$_{28}$H$_{24}$N$_2$O$_4$: C, 63.86; H, 4.07. Found: C, 63.04; H, 3.93. [h] Recrystallized from hexane. B. König and St. V. Kostanecki, *Ber.*, **39**, 4027 (1906), gave no yield for their product. [i] P. J. Montagne, *Rec. trav. chim.*, **27**, 327 (1908). [j] Although C. Torres, *Anales soc. españ. fís. quím.*, **24**, 82 (1926); *C. A.*, **20**, 2158 (1926), reported that the oxime of his product melted at 135–136°, the ketoxime melted at 151–152° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for C$_{15}$H$_{15}$NO$_2$: C, 74.66; H, 6.27. Found: C, 74.53; H, 6.21. [k] Recrystallized from heptane. [l] Employing equimolecular quantities of the reactants, the product was obtained in 62% yield. *Anal.* Calcd. for C$_{12}$H$_{10}$O$_2$S: S, 14.65. Found: S, 14.28. The compound has recently been prepared by Ng. D. Buu-Hoï, Ng. Hoán and Ng. D. Xuong, *Rec. trav. chim.*, **69**, 1083 (1950), in 80% yield. [m] The yield dropped to 35% when 2.0 g. of iodine was employed. The product was recrystallized from hexane. There was also isolated 13.0 g. of di-(4-chlorobenzoyl)-thiophene, m.p. 238–239° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for C$_{18}$H$_{10}$Cl$_2$O$_2$S: Cl, 19.62. Found: Cl, 19.38. Buu-Hoï and co-workers (*cf.* preceding reference) obtained a 71% yield of 2-(4-chlorobenzoyl)-thiophene. [n] *Anal.* Calcd. for C$_{11}$H$_7$ClOS: C, 59.32; H, 3.06; Cl, 15.95. Found: C, 59.24; H, 3.17; Cl, 15.95. Buu-Hoï, Hoán and Xuong [*cf.* note (*l*)] reported a 53% yield. [o] *Anal.* Calcd. for C$_{11}$H$_6$Cl$_2$OS: C, 51.38; H, 2.35; Cl, 27.58; S, 12.47. Found: C, 51.48; H, 2.44; Cl, 27.40; S, 12.43. The conventional Friedel–Crafts procedure [*cf.* note (*l*)] afforded a 77% yield.

Reaction of N,N-Dimethylaniline with Benzoyl Chloride.—A solution of 20.0 g. of iodine, 70.3 g. (0.50 mole) of benzoyl chloride and 121.2 g. (1.0 mole) of N,N-dimethylaniline was refluxed for 10 hours, cooled, washed with dilute sodium hydroxide, dried over anhydrous potassium carbonate and distilled *in vacuo*. The yellow oil, b.p. 189° (0.9 mm.), weighing 45.0 g., crystallized on cooling and was recrystallized from hexane. The white crystals, m.p. 164–165°, showed no depression in melting point on admixture with an authentic sample of benzanilide.[11]

Anal. Calcd. for C$_{13}$H$_{11}$NO: C, 79.18; H, 5.57; N, 7.30. Found: C, 79.23; H, 5.58; N, 7.13.

In a similar manner there was obtained 35.3 g. of a red oil, b.p. 121° (1.0 mm.), from a mixture of 24.2 g. (0.20 mole) of the tertiary amine, 42.2 g. (0.30 mole) of benzoyl chloride and 0.8 g. of iodine. The amide, crystallized from heptane and recrystallized to constant melting point from the same solvent, melted at 63.5–64.5°.[11]

Anal. Calcd. for C$_{14}$H$_{13}$NO: C, 79.59; H, 6.20; N, 6.13. Found: C, 79.54; H, 6.28; N, 6.24.

Hydrolytic cleavage with hydrochloric acid[11] afforded benzoic acid, identified by the fact that its melting point was not depressed when mixed with an authentic sample, and N-methylaniline, identified similarly as its hydrochloride, m.p. 121–123°.

Reaction of N,N-Dimethylaniline with Iodine.—A mixture of 24.2 g. (0.2 mole) of N,N-dimethylaniline and 8.0 g. of iodine, refluxed for 3 hours, deposited, by sublimation in an air condenser during the reflux period, 6.0 g. of the methiodide of N,N-dimethylaniline, m.p. 213–214°. Mixed with an authentic sample, there was no depression in melting point.

Anal. Calcd. for C$_9$H$_{14}$IN: C, 41.22; H, 5.34. Found: C, 40.99; H, 5.35.

Benzylation of Anisole.—From a mixture of 32.4 g. (0.3 mole) of anisole, 18.9 g. (0.15 mole) of benzyl chloride and 6.0 g. of iodine, refluxed 14 hours, there was isolated (Method B) 15.0 g. (51%) of a yellow oil, b.p. 106–108° (0.04 mm.). A sample of the distillate, after hydrobromic acid demethylation, yielded *p*-benzylphenol, m.p. 84.5–85.5°.[12]

There was also obtained 9.6 g. (22%) of a higher boiling fraction, b.p. 165–167° (0.09 mm.), presumed to be 2,4-dibenzylanisole.

Anal. Calcd. for C$_{21}$H$_{20}$O: C, 87.46; H, 6.99. Found: C, 87.04; H, 6.67.

From mixtures of 1.0 mole of thiophene or 2-chlorothiophene, 0.5 mole of benzyl chloride and 7.5 g. of iodine which were refluxed 14 hours, only starting materials could be recovered.

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(11) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Company, New York, N. Y., 1947, pp. 185, 403 and 413.

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd edition, 1948, p. 272.

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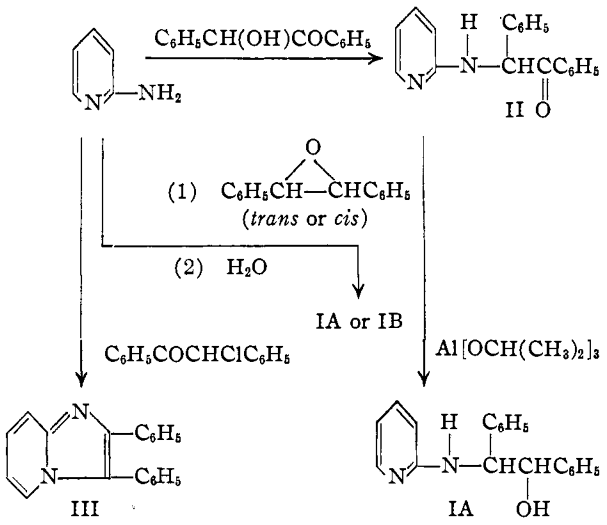
Use of 2-Aminopyridine in the Voigt Reaction

BY IRVING ALLAN KAYE, CHESTER L. PARRIS AND WILLIAM J. BURLANT

RECEIVED SEPTEMBER 18, 1952

The synthesis of the two stereochemical isomers of N-(2-pyridyl)-1,2-diphenyl-2-aminoethanol (I) was desired as part of a program involving the preparation for antimitotic evaluation of a number of N-substituted compounds related to 1,2-diphenylethylamine.[1,2] The products were obtained from, and their stereochemical configurations assigned[3,4] on the basis of, the reaction between 2-aminopyridine and the isomeric stilbene oxides in the presence of lithium amide. The *erythro*-aminoalcohol (IA) (from *trans*-stilbene oxide) was more satisfactorily prepared by aluminum isopropoxide reduction of N-(2-pyridyl)-desylamine (II). The preparation of the latter from 2-aminopyridine and benzoin represents an extension of the Voigt reaction to a heterocyclic amine containing a nitrogen–carbon–nitrogen system. This does not appear to be general, however, in view of the failure of 2-benzylaminopyridine, 2-aminopyrimidine, 2-aminothiazole or 2-aminolepidine to react.

Heating a mixture of 2-aminopyridine with desyl chloride gave the cyclized product (III), 2,3-diphenylimidazo[1,2-a]pyridine, instead of the desired ketone (II).



Experimental[5]

Intermediates.—α-Phenylcinnamic acid, m.p. 163–167°, was prepared in 73% yield by the method of Buckles and Hausman[6] and purified by acidification of its ether-washed alkaline solution. Decarboxylation, by refluxing a quinoline solution of the compound in the presence of copper chromite[7] for 3 hours instead of the recommended 1.5 hours,[8] gave an 80% yield of *cis*-stilbene, b.p. 128–135° (2 mm.), and a 7% yield of *trans*-stilbene, m.p. 121–123°. The latter was better obtained by reduction of benzoin.[9,10] The stilbene oxides were prepared by the procedure for styrene oxide.[11] *cis*-Stilbene oxide,[8] b.p. 126–132° (4 mm.), was isolated in 72% yield, after a reaction time of 40 hours; the *trans* isomer,[3] m.p. 64–67°, obtained in 80% yield, required 134 hours.

Benzoylcarbinol, prepared from phenacyl bromide by the potassium formate method of Julian, *et al.*,[12] for the synthesis of α-hydroxy-β-phenylpropiophenone, was obtained in 72% yield, m.p. 89.5–90.5°.[13]

Anal. Calcd. for $C_8H_8O_2$: C, 70.60; H, 5.93. Found: C, 70.64; H, 5.96.

threo-**N-(2-Pyridyl)-1,2-diphenyl-2-aminoethanol (IB).**—A mixture of 4.75 g. (0.05 mole) of 2-aminopyridine, 10.8 g. (0.055 mole) of *cis*-stilbene oxide, 1.3 g. of 98% lithium amide and 100 ml. of dry toluene was refluxed for 24 hours. On treating the cooled reaction mixture with ice-water, a precipitate appeared. This was separated by filtration, washed with water and air-dried. The tan powder weighed 8.5 g., m.p. 170–175°. An additional 0.35 g. of product, m.p. 168–173°, obtained by concentrating the toluene solution, raised the yield to 61%. The melting point remained constant at 177.5–178.5° after three recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25. Found: C, 79.02; H, 6.51.

N-(2-Pyridyl)-desylamine (II).—A mixture of 63.7 g. (0.3 mole) of benzoin, 31.0 g. (0.33 mole) of 2-aminopyridine, 200 ml. of toluene and 6 ml. of concd. hydrochloric acid was refluxed for 20 hours; the water separating during the reaction was collected in a moisture trap. After cooling to room temperature, a small amount of an unidentified yellow solid was removed by filtration. The solvent was removed from the filtrate by a vacuum distillation and the oily residue crystallized by rubbing with hexane. The orange-yellow solid, m.p. 79–91°, weighing 72.1 g. (83%) after air-drying, was recrystallized four times from isopropyl alcohol, m.p. 106–108°.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.57; H, 5.60; N, 9.68.

erythro-**N-(2-Pyridyl)-1,2-diphenyl-2-aminoethanol (IA).**—From 86.5 g. (0.3 mole) of N-(2-pyridyl)-desylamine and 121.4 g. of a 50% solution of aluminum isopropoxide in 400 ml. of dry isopropyl alcohol[14] there was obtained 83 g. (95%) of crude product which melted at 156.5–157.5° after five recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.61; H, 6.28; N, 9.82.

This isomer was also obtained, in 65% yield, but less conveniently, by lithium aluminum hydride reduction[15] of the aminoketone, m.p. 154–156°. From *trans*-stilbene oxide, by the method described for the preparation of the *threo*-aminoalcohol (IB), there was obtained a 50% yield of crude product which melted at 154–156° after two recrystallizations from isopropyl alcohol. There was no depression in melting point on admixture with product prepared by either the aluminum isopropoxide or lithium aluminum hydride reduction of the aminoketone.

2,3-Diphenylimidazo[1,2-a]pyridine (III).—A mixture of 11.5 g. (0.05 mole) of desyl chloride[16] and 14.1 g. (0.15 mole) of 2-aminopyridine was heated in an oil-bath maintained at 110–120° for three hours. The melt was dissolved in benzene. The solution was washed with water and the solvent then removed by distillation. The oily residue, crystallized by rubbing with hexane, was recrystallized from isopropyl alcohol. The product weighed 5.10 g. (38%), m.p. 145–150°. The melting point remained constant at 151.5–153° after two further recrystallizations from isopropyl alcohol.

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[1] I. A. Kaye and C. L. Parris, *J. Org. Chem.*, **16**, 1859 (1951).

[2] I. A. Kaye and C. L. Parris, This Journal, **74**, 1566 (1952).

[3] R. E. Lutz, J. A. Freek and R. S. Murphey, *ibid.*, **70**, 2015 (1948).

[4] R. E. Lutz and R. S. Murphey, *ibid.*, **71**, 478 (1949).

[5] Melting points are corrected, boiling points are not.

[6] R. E. Buckles and E. A. Hausman, This Journal, **70**, 415 (1948), and R. E. Buckles, M. P. Bellis and W. D. Coder, Jr., *ibid.*, **73**, 4972 (1951).

[7] W. A. Lazier and H. R. Arnold in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 142.

[8] T. W. J. Taylor and C. E. J. Crawford, *J. Chem. Soc.*, 1130 (1934). The reference in note 28(a) of ref. (3) to this publication for the preparation of *cis*-stilbene oxide is in error.

[9] R. L. Shriner and A. Berger in *Org. Syntheses*, **23**, 86 (1943).

[10] A sample of benzoin was generously supplied by the Heyden Chemical Corp.

[11] H. Hibbert and P. Burt, in "Organic Syntheses," Coll. Vol. I, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 494.

[12] P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, This Journal, **67**, 1203 (1945).

[13] G. R. Cebrián, *Anales real soc. españ. fís y quím., Ser. B*, **44**, 587 (1948); *C. A.*, **42**, 8176 (1948), obtained a 60% yield by the conventional potassium acetate procedure.

[14] A. L. Wilds in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, chapter 5.

[15] W. G. Brown in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, chapter 10.

[16] A. M. Ward in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.77; H, 5.17; N, 10.14.

Under milder conditions, cyclization also occurred when phenacyl bromide was used in place of desyl chloride. Using the procedure of Julian, *et al.*, for the preparation of α-anilinopropiophenone[12] there was obtained a quantitative yield of 2-phenylimidazo[1,2-a]pyridine, m.p. 135–136°, after two recrystallizations from hexane. With sodium carbonate or sodium acetate replacing the sodium bicarbonate in this procedure, the yield dropped to 88 and 33%, respectively.

Anal. Calcd. for $C_{13}H_{10}N_2$: C. 80.38; H, 5.19. Found: C, 80.14; H, 5.34.

The picrate melted at 236–238° after two recrystallizations from acetone.[17]

Anal. Calcd. for $C_{13}H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 53.90; H, 3.10. Found: C, 54.39; H, 3.06.

Reaction of 2-Aminopyridine with Benzoylcarbinol.—In an effort to gain additional insight into the mechanism of the Voigt reaction,[3,12] benzoylcarbinol was treated with 2-aminopyridine. Using the procedure employed in the preparation of N-(2-pyridyl)-desylamine (II), there was obtained from 13.6 g. (0.1 mole) of benzoylcarbinol, 10.3 g. (0.11 mole) of 2-aminopyridine, 100 ml. of toluene and 2 ml. of concd. hydrochloric acid, 5.5 g. of a pale yellow solid, b.p. 142–144° (10 mm.). The compound melted at 150° after two recrystallizations from isopropyl alcohol and showed no depression in melting point when mixed with an authentic sample of 2-aminopyridine benzoate melting at 152–153°.

Anal. Calcd. for $C_3H_6N_2 \cdot C_7H_6O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.17; H, 5.42; N, 12.82.

The picrate of the free base melted at 216–218°. No depression in melting point was observed on admixture with an authentic sample of 2-aminopyridine picrate.[18]

Acknowledgment.—This investigation was supported by a research grant from the National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service.

[17] N. Campbell and E. B. McCall. *J. Chem. Soc.*, 2411 (1951). The picrate of their cyclized product, m.p. 228–229°, did not give a satisfactory nitrogen analysis.

[18] W. Marckwald, *Ber.*, **27**, 1317 (1894).

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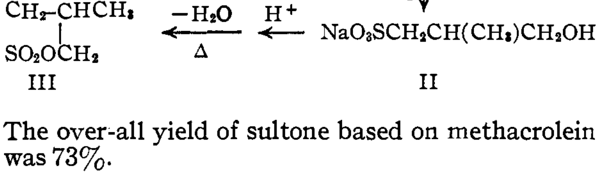
Reactions of Acrolein and Related Compounds. VIII. Preparation of Sultones

BY CURTIS W. SMITH, DOUGLAS G. NORTON AND SEAVER A. BALLARD

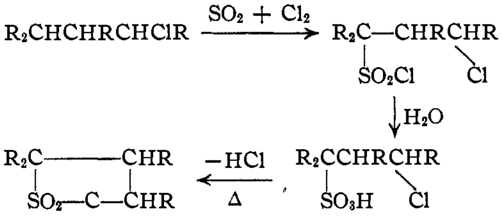
RECEIVED SEPTEMBER 16, 1952

A novel and convenient synthesis of the known and highly reactive 3-hydroxy-2-methyl-1-propanesulfonic acid sultone hereinafter called β-methyl-γ-propanesultone (III) has been realized and may be outlined as



The over-all yield of sultone based on methacrolein was 73%.

Several aliphatic γ-sultones have been previously prepared by Helberger[1,2] and by Asinger[3] and their associates. The method used by these workers involved sulfochlorination of alkyl halides as shown in the scheme



The aliphatic γ-sultones have been shown[1,4] to undergo readily a wide variety of reactions.

Earlier attempts by Marckwald and Frahne to synthesize 3-hydroxy-1-propanesulfonic acid sultone, γ-propanesultone, were unsuccessful.[5] They added bisulfite to acrolein and to allyl alcohol and reduced the acrolein adduct with potassium amalgam presumably to the 3-hydroxy-1-propanesulfonate, but were unable to complete the conversion to the sultone.

In the present process a slight excess (2%) of methacrolein was added to the aqueous solution of sodium bisulfite with the view of removing as completely as possible any bisulfite which might poison the catalyst in the subsequent hydrogenation. The resultant solution was hydrogenated directly over Raney nickel. Saturation of the concentrated reaction mixture with hydrogen chloride resulted in the precipitation of sodium chloride which was removed by filtration. Removal of solvent from the filtrate left a light yellow, viscous oil which on distillation under reduced pressure gave the known[3] β-methyl-γ-propanesultone (III).

The fact that water and not hydrogen chloride was eliminated during this distillation establishes the fact that no significant amount of the hydroxy acid was converted to the chloroacid during treatment with hydrochloric acid.

β-Methyl-γ-propanesultone also has been prepared through the peroxide-catalyzed addition of sodium bisulfite to methallyl alcohol. The yield of sultone based on methallyl alcohol charged was 52%. Probably the reason the yield is lower here than from methacrolein is that in this latter case the initial addition proceeded to only about 88% conversion.

Preparations of γ-propanesultone were carried out from acrolein and from allyl alcohol by procedures identical with the above. The melting point of the product was in agreement with that given by Helberger.[1] The yield from acrolein was 16% while that from allyl alcohol was only 5%.

In addition to the conversion of the aldehyde group of the bisulfite adduct of methacrolein to a

[1] J. H. Helberger. *Reichsamt Wirtshaftaufbau Chem. Br. Pruf. Nr.*, **15**, (U. S. Office of Publication Board. P.B. 52013) 269 (1942); *C. A.*, **41**, 4101 (1947).

[2] J. H. Helberger, G. Manecke and H. M. Fischer. *Ann.*, **562**, 23 (1949); *C. A.*, **43**, 6569 (1949).

[3] F. Asinger, F. Ebeneder and H. Eckholdt, U. S. Office of Publication Board, P.B. 70183, Frame 893.

[4] J. H. Helberger, G. Manecke and R. Heyden, *Ann.*, **565**, 22 (1949).

[5] W. Marckwald and H. H. Frahne, *Ber.*, **31**, 1854 (1898).

hydroxyl group it has also been converted to an amine, 3-amino-2-methyl-1-propanesulfonic acid, by hydrogenation over Raney nickel in the presence of concentrated ammonium hydroxide.

Experimental

Sodium 3-Hydroxy-2-methyl-1-propanesulfonate from Methacrolein.—Methacrolein, 154 g. (2.2 moles), was added dropwise with stirring and cooling to a solution of 190 g. (1 mole) of sodium metabisulfite in 520 ml. of water at 6–8°. When about 95% of the methacrolein had been added, the temperature rose sharply to 15–20° although the rate of addition had not been changed. During the addition of the remaining methacrolein the temperature dropped to 5°.

An attempt to isolate the sodium salt of β-sulfoisobutyraldehyde gave a glass which could not be crystallized. Hydrogenation of the above reaction mixture over Raney nickel at 50° and 1500 p.s.i. was complete in one hour. The catalyst was still active after the run, but the third run on the same catalyst was only 35% hydrogenated in 3.5 hours.

The catalyst was removed by filtration and the product was concentrated to dryness. The product weighed 371 g. (19 g. over theory) and probably still contained water. A small sample of the sodium 3-hydroxy-2-methyl-1-propanesulfonate which was recrystallized from methanol melted at 216–217°.

Anal. Calcd. for $C_4H_9O_4SNa$: C, 27.27; H, 5.15; Na, 13.1. Found: C, 27.30, 27.48; H, 5.15, 5.23; Na, 12.9, 13.0.

β-Methyl-γ-propanesultone.—A 186-g. sample of the above crude sodium 3-hydroxy-2-methyl-1-propanesulfonate was dissolved in 1400 ml. of hot methanol and treated with an excess of gaseous hydrogen chloride. After the mixture had been cooled, the sodium chloride which separated was collected on a filter. The methanol was evaporated from the filtrate and the product was distilled from a claisen flask. The slightly yellow distillate, b.p. 115–130° (1.5 mm.), weighed 100 g. This corresponds to a 73.5% yield. The boiling point reported by Asinger[8] for this sultone was 135° (5 mm.). β-Methyl-γ-propanesultone obtained by redistillation through a Vigreux column had the following properties: b.p. 89–91° (<0.5 mm.), n^{30}_D 1.4518, d^{30}_4 1.2931, 1.2932, soluble in acetone, chloroform and benzene but insoluble in cold water and petroleum ether. After recrystallization from ether, the sultone melted at 28.8–29.3°.

Anal. Calcd. for $C_4H_8O_3S$: C, 35.28; H, 5.92; sapn. equiv., 136. Found: C, 35.56, 35.52; H, 5.95, 5.94; sapn. equiv., 136.

On standing in stoppered, clear-glass bottles, crude samples of the sultone turned dark but decomposition was slight since redistillation gave high recovery of product.

Sodium 3-Hydroxy-2-methyl-1-propanesulfonate and β-Methyl-γ-propanesultone from Methallyl Alcohol.—A mixture of 36 g. (0.5 mole) of methallyl alcohol, 47.5 g. (0.25 mole) of sodium metabisulfite, 1.5 ml. of 2,2-bis-(*t*-butylperoxy)-butane, 60 ml. of water and 100 ml. of methanol was heated with shaking in a stainless steel vessel at 130° for one hour. Iodine titration of the product indicated 12.3% unreacted bisulfite. The product was concentrated to a heavy sirup under reduced pressure. Following the addition of 50 ml. of concentrated hydrochloric acid to the sirup, the resulting slurry was saturated with gaseous hydrogen chloride. The precipitated sodium chloride was removed by filtration and the product was concentrated under reduced pressure to a thick sirup which was distilled from a claisen flask. The distillate, b.p. 110–115° (1 mm.), wt. 28 g., represents a 52% yield. Recrystallization of 2.5 g. from ether gave 2 g. of product which alone and in mixture with β-methyl-γ-propanesultone from methacrolein melted at 28.5–29°.

γ-Propanesultone was prepared from acrolein (16% yield) and from allyl alcohol (5% yield) by procedures essentially identical to the above. The sultone from acrolein had the following properties: b.p. 95–100° (1 mm.), n^{20}_D 1.4585, m.p. 29–30° (from equal amounts of cyclohexane and benzene). Helberger[1] reports a melting point of 31°.

Anal. Calcd. for $C_3H_6SO_3$: ester value, 0.819 eq./100 g. Found: ester value, 0.796 eq./100 g.

3-Amino-2-methyl-1-propanesulfonic Acid.—A 0.6-mole batch of sodium β-sulfoisobutyraldehyde was prepared by the method described above. Ammonia, 62 g. (3.65 moles), was added to the product and the mixture was hydrogenated over Raney nickel at 100° and 1000 p.s.i. The catalyst was removed by filtration and the filtrate was evaporated to a hygroscopic glass. This material was acidified with an excess of concentrated hydrochloric acid and the sodium chloride was removed by filtration. After evaporation of the solvent the product was recrystallized from aqueous methanol giving 3-amino-2-methyl-1-propanesulfonic acid, m.p. 260–265°, in 44% yield based on methacrolein.

Anal. Calcd. for $C_4H_{11}O_3NS$: C, 31.36; H, 7.24; N, 9.15; S, 20.93. Found: C, 31.31; H, 7.33; N, 8.87; S, 20.93.

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Some Ester Analogs of DDT

BY WALTER T. SMITH, JR., AND JOHN W. RYAN

RECEIVED OCTOBER 6, 1952

Various esters of trichloroacetic acid have been reported in the literature.[1–3] However, 4,4′-dichlorobenzohydryl trichloroacetate has not been reported previously. This compound is of interest since it has some of the same structural characteristics of DDT, but differs by the insertion of the ester linkage into the molecule. In this paper is reported the preparation of this ester along with the preparation of 4-chlorobenzohydryl trichloroacetate and benzohydryl trichloroacetate. 4-Chlorobenzohydryl trichloroacetate is of particular interest because it contains an asymmetric carbon and offers the future possibility of comparing the insecticidal activity of its optically active forms.

These esters were conveniently prepared by refluxing a solution of the alcohol and trichloroacetic acid in benzene in a flask fitted with a water trap[4] and reflux condenser. An excess of trichloroacetic acid was used to minimize the amount of unreacted alcohol remaining in the reaction mixture. The excess trichloroacetic acid was removed by extraction with dilute alkali. The esterification proceeded rapidly and was complete in about one hour.

The esters decomposed when distilled at reduced pressure and could only be isolated in a pure state by a tedious process of crystallization. The most satisfactory solvent for inducing crystallization was isoamyl acetate. After the esters were obtained in a crystalline form, they could be recrystallized from ethyl alcohol. This last recrystallization was necessary in order to remove traces of isoamyl acetate, which were otherwise quite difficult to remove.

Preliminary tests indicate that these esters have considerable activity against red spiders, but little or no activity when tested against house flies, aphids, milkweed bugs, bean beetle larvae and army worms. The authors are indebted to the Rohm and Haas Company for the testing of these compounds.

The decomposition of the esters during attempted

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(1) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

(2) T. R. Liston and W. M. Dehn, THIS JOURNAL, **60**, 1264 (1938).

(3) H. Hibbert and M. E. Grieg, *Can. J. Research*, **4**, 254 (1934).

(4) E. W. Dean and D. D. Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

distillation was given further study in the case of benzohydryl trichloroacetate. When this ester was heated in a distilling flask under reduced pressure, a 70% yield of benzohydryl chloride was obtained. The identity of the benzohydryl chloride was established by analysis and by conversion to dibenzohydryl ether.[5] The decomposition also resulted in the evolution of hydrogen chloride and carbon dioxide. Quantitative determination of the hydrogen chloride in the evolved gases showed that nearly one-third of the chlorine in the ester could be accounted for in this way. No free chlorine could be detected in the gaseous products.

When the thermal decomposition of benzohydryl trichloroacetate was carried out at atmospheric pressure, the yield of benzohydryl chloride was reduced to 39% and a 17% yield of tetraphenylethylene was also obtained. The tetraphenylethylene is probably a secondary product of the decomposition, since its formation during the distillation of benzohydryl chloride at atmospheric pressure has been previously reported.[6]

Experimental

4-Chlorobenzohydrol and 4,4'-Dichlorobenzohydrol.—These alcohols were prepared in about 85% yield by reduction of the corresponding ketone with aluminum isopropoxide according to the procedure given by Wilds.[7] The authors are grateful to the Heyden Chemical Corporation for the sample of 4,4'-dichlorobenzophenone used in this work.

Benzohydryl Trichloroacetate.—Benzohydrol (18.4 g., 0.1 mole) and 18 g. (0.11 mole) of trichloroacetic acid were refluxed with 200 ml. of benzene in a flask attached to a water trap.[4] When the theoretical amount of water was collected, the solution was cooled and the unreacted trichloroacetic acid was removed by extraction with 10% sodium bicarbonate solution. The benzene was evaporated under reduced pressure and the remaining oil was taken up in 12 ml. of isoamyl acetate. The solution was kept at −5° for two days. The large crystals which formed were removed by filtration. The filtrate was concentrated to approximately two-thirds of its volume and placed in the refrigerator for two weeks. The resulting crystals were removed, combined with the first crop and recrystallized again from isoamyl acetate. The filtrate was concentrated in order to get good recovery of the product. It was necessary to pulverize the crystals in a mortar and dry them for 24 hours in a desiccator containing flaked paraffin in order to free them of isoamyl acetate. The product was then recrystallized from 95% ethanol to give 21 g. (63%) of benzohydryl trichloroacetate melting at 49.5–51°.

Anal. Calcd. for $C_{15}H_{11}Cl_3O_2$: C, 54.65; H, 3.36; Cl, 32.27. Found: C, 54.42; H, 3.24; Cl, 32.12.

4-Chlorobenzohydryl Trichloroacetate.—By the procedure outlined above 9 g. (0.055 mole) of trichloroacetic acid and 10.6 g. (0.05 mole) of 4-chlorobenzohydrol gave 8 g. (44%) of 4-chlorobenzohydryl trichloroacetate melting at 45–46°.

Anal. Calcd. for $C_{15}H_{10}Cl_4O_2$: Cl, 38.95. Found: Cl, 38.78.

4,4'-Dichlorobenzohydryl Trichloroacetate.—By the same method used for benzohydryl trichloroacetate, 8.4 g. (0.033 mole) of 4,4'-dichlorobenzohydrol and 6 g. (0.04 mole) of trichloroacetic acid gave 7.5 g. (57%) of 4,4'-dichlorobenzohydryl trichloroacetate melting at 59–59.5°.

Anal. Calcd. for $C_{15}H_9Cl_5O_2$: Cl, 44.48. Found: Cl, 44.43.

Pyrolysis of Benzohydryl Trichloroacetate.—Benzohydryl trichloroacetate was prepared as described above from 20 g. (0.1 mole) of benzohydrol and 18 g. (0.11 mole) of trichloroacetic acid. After removal of benzene, the residue was distilled under reduced pressure. Decomposition started immediately and a yellow liquid distilled slowly at 138–140° (3 mm.). The distillate was redistilled to give 14 g. (70%) of benzohydryl chloride.

Anal. Calcd. for $C_{13}H_{11}Cl$: C, 76.9; H, 5.44. Found: C, 76.55; H, 5.44.

The benzohydryl chloride was further identified by conversion to dibenzohydryl ether melting at 109°.[5]

In another pyrolysis, 25 g. (0.076 mole) of benzohydryl trichloroacetate was placed in a modified claisen flask fitted with a condenser for distillation. The flask was heated for 5 hours in a metal-bath at 280°. Some of the gas evolved was passed into barium hydroxide solution to give an immediate precipitate of barium carbonate. When the gas evolved was passed into water, the water produced a white precipitate of silver chloride when a few drops of silver nitrate solution was added. Chlorine could not be detected in the gaseous mixture by testing with potassium iodide and starch. The pressure in the distillation assembly was then reduced to 1.5 mm. and the flask was heated again. Benzohydryl chloride (4 g., 39%) was collected at 132–134° (1.5 mm.).

The tarry residue in the flask was removed by extraction with benzene after which the benzene was removed by evaporation and the residue was dried in an oven at 110°. The residue was then placed in a soxhlet extractor and extracted with methanol. The methanol was evaporated and the residue was recrystallized three times from benzene to give 2.1 g. (17%) of tetraphenylethylene, identified by melting point and mixed melting point with an authentic sample.

In another pyrolysis of benzohydryl trichloroacetate, analysis of the evolved gases showed that 31.6% of the total chlorine in the benzohydryl trichloroacetate was evolved as hydrogen chloride during the decomposition.

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[5] E. Wedekind and K. Schenk, *Ber.*, **44**, 201 (1911).

[6] O. Anselmino, *Ber. deut. pharm. Ges.*, **16**, 390 (1906).

[7] A. L. Wilds in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 203.

Prediction of Hydrocarbon Burning Velocities by the Modified Semenov Equation

BY P. L. WALKER, JR., AND C. C. WRIGHT

RECEIVED SEPTEMBER 26, 1952

The authors,[1] using the thermal theory of Semenov, and Simon,[2] using the diffusion theory of Tanford and Pease, have satisfactorily correlated the experimental burning velocities of a majority of the hydrocarbon–air mixtures investigated by assuming the specific reaction rate constants in the two equations independent of hydrocarbon. The predicted burning velocities of acetylene and ethylene, however, deviated markedly from experimental results for both theories. It was, therefore, concluded that the rate constants for the combustion of these hydrocarbons vary noticeably from all other hydrocarbons investigated.

In the previous correlation by the Semenov equation, due to lack of sufficient data, the energy of activation of all hydrocarbons for the combustion reaction was assumed to be 40 kcal./mole, which approximates the available low temperature data on the oxidation of hydrocarbons. Recent work by Fenn,[3] where he was able to associate lean limit flame temperatures of hydrocarbons with their activation energies, shows that high temperature activation energies for hydrocarbon combustion are considerably lower than the value of 40 kcal./

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[1] P. L. Walker, Jr., and C. C. Wright, THIS JOURNAL, **74**, 3769 (1952).

[2] Dorothy Martin Simon, *Ind. Eng. Chem.*, **43**, 2718 (1951).

[3] John B. Fenn, *ibid.*, **43**, 2865 (1951).

mole taken from hydrocarbon oxidation data, and, furthermore, that ethylene and acetylene have activation energies markedly below those of the straight chain hydrocarbons. Using the new activation energies and experimental flame temperatures (which are thought by the authors to be preferable to adiabatic temperatures), the burning velocities of ethylene and acetylene relative to propane, as predicted by the Semenov equation, have been reevaluated, as shown in Table I.

TABLE I

MAXIMUM BURNING VELOCITIES OF HYDROCARBON FLAMES

Hydrocarbon	Vol. fuel, %	Activation energy,[3] kcal./mole	Exp. flame temp., °K.	Burning velocity cm./sec. Exptl.	Burning velocity cm./sec. Sem. eqn.
Propane	4.5	26.1	2158[a]	39.0[d]	39.0
Ethylene	7.4	23.6	2238[a]	68.3[d]	71.0
Acetylene	10.4	20.4	2480[b]	141.0[c]	152.5

[a] G. W. Jones, B. Lewis, J. B. Friauf and G. St. J. Perrott, THIS JOURNAL, **53**, 869 (1931). [b] H. Behrens and F. Rossler, *Z. Naturforsch.*, **5a**, 311 (1950). [c] O. Levine and M. Gerstein, *Natl. Advisory Comm. Aeronaut.*, RM E51JO5, 1951. [d] M. Gerstein, O. Levine and E. L. Wong, THIS JOURNAL, **73**, 418 (1951).

These new results give insight into the character of the variation of the specific reaction rate constant in the Semenov equation for ethylene and acetylene as compared to other hydrocarbons. The simplified Semenov equation[1] contains the specific reaction rate constant in the form, $k = Ke^{-E/RT}$. In the above correlation, the steric factor, K, by necessity is assumed independent of hydrocarbon, thus implying that variation in the specific reaction rate constant at a given temperature is simply due to a variation in the energy of activation. The fact that the above correlation is successful would seem to indicate that the steric factor of acetylene and ethylene for the combustion reaction is not greatly different from that of other hydrocarbons. It also emphasizes the important role which activation energy plays in determining the fundamental burning velocity of a hydrocarbon. Perhaps the major significance of the results, however, is that the activation energies of hydrocarbons determined from lean limit and ignition energy data bring the flame speed predictions into line with experimental results, suggesting that the same mechanism may be important in the different combustion phenomena.

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The Absence of Quaternary Salt Formation between Phosphoryl Chloride and Pyridine[1]

BY B. M. ZEFFERT, P. B. COULTER AND RUDOLPH MACY

RECEIVED SEPTEMBER 8, 1952

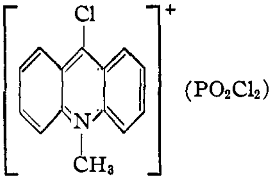
The Grignard reagent, RMgX, can be used to place alkyl or aryl groups on the phosphorus atom in $POCl_3$; when the reaction is conducted according to the normal procedure (addition of $POCl_3$ to the Grignard reagent in ether), all three chlorine atoms are replaced to produce phosphine oxides, R_3PO. It was shown[2] that one Cl atom can be blocked by the preliminary synthesis of an amido compound, $R_2N-POCl_2$, which can be isolated and put through the Grignard reaction, thus placing two R groups on the phosphorus atom.

One Cl atom can also be blocked in Grignard reactions if the $POCl_3$ is first added to N-methylacridone to form a 1:1 complex salt.[3] This compound was isolated[3,4] and the authors presented evidence to show that salt formation (Formula I) occurs through interaction of $POCl_3$ and the carbonyl group of the acridone. Kosolapoff[5] later found that R_2POCl compounds are produced predominantly, in Grignard reactions of $POCl_3$ in ether solution, if pyridine is first added to the $POCl_3$ in equimolar amounts. He ascribed this effective blocking of one Cl atom to quaternary salt formation between pyridine and $POCl_3$ and reported the reaction as

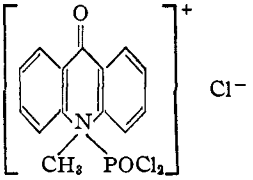
$$POCl_3 + C_5H_5N \longrightarrow C_6H_5N(POCl_2)Cl \xrightarrow[(HOH)]{2RMgX} R_2PO_2H$$

Kosolapoff felt that the reactions described by Gleu and Schubert involved a similar quaternary nitrogen salt (Formula II) and that phosphonic acids, $RPO(OH)_2$, could be synthesized by this method if other complexes of pyridine and $POCl_3$ could be formed. He was unable to block two Cl atoms by doubling the ratio of pyridine to $POCl_3$ and suggested that the larger complexes might be stable only at low temperatures.[5] The existence of the 2:1 compound at normal temperatures had been reported previously[6] and later disputed with good evidence.[7]

The present work was initiated to determine the temperatures at which the postulated complex compounds of $POCl_3$ and pyridine exist, and thus to define conditions for the preparation of phosphinic and phosphonic acids in good yields by means of the Grignard reaction.



Formula I



Formula II

Materials.—The $POCl_3$ used was distilled at 106.5–106.9° from a sample of Mallinckrodt Analytical Reagent material. The freezing point of the distillate was 1.02°; literature values are: b.p. 106.4–106.7°, f.p. 1.17°.[8]

The pyridine was obtained from the Eastman Kodak Co. and distilled over barium oxide prior to use; b.p. 114–115.5°, f.p. −42.3°, $n^{25}\text{D}$ 1.5061; literature values are: b.p. 115.5°[9]; f.p. −42.0°[10]; $n^{25.2}\text{D}$ 1.5070.[11]

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[1] Abstracted from an M.S. thesis submitted by B. M. Zeffert to the Graduate School, University of Maryland.

[2] G. M. Kosolapoff, THIS JOURNAL, **71**, 369 (1949).

[3] K. Gleu and A. Schubert, *Ber.*, **73**, 805 (1940).

[4] K. Gleu, S. Nitzsche and A. Schubert, *ibid.*, **72**, 1093 (1939).

[5] G. M. Kosolapoff, THIS JOURNAL, **72**, 5508 (1950).

[6] D. R. Boyd and D. E. Ladhams, *J. Chem. Soc.*, 215 (1928).

[7] W. Gerrard, *ibid.*, 106 (1945).

[8] D. M. Lichty, THIS JOURNAL, **34**, 1440 (1912).

[9] J. Timmermans, "Physico-Chemical Constants of Pure Compounds," Elsevier Publ. Corp., New York, N. Y., 1950.

[10] G. S. Parks, S. S. Todd and W. A. Moore, THIS JOURNAL, **58**, 398 (1936).

[11] "International Critical Tables," p. 80, Vol. VII.

Apparatus and Procedures.—The thermistor-cryostat used for the freezing point determinations has been described in a previous publication from this Laboratory.[12] The equipment was modified by substituting a line-operated power supply for the dry cells previously used for the Wheatstone bridge. This source was suitably regulated, rectified and tapped to provide the small d.c. voltages required.

The appearance of solid phases above the binary freezing points and certain anomalous arrests obtained on thermal analysis of the time–temperature curves in preliminary runs were found to be caused by moisture contamination of the solutions. The solids thus produced have been described as $2C_5H_5N$-$POCl_2(OH)$ and C_5H_5N-HCl.[7] Rigorous precautions were then taken to prevent absorption of water into the system. Dry pyridine was obtained by distillation over barium oxide, and subsequent storage over this drying agent. Crystallization from the melt was used to purify $POCl_3$, but the manipulations required in transfers allowed deterioration, and efficient use of drying agents in storage was precluded by the irreversible reaction of $POCl_3$ with water. The highest freezing point we obtained for $POCl_3$ was with a recrystallized sample distilled directly into the cryostat, and it was not until solutions were prepared by distilling recrystallized $POCl_3$ into the solution-mixing bottles that cloudiness of mixtures was entirely prevented. All other transfers (of pyridine to mixing bottles, and of solutions to cryostat) were conducted in a controlled atmosphere box at zero-humidity meter reading. Solutions prepared in this manner did not precipitate solid on mixing, nor exhibit any evidence of phase changes above the binary freezing points.

Results

The temperature–composition relationship for pyridine and $POCl_3$, which is given in Table I, shows no compound formation in the binary system. Second arrests were observed at −55.6 to −55.7°.

TABLE I

PYRIDINE–PHOSPHORYL CHLORIDE SYSTEM

Composition, mole % pyridine	Freezing point, °C.
100	−42.3
93.2	−46.0
87.5	−49.4
77.5	−55.3
76.9 eutectic (extrapd.)	−55.6
74.1	−52.5
63.7	−40.6
54.0	−31.4
42.9	−23.1
30.5	−15.0
20.4	− 9.3
4.78	− 1.26
0	1.02

The Clausius–Clapeyron equation in the form

$$\ln N = -L_f \Delta T / R T_0 T_1$$

where N is the mole fraction of solvent, L_f its heat of fusion, R the gas constant, and T_0 and T_1 the freezing points of pure solvent and of solution, respectively, serves as a criterion for estimation of the deviations of solutions from ideal behavior. The L_f of $POCl_3$ calculated thereby, using observed freezing points of dry solutions, was essentially constant to about 50 mole %, and was only 4% lower at the eutectic than at 95 mole % $POCl_3$. The calculated 3.18 kcal./mole is the same as the literature value obtained from freezing point data with other solutes.[13] Similarly, the L_f for pyridine was calculated from freezing points on the other side of the eutectic. The obtained value of 1.96 kcal./mole was constant within experimental error from 7 mole % $POCl_3$ to the eutectic point. The best literature value is 1.97 kcal./mole, obtained by direct measurement.[10]

Further evidence of the ideal behavior of this system was obtained by comparison with a concentrated solution of benzene in $POCl_3$. The latter system has been shown to deviate only slightly from ideal behavior at low $POCl_3$ content.[14] A 37.7 mole % benzene solution froze at −19.7°, which is the same temperature obtained for an equally concentrated pyridine solution in the same solvent.

Phosphoryl Chloride–α-Picoline System.—When it became apparent, during the preliminary work, that no compounds were formed in the pyridine–$POCl_3$ system, it was attempted to produce quaternary salts between $POCl_3$ and a more alkaline pyridine base. α-Picoline (K_b 3.2×10^{-8}) is approximately ten times more basic than pyridine (K_b 3.0×10^{-9})[15] and a fresh sample of practical grade Eastman Kodak α-picoline (b.p. 126–130°) was available. The sample contained small percentages of other pyridine bases. Eight mixtures with $POCl_3$ were prepared and measured, points being obtained between zero and 80 mole % α-picoline which were very close to values obtained with pyridine Mixtures of greater than 80 mole % α-picoline did not crystallize, even with seeding, at temperatures several degrees below the expected freezing points, and the complete temperature–composition diagram was not obtained. Sufficient data were obtained, however, to indicate the absence of compound formation at molar ratios of less than 3:1 of α-picoline to $POCl_3$, and to reveal the closeness to ideal behavior of the system.

Discussion

The phase diagram of the pyridine–$POCl_3$ system shows that no addition compounds are formed at atmospheric pressure and no binary complexes of these components are to be expected in the presence of additional components. The freezing point depressions show there is negligible association even in the liquid phase. The postulation that pyridine improves the yields of phosphinic acids in Grignard reactions of $POCl_3$ by complexing with the latter compound[5] must therefore be ruled out. The fact remains, however, that pyridine is effective in this reaction; this effectiveness must therefore be due to change in the reaction medium. In a publication[16] which appeared during the course of the present work, it was stated that the relative proportion of Grignard reagent, the reaction temperature and basicity of solvent are factors affecting the yields in Grignard reactions. When the ratio of RMgX to reactant to be substituted is small, or the temperature is lowered, or solvents of high basicity are used, the reaction rates are reduced. Thus, it

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appears reasonable that the mechanism whereby pyridine prevents complete substitution of $POCl_3$ to R_3PO involves an effective reduction in Grignard reagent concentration, probably by association with RMgX. The suggestion that phosphonic acids may be produced in better yield by using larger proportions of pyridine at lower temperatures[5] may be valid, but not because of blocking Cl atoms in $POCl_3$. Work has been started in this Laboratory to study quantitatively the effect of bases on Grignard reactions involving $POCl_3$ and related compounds.

The work with pyridine and α-picoline indicates that $POCl_3$ probably does not form quaternary salts with any pyridine bases. Actually, compounds have been isolated between $POCl_3$ and acids such as SO_3[17] and $SnCl_4$.[18] In light of the results obtained with pyridine bases, formula I, may be considered a more likely structure than formula II. An incidental result of the present work is that doubt is cast on the postulated reaction mechanism in a recent paper,[19] which requires quaternary compound formation between $POCl_3$ and a pyrazine derivative.

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CHEMICAL CORPS CHEMICAL AND
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COMMUNICATIONS TO THE EDITOR

THE NATURE OF THE XANTHINE OXIDASE FACTOR

Sir:

A factor(s) in liver residue and soy flour which increases the level of liver and intestinal xanthine oxidase when fed to weanling rats has been described by Westerfeld and Richert.[1,2,3,4] An excellent assay for this factor utilizing rat intestine also has been described by these authors.[5] However, the nature and mode of action of this substance(s) is unknown.

During the course of fractionation studies on liver residue it was found that the xanthine oxidase factor(s) could be partially liberated by autoclaving in water. The activity of the extracts so obtained was found to be dialyzable and stable to severe acid or alkaline treatment.

When liver residue or extracts from liver residue were ashed, the activity, surprisingly enough, was found to be unaltered. The inorganic material so obtained, when assayed spectrographically,[6] was found to contain many elements among which were Al, Sb, Ba, B, Cr, Co, Pb, Mo, Ni, Ag, Sn, Ti, V and Zn. The more "common" elements such as K, P, Na, Cu, Fe, Si, Mg and Mn were also present. In addition, the activity of liver residue or its ash could be replaced by including a supplement of Hoagland's A-Z solution[7] in the diet of rats. Further investigation with single salt supplements revealed that the ingestion of molybdate ion is responsible for the increased xanthine oxidase levels.

The addition of as little as 1 mg. of sodium molybdate/kg. diet or the injection of 10γ subcutaneously gave values for xanthine oxidase equal to that obtained when 10% liver residue was fed. Table I shows some typical data. Preliminary studies indicate that no other element is able to replace molybdenum and the highly specific nature of this effect is therefore apparent.

TABLE I

EFFECT OF LIVER RESIDUE, LIVER RESIDUE FRACTIONS AND MOLYBDATE ION ON RAT INTESTINAL XANTHINE OXIDASE VALUES

Supplement added to basal diet/kg.	Average X. O. value. c.mm.O_2 uptake/ unit time/unit wgt. of intestine
None	4.4
10% liver residue (LR)	25.6
Liver residue extract (LRE) ≈16% LR	32.0
Ash of LR ≈ 10% LR	28.2
Ash of LRE ≈ 20% LR	26.9
Dialyzed LRE ≈ 20% LR	5.1
Sodium molybdate, 1 mg.	23.5

To our knowledge, this represents the first report suggesting an *in vivo* role for molybdate in an animal enzyme system. The possible importance of this finding on the role of molybdenum in animal nutrition is of course obvious. Studies are now in progress to elucidate the precise role of molybdenum on the activity of xanthine oxidase.

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[6] We are indebted to Mr. W. L. Dutton and his staff of the Stamford Research Laboratories, American Cyanamid Co., for the spectrographic analysis.

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