of the ionic strength, determined from a smoothed plot of the above data, is given in Table IV.

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COLUMBIA 1, SOUTH CAROLINA

NOTES

Long-chain Aliphatic Semicarbazides[1]

BY J. D. CHANLEY, STELLA KALICHSTEIN AND E. M. GINDLER

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We wish to report the synthesis of a few long-chain aliphatic semicarbazides: 4-pentadecyl- (I), 4-heptadecyl- (II), 4-octadecyl- (III) and 2-methyl-4-heptadecyl semicarbazide (IV). As far as we are aware there is no mention in the literature of any long-chain semicarbazides. The semicarbazone derivatives of ketones—obtained from them—are soluble in petroleum ether. This property may prove useful in the isolation of ketones. The combined hydrophilic and hydrophobic features of these semicarbazides render them suitable for spreading in monomolecular layers and present the possibility of employing them as carbonyl reagents at interfaces. The monomolecular film properties of these compounds and their derivatives, described below, have been investigated in these laboratories and will be the subject of a separate communication.

The syntheses of compounds I, II and IV were accomplished in good yield by the addition of anhydrous hydrazine in the first two cases and anhydrous methylhydrazine in the latter instance to the appropriate isocyanate. The reaction sequence is

$$\mathrm{R{-}CO{-}Cl} \xrightarrow{\mathrm{NaN_3}} \mathrm{R{-}CO{-}N_3} \xrightarrow{\Delta}$$

$$\mathrm{R{-}N{=}C{=}O} \xrightarrow{\mathrm{R'NHNH_2}} \mathrm{RNHCONR'NH_2}$$

$\mathrm{R} = \mathrm{C_{15}H_{31}}$ (I) or $\mathrm{C_{17}H_{35}}$ (II, IV); $\mathrm{R'} = \mathrm{H}$ (I, II) or $\mathrm{CH_3}$ (IV)

The synthesis of 4-octadecyl semicarbazide (III) was accomplished, albeit in very poor yield, by the interaction of anhydrous hydrazine on the ethyl carbamate derivative of octadecylamine. The reaction sequence is

$$\mathrm{R{-}NH_2} \xrightarrow{\mathrm{ClCOOEt}} \mathrm{RNHCOOEt} \xrightarrow{\mathrm{NH_2NH_2}} \mathrm{RNHCONHNH_2}$$

$\mathrm{R} = \mathrm{C_{18}H_{37}}$ (III)

The monosubstituted semicarbazide reacted readily with aldehydes and ketones to give the corresponding semicarbazone derivatives in high yield. In contrast the disubstituted semicarbazide, compound IV, although reacting readily and in high yield with benzaldehyde, is very sluggish in its reactivity toward ketones. We were able, however, to obtain the cyclohexanone derivative. This difference in behavior toward ketones has previously been described by Evans and Gillam in the instance of semicarbazide and 2-methyl semicarbazide.[2] A comparison of the ultraviolet absorption spectra in 95% ethanol of the benzaldehyde derivative of compound II, $\lambda_{\max}$ 285 mμ, $\epsilon_{\max}$ 19,500 and of compound IV, $\lambda_{\max}$ 293 mμ, $\epsilon_{\max}$ 20,800, shows a shift to longer wave length of 8 mμ, in the case of the 2-methyl-substituted semicarbazide. The same phenomenon has been observed by the above authors[2] for 2-methylsemicarbazone and semicarbazone derivatives of a variety of aromatic aldehydes.

Experimental

All spectra were obtained in 95% ethanol with a Beckman spectrophotometer, Model DU.

Stearoyl and palmitoyl chloride were distilled before use. Octadecylamine, m.p. 53.2°, was obtained from Armour and Company, Chicago 9, Ill. The preparation of compounds I, II and IV was essentially the same and is illustrated in the instance of 4-heptadecylsemicarbazide. The isocyanates were prepared essentially according to the method given for the preparation of undecyl isocyanate,[3] except that it was found desirable to isolate the intermediate acid azide.

4-Heptadecyl semicarbazide (II).—To a well cooled (5–15°), vigorously stirred solution of sodium azide (3.31 g., 0.051 mole) in 22 ml. of water and 16 ml. of acetone a solution of stearoyl chloride (11 g., 0.037 mole) in 11 ml. of acetone was added at such a rate that the temperature remained between 5 and 15°. The mixture was stirred for approximately 45 minutes and the heavy white precipitate of the azide was removed by filtration, washed thoroughly with water and pressed dry; yield 17 g. The azide is quite stable and may be dried in a vacuum desiccator overnight over calcium chloride. The slightly wet azide was dissolved in benzene (125 ml.), dried overnight over sodium sulfate at 15°, filtered, refluxed for one hour, cooled in ice and 7 ml. of anhydrous hydrazine was added rapidly with hand swirling. The solid reaction product was removed by filtration, washed with benzene and water and dried overnight *in vacuo* over calcium chloride; yield 9.0 g., m.p. 90–95°. Three recrystallizations from ethanol or methanol gave 5 g. of pure material; m.p. 100–100.5°.

Anal. Calcd. for $\mathrm{C_{18}H_{39}N_3O}$: C, 68.95; H, 12.54; N, 13.40. Found: C, 69.03; H, 12.12; N, 13.70.

4-Pentadecylsemicarbazide (I) prepared as above from palmitoyl chloride, etc., after recrystallization from methanol or ethanol, melted at 100–101°.

Anal. Calcd. for $\mathrm{C_{16}H_{35}N_3O}$: C, 67.32; H, 12.36; N, 14.72. Found: C, 67.30; H, 12.06; N, 15.02.

2-Methyl-4-heptadecylsemicarbazide (IV) was prepared essentially according to the method given above with the following modifications. To the benzene solution of heptadecyl isocyanate, anhydrous methylhydrazine was added. Since the semicarbazide is soluble in benzene, dry HCl was passed into the benzene solution and the precipitated mixture of semicarbazide hydrochloride and methylhydrazine hydrochloride was collected, dissolved in ethanol and decomposed with an excess of dilute aqueous sodium hydroxide

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[1] This work was supported by a Grant-in-Aid from the Permanent Science Fund of the American Academy of Arts and Sciences to Dr. Harry Sobotka.

[2] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

[3] *Org. Syntheses*, **24**, 94 (1944).

solution. The free semicarbazide was collected by filtration and recrystallized from absolute ethanol; yield 60%, m.p. 83–84°.

Anal. Calcd. for $C_{19}H_{41}N_3O$: C, 69.72; H, 12.53; N, 12.84. Found: C, 69.46; H, 12.28; N, 12.80.

Preparation of 4-Octadecylsemicarbazide (III). Ethyl Octadecylaminecarbamate.—To a well stirred ice cold suspension of octadecylamine (13.5 g., 0.05 mole) in 125 ml. of ether, contained in a three-neck flask, ethyl chloroformate (2.7 g., 0.025 mole) in 15 ml. of ether was added over a period of 30 minutes. To this mixture a solution of sodium hydroxide (2 g. in 35 ml. of water) and a solution of ethyl chloroformate (2.7 g. in 15 ml. of ether) were added simultaneously over a period of 1.5 hours. The ice-bath was removed and the mixture allowed to react for a further hour, at the end of which time a clear ether layer was obtained. The ether layer was washed with 10% sodium carbonate, water, dried over sodium sulfate and evaporated to dryness. The residue 13.3 g., m.p. 66–67°, was recrystallized from ethanol and pure material (m.p. 67–68°) was obtained as plates, which changed to needles at 60°.

Anal. Calcd. for $C_{21}H_{43}NO_2$: C, 73.84; H, 12.68; N, 4.10. Found: C, 74.32; H, 12.60; N, 4.11.

A sealed tube containing 3.0 g. of the above carbonate, 0.43 ml. of anhydrous hydrazine and 5 ml. of absolute alcohol was heated over a period of 22 hours at 130°. The residue after removal of excess hydrazine and alcohol was treated with ether and the ether insoluble material, Compound III, 0.26 g., m.p. 102–103°, was collected and recrystallized from ethanol; m.p. 104–106°.

Anal. Calcd. for $C_{19}H_{41}N_3O$: C, 69.67; H, 12.62; N, 12.83. Found: C, 69.60; H, 12.20; N, 12.62.

Dry HCl was passed through the dried ether layer and the precipitated hydrochloride (0.6 g., m.p. 103–115°) yielded after many recrystallizations from ethanol a small amount of octadecylamine hydrochloride (m.p. 159–161°) and mixed melting point with an authentic sample (m.p. 162–163°) showed no depression.

Anal. Calcd. for $C_{18}H_{40}NCl$: N, 4.58. Found: N, 4.48.

The final ether solution, after washing with 10% NaOH, water and drying over sodium sulfate yielded on evaporation, 1.8 g. of the original carbamate (m.p. 67–68°).

All the derivatives listed below were prepared in essentially the same manner, except as indicated, and the procedure is illustrated by the following example.

Heptadecylsemicarbazone of Benzaldehyde.—A solution of heptadecylsemicarbazide (1.0 g., 0.003 mole) and benzaldehyde (0.67 g., 0.006 mole) in 25 ml. of methanol containing two drops of glacial acetic acid was heated for a short time on a steam-bath and allowed to stand overnight. The crystalline precipitate was recrystallized from methanol and melted at 79–79.5°, yield 1.0 g., λ_{max} 285 mμ, ϵ_{max} 19,500.

Anal. Calcd. for $C_{25}H_{43}N_3O$: C, 74.76; H, 10.79; N, 10.47. Found: C, 75.53; H, 11.00; N, 10.36.

The semicarbazone of benzaldehyde shows λ_{max} 282 mμ, ϵ_{max} 24,000.

4-Pentadecylsemicarbazone of benzaldehyde after recrystallization from ethanol melted at 73–74°.

Anal. Calcd. for $C_{23}H_{39}N_3O$: C, 73.95; H, 10.50; N, 11.25. Found: C, 74.03; H, 10.17; N, 10.90.

2-Methyl-4-heptadecylsemicarbazone of benzaldehyde after recrystallization from methanol melted at 100–101°, λ_{max} 293 mμ, ϵ_{max} 20,800.

Anal. Calcd. for $C_{26}H_{45}N_3O$: C, 75.13; H, 10.91; N, 10.11. Found: C, 75.51; H, 10.86; N, 10.31.

Heptadecylsemicarbazone of Formaldehyde.—The crude product was dissolved in ether, filtered from insoluble purity, and the ether residue recrystallized several times from methanol and dried *in vacuo* over P_2O_5. Five grams of compound IV yielded 2.5 g. of the pure semicarbazone derivative, m.p. 66–68°.

Anal. Calcd. for $C_{19}H_{39}N_3O$: C, 70.09; H, 12.08; N, 12.92. Found: C, 70.18; H, 11.79; N, 12.68.

The above material on hydrogenation in glacial acetic acid with platinum oxide as catalyst absorbed the equivalent of one mole of hydrogen. However, the sought-for 1-methyl-4-heptadecylsemicarbazide could not be isolated in any state of purity.

4-Heptadecylsemicarbazone of cyclohexanone after recrystallization from methanol melted at 66–67°, yield 80%.

Anal. Calcd. for $C_{24}H_{47}N_3O$: C, 73.23; H, 12.03; N, 10.67. Found: C, 74.03; H, 11.80; N, 10.40.

4-Pentadecylsemicarbazone of cyclohexanone after recrystallization from methanol melted at 62–63°.

Anal. Calcd. for $C_{22}H_{43}N_3O$: C, 72.27; H, 11.85; N, 11.49. Found: C, 71.98; H, 10.77; N, 11.47.

2-Methyl-4-heptadecylsemicarbazone of Cyclohexanone.—One gram of the semicarbazide (0.003 mole) and 0.58 g. of cyclohexanone (0.006 mole) in 10 ml. of ethanol containing 3 drops of glacial acetic acid were refluxed for a few minutes and allowed to stand overnight. The alcohol was removed by evaporation and the residue treated with petroleum ether, b.p. 40–60°. The insoluble starting material was removed and the filtrate after evaporation to a small volume yielded after cooling overnight in the ice-chest 250 mg. of the slightly yellow semicarbazone, m.p. 44–48°.

Anal. Calcd. for $C_{25}H_{49}N_3O$: C, 73.62; H, 12.12; N, 10.32. Found: C, 73.24; H, 12.09; N, 10.48.

4-Heptadecylsemicarbazone of cholestenone after recrystallization from ethyl acetate–methanol mixture melted at 78–80°, λ_{max} 273.5 mμ, ϵ_{max} 25,000.

Anal. Calcd. for $C_{45}H_{81}N_3O$: C, 79.46; H, 12.00; N, 6.18. Found: C, 79.10; H, 11.45; N, 6.45.

Acknowledgment.—We wish to express our thanks to Dr. Harry Sobotka for his interest and helpful suggestions.

DEPARTMENT OF CHEMISTRY
THE MOUNT SINAI HOSPITAL
NEW YORK 29, N. Y.

Alkaloid Biogenesis. IV. The Non-availability of Nicotinic Acid-Carboxyl-C^{14} and its Ethyl Ester for Nicotine Biosynthesis[1]

BY R. F. DAWSON,[2] DAVID R. CHRISTMAN AND R. CHRISTIAN ANDERSON

RECEIVED JUNE 4, 1953

For reasons of structural analogy and biological ubiquity, nicotinic acid has been regarded as a possible precursor of the pyridine moiety of the Nicotiana alkaloids.[3] Attempts to secure analytical increases in nicotine content of excised tobacco leaves by feeding solutions of nicotinic acid through cut stems and the transpiration stream have yielded conflicting and inconclusive results.[4] In large part, this is due to the fact, recently demonstrated, that matured excised tobacco leaves do not possess the capacity to synthesize nicotine.[4] The synthetic ability of tobacco roots, on the other hand, has been repeatedly affirmed. This fact, together with the ability of excised tobacco roots to grow indefinitely in sterile culture and to produce nicotine at predictable rates under standard conditions have provided the basis for an isotopic test of the availability of nicotinic acid and its ethyl ester as precursors for nicotine biosynthesis.

Experimental

Nicotinic-C^{14} Acid.—Carboxyl-labeled nicotinic acid was prepared from 3-bromopyridine, *n*-butyllithium and $C^{14}O_2$,

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[1] Research carried out under the auspices of the U. S. Atomic Energy Commission.

[2] Department of Botany, Columbia University, New York 27, N. Y.

[3] E. Winterstein and G. Trier, "Die Alkaloide," 2nd Ed., Borntraeger, Berlin, 1931, pp. 1031.

[4] *Cf.* R. F. Dawson, "Advances in Enzymology," Interscience Publishers, Inc., Vol. 8, 1948, for review.

TABLE I

DATA ON NICOTINE FROM C^{14} FEEDING EXPERIMENTS

	Compound supplied to cultures	1 No. of cultures	2 Length of culture, days	3 Nicotine per culture, mg.	4 Yield of dipicrate, mg.	5 Radioactivity of dipicrate[a]	
						Possible[b]	Found
A	7.5 mg. nicotinic acid	10	12	0.99	24.3	6.7×10^4	2
B	None	10	12	0.98–1.20	..	....	..
C	15 mg. ethyl nicotinate	15	14	0.82	30	2.2×10^3	8
D	15 mg. ethyl nicotinate	15	15	0.76	22.4	2.2×10^3	6
E	None	15	14–15	0.72–0.90	..	....	..
F	Nicotine dipicrate control		...	....	..	0	4

[a] As c.p.m./cm.^{2} of $BaCO_3$ at infinite thickness. C.p.m./cm.^{2} $\times 6.16 \times 10^{-3}$ = mμc./mg. C. [b] If every nicotine molecule had been derived from nicotinic acid or ethyl ester plus an inactive C_5 precursor.

followed by high vacuum sublimation,[5] radioactivity, 3.59, μc./mg. C.

Ethyl-C^{14} Nicotinate.—A mixture of 1.921 g. of nicotinic acid and 0.058 g. of the nicotinic C^{14} acid was suspended in ether. A solution of diazoethane in ether was added slowly, with stirring, until the nicotinic acid was completely dissolved and nitrogen was no longer evolved upon further addition of diazoethane. The ether was removed under reduced pressure and the ester transferred to a small distilling flask, from which it was distilled at less than 0.1 mm. The distillate had a refractive index nearly identical to that of an authentic sample of ethyl nicotinate. It weighed 2.18 g., a yield of 90%. The radioactivity was about 0.1 μc./mg. C.

Root Cultures.—Tobacco roots (*Nicotiana tabacum*, var. Turkish) were grown according to the procedures of White[6] except for the addition to White's medium of traces of copper and molybdenum. Under uniform growth conditions (incubation at 30°, culture fluid volume 33 ml.) each root tip (initially 2–3 cm. long) produced in 5 weeks 20 mg. of dry tissue and 0.5 mg. of nicotine.

Feeding the Radioactive Compounds.—Aqueous solutions of the acid or of its ester were autoclaved and pipetted aseptically into the culture flasks after 12–15 days of root growth. For another 14–16 days, during which growth occurred uninterruptedly, the cultures were incubated in the dark at 30°. At the end of this time, the contents of the flasks were quantitatively removed, the tissues ground in a mortar with sharp sand and 3 ml. of 10% trichloroacetic acid, the combined fluids brought to boiling and filtered. The resulting extract was then continuously extracted with ether from an excess of $Mg(OH)_2$ for 36 hours.

Isolation and Estimation of Nicotine.—Excess ether was removed from the above extracts over *ca.* 20 ml. *N* HCl on a water-bath. The remaining acidic solution of nicotine was made to 25 ml. with *N* HCl, mixed well and optical densities measured at 236, 259.5 and 282 mμ in a Beckman model DU spectrophotometer at 0.5 mm. slit width. Previous experience has shown that the nicotine content of such extracts estimated by the method of Willits, Swain, Connelly and Brice[7] agreed closely with estimates based upon measurements of the optical densities of steam distillates.

For isolation of the alkaloid, the acidic solutions remaining from the above procedure were recombined, made alkaline with NaOH and extracted continuously in a modified Soxhlet apparatus for 12 hours. The ethereal solutions were distilled over aqueous picric acid solution and the resulting samples of nicotine dipicrate were diluted with equal amounts of carrier and recrystallized to appropriate melting point (*ca.* 224°). These picrates were converted to $BaCO_3$ by the wet combustion method of Van Slyke and Folch[8] as modified in this Laboratory.[9] The resulting $BaCO_3$ was collected on disks of standard geometry and counted for 32 minutes in a nucleometer at infinite thickness.[10]

The well-known difficulty of securing complete combustion of nicotine was overcome by using 20–30 minutes of digestion. Careful tests of quantitative recovery of carbon as CO_2 indicated the efficacy of this procedure. In routine operation, however, the narrow margin between complete distillation of CO_2 and carry-over of nitric acid arising from the relatively large quantity of picric acid in the alkaloid dipicrate prevented use of this procedure for obtaining analytical figures for carbon. Because of this difficulty, moreover, distillations of CO_2 in the purification step were so conducted as to be complete for this gas even though some nitric acid was also obtained. The net result was, of course, that many routine analytical figures for carbon were high. In subsequent experiments, the oxalic acid salt of nicotine has been employed with far more satisfactory results.

Results

Table I contains the results of the culture experiments. The negligible activity of the carbonate samples indicates that neither nicotinic acid nor its ethyl ester had been incorporated into nicotine during the culture period. In view of the comparative length of the latter, it seems safe to conclude that nicotinic acid is unavailable directly and that the carboxyl carbon is unavailable indirectly as a source of alkaloid intermediates in the cell.

These results cannot have been complicated by the failure of the roots to absorb nicotinic acid or its ester. Experience in the laboratory of the senior author has shown that nicotinic acid is readily absorbed by excised roots, embryos and leaves of various species of plants including tobacco. Furthermore, Beevers, Goldschmidt and Koffler have recently demonstrated the utility of esters of biologically active, chemically weak acids in overcoming permeability difficulties.[11]

The possibility that nicotinic acid may have been used in a competitive process and hence removed from the sphere of alkaloid biosynthesis was removed by showing that radioactive nicotinic acid could be extracted from the aqueous residue left after the removal of nicotine. These residues were extracted continuously with ether, first in the presence of 2 *N* HCl and later at *p*H 3.0 in order to remove nicotinic acid. The acid was transferred from ether to *N* HCl (25 ml.) and its concentration estimated by suitable measurements in the ultraviolet. Approximately 2 mg. of nicotinic acid was recovered from the cultures which had been supplied with the free acid (row A, Table I). Upon removal of solvents the residue showed an activity of 0.75 μc./mg. C.[12] When the same procedure was applied to the residues from the alkaloid extraction of the ethyl nicotinate experiment, a

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(5) A. Murray, III, W. W. Foreman and W. Langham, THIS JOURNAL, **70**, 1037 (1948).

(6) P. R. White, "A Handbook of Plant Tissue Culture," Cattell Press, Lancaster, Pa., 1943.

(7) C. O. Willits, M. L. Swain, J. A. Connelly and B. A. Brice, *Anal. Chem.*, **22**, 430 (1950).

(8) D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).

(9) R. Steele and T. Sfortunato, Brookhaven National Laboratory publication BNL-T-6 (1949).

(10) R. Christian Anderson, Y. Delabarre and Aksel A. Bothner-By, *Anal. Chem.*, **24**, 1298 (1952).

(11) H. Beevers, E. P. Goldschmidt and H. Koffler, *Arch. Biochem.*, **39**, 236 (1952).

(12) These analyses were performed by oxidation of the samples to CO_2 on a standard micro-combustion train, followed by counting the CO_2 in gas counting tubes with a proportional counter. See footnote 9.

strongly absorbing solution was obtained which possessed peaks at 229 and 282 mμ and a minimum at 245 mμ. This material was hydrolyzed with 2 *N* HCl in the autoclave and again extracted with ether in the above manner. *Ca.* 0.5 mg. of active nicotinic acid was obtained; its specific activity was not determined. The nature of the absorbing substance(s) in the first extract at *p*H 3.0 is unknown.

It was noted that the insolubles from the ethyl nicotinate root cultures, after precipitation with trichloroacetic acid at 100°, were radioactive to the extent of 0.008 mμc./mg. C.[12] This fraction normally contains cellulose, protein and other high molecular weight substances.

Inasmuch as nicotinic acid has recently been shown to originate from nicotine during the fermentation of cigar filler tobacco,[13] it thus appears that whatever relationship the two may have in the living plant is confined to the catabolic side of metabolism and is unconcerned with nicotine biosynthesis.

[13] W. G. Frankenburg and A. M. Gottscho, *Ind. Eng. Chem.*, **44**, 301 (1952).

CHEMISTRY DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, LONG ISLAND, N. Y.

N-Nitrosoacetanilide as Polymerization Initiator

BY DELOS F. DETAR[1] AND CONSTANCE S. SAVAT[2]

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It has been shown by Blomquist, Johnson and Sykes[3] and by Hey and Misra[4] that substituted N-nitrosoamides will initiate the polymerization of styrene, methyl methacrylate and acrylonitrile. N-Nitrosoacetanilide itself does not appear to have been tested as an initiator. Although the initiator action suggests that free radicals are being produced as shown in the equation

$$\mathrm{ArN(NO)acyl} \longrightarrow \mathrm{ArN{=}NOacyl} \longrightarrow \mathrm{Ar.} + \mathrm{N_2} + \mathrm{acyl}$$

it was found experimentally by both groups of workers that a bromine-containing aryl group gave a bromine-containing polymer but that strangely enough bromine in the acyl group showed much less tendency to become incorporated in the polymer. This result seems to be in marked contrast to the behavior of *p*-bromobenzoyl peroxide[5] with styrene, which leads to incorporation of more bromobenzoate residue than bromophenyl residue.

Since we have been interested in potential sources of free radical intermediates, we have carried out some further polymerization experiments with N-nitrosoacetanilide to see whether this compound might possibly be a cationic initiator (a conceivable explanation of the bromine results) and to get further data about the initiator efficiency. Methyl methacrylate, acrylonitrile and styrene were polymerized, and qualitatively less polymerization occurred in the presence of *sym*-trinitrobenzene. Vinyl acetate and vinylpyridine showed little if any polymerization. Isobutylene was unaffected; there seemed to be no trace even of low molecular weight material such as trimers or tetramers. In six experiments the weight of the residue was zero within the experimental error after subtracting out the weight of the initiator products and of the inhibitor (Table I).

TABLE I

ATTEMPTED POLYMERIZATION OF ISOBUTYLENE

C_4H_8, g.	Nitroso-acetanilide, mmoles	*sym*-Trinitro-benzene, mmoles	Wt. of residue Obsd.	Wt. of residue Expected[a]
7.3	0	0	0	0
6.3	1	0	0.17	0.13
7.4	1	1	.24	.23
6.8	2	0	.33	.26
7.2	2	2	.53	.46
6.9	4	0	.51	.53
6.9	4	4	.93	.93

[a] Allowing for loss of nitrogen from the N-nitrosoacetanilide.

The styrene experiments are reported in Table II. Azo compounds and other products of initiator decomposition made all of the polymers highly colored.

TABLE II

AMOUNT OF POLYSTYRENE FORMED WITH N-NITROSOACETANILIDE AS INITIATOR

87 mmoles (9.2 g., 10 cc.) styrene used in each run

Nitroso-acetanilide, mmoles	*sym*-Trinitro-benzene, mmoles	Wt. polymer + NA residue (+ TNB) I[a]	Wt. polymer + NA residue (+ TNB) II[a]	Net wt. of polymer I[a]	Net wt. of polymer II[a]
0	0	0.00	0.00	0.00	0.00
0.5	0	0.86	0.96	0.79	.89
1	0	1.46	1.14	1.29	.97
2	0	1.55	1.24	1.28	.97
4	0	1.91	1.52	1.38	.99
8	0	2.47	1.93	1.41	.87
0.5	0.25	0.47	0.17	0.34	.04
1	0.5	.64	.34	.40	.10
2	1	.87	.63	.40	.16
4	2	1.42	1.19	.49	.26

[a] I. Tubes allowed to stand at 2–4° in the dark for five days, contents then poured into beakers and allowed to evaporate to constant weight at room temperature and atmospheric pressure. II. Reaction for two days in the dark at room temperature.

The effect of trinitrobenzene and the fact that the acrylates are polymerized readily while styrene is polymerized poorly[6] and isobutylene not at all are consistent with the hypothesis that a free radical rather than a cationic polymerization is taking place.

The low yields of polystyrene may result from such factors as inhibition due to reaction products and to wastage of initiator. But even in the complete absence of these effects only a low yield of polymer is to be expected for such a fast decomposing initiator. For a first order initiation reaction of 100% efficiency and for a bimolecular termination process without inhibition the amount of polymer

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[1] Department of Chemistry, University of South Carolina, Columbia, S. C.

[2] From the M.S. Thesis of Constance S. Savat, 1950.

[3] A. T. Blomquist, J. R. Johnson and H. J. Sykes, THIS JOURNAL, **65**, 2446 (1943).

[4] D. H. Hey and G. S. Misra, *Discussions Faraday Soc.*, **2**, 279 (1947).

[5] P. D. Bartlett and S. G. Cohen, THIS JOURNAL, **65**, 543 (1943).

[6] C. Walling, E. R. Briggs, W. Cummings and F. R. Mayo, *ibid.*, **72**, 48 (1950).

expected is given by eq. 1. S_0 and S_∞ are styrene concentrations at zero time and at "infinite" time

$$\log_{10}(S_0/S_\infty) = 2(0.434)k_2(1/k_1k_3)^{1/2}(\mathrm{NA}_0)^{1/2} \qquad (1)$$

NA_0 is the initial nitrosoacetanilide concentration, and k_1, k_2 and k_3 are rate constants for initiation, propagation and termination. Using the reported values of the rate constants ($k_1 = 7.7 \times 10^{-5}$, $k_2 = 44$, $k_3 = 2.4 \times 10^7$)[7,8] the maximum amount of polymer expected is as follows: with nitrosoacetanilide initially at 0.05 M (the 0.5 mmole experiment of Table II) about 37%, at 0.1 M about 48%. The maximum amount of polymer is increased at lower temperatures since k_1 has a higher temperature coefficient than either k_2 or k_3: 22 kcal., as compared with 7 kcal. or less.[7,8]

Experimental Part

N-Nitrosoacetanilide.—This was prepared by the method of DeTar.[9] The monomer samples were distilled before use to remove inhibitor.

Isobutylene Experiments.—A series of tubes of Pyrex glass was prepared, and weighed amounts of N-nitrosoacetanilide and of trinitrobenzene added. Phillips Pure Grade (99 mole % min.) isobutylene was distilled into these tubes which were immersed in a trichloroethylene both at solid carbon dioxide temperature. The tubes were sealed, placed in shields and allowed to remain at room temperature for 24 hours. The tubes were cooled, the capillary tips broken, and the isobutylene allowed to evaporate at room temperature and atmospheric pressure. The top of the tube was cut off, the tube weighed, rinsed thoroughly with methylene chloride, and weighed again in order to determine the weight of residue. The results are given in Table I.

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[7] W. S. M. Grieve and D. H. Hey, *J. Chem. Soc.*, 1800 (1934); R. Huisgen and G. Horeld, *Ann.*, **562**, 137 (1949).

[8] M. S. Matheson, E. E. Auer, E. B. Bevilacqua and E. J. Hart, THIS JOURNAL, **73**, 1704 (1951).

[9] D. F. DeTar, *ibid.*, **73**, 1446 (1951).

BAKER LABORATORY OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, NEW YORK

Reactions of N-Nitroso-2-acetamidobenzophenone

BY DELOS F. DETAR[1] AND CONSTANCE S. SAVAT

RECEIVED APRIL 6, 1953

We have been interested in reactions which may produce the *o*-benzoylphenyl radical (and other similar radicals) in our study of the mechanisms of certain free radical reactions.[2] The decomposition of diazotized 2-aminobenzophenone under alkaline conditions is under study at present as a source of these radicals. The thermal decomposition of N-nitroso-2-acetamidobenzophenone is a related reaction which might also be expected to yield the desired radical.[3] A preliminary study of this nitroso compound has given interesting results, but the reactions of this compound are too complex to be useful for our purposes at the present time.

In benzene solution N-nitroso-2-acetamidobenzophenone gives 2-benzoylbiphenyl 15%, fluorenone 7%, and unidentified higher molecular weight products. In methanol acidified with sulfuric acid the products were fluorenone 20%, 2-methoxybenzophenone 40% and 2-aminobenzophenone 40%. In acetic acid the products were fluorenone 23%, 2-acetoxybenzophenone 25% and 45% of 2-aminobenzophenone. The reactions in methanol and in acetic acid thus seem to be ionic reactions.

Experimental Part

N-Nitroso-2-acetamidobenzophenone.—2-Aminobenzophenone was prepared from N-tosylanthranoyl chloride, benzene and aluminum chloride.[4] Acetylation with acetic anhydride gave 2-acetamidobenzophenone, m.p. 87–88.5°; Lothrop and Goodwin[5] report a m.p. of 88°. This was converted to the nitroso compound. To 8 g. of the amide, 12 g. of potassium acetate, 56 ml. of glacial acetic acid, 24 ml. of acetic anhydride was added 4.6 g. of nitrosyl chloride in 13.4 g. of acetic anhydride during ten min. at 5°; after an hour at 0°, the mixture was stirred with 800 ml. of ice-water to precipitate the nitrosoamide. This was recrystallized from 125 ml. of acetic acid plus added water, giving 52% of yellow crystals, m.p. 72° dec. It is not stable at room temperature, but can be preserved for several days at Dry Ice temperature.

Anal. Calcd. for $C_{15}H_{12}O_3N_2$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.20; H, 4.63; N, 11.07.

Reactions.—The following thermal decomposition reactions of N-nitroso-2-acetamidobenzophenone were studied: 2 g. of the nitrosamide in 20 ml. of benzene for 15 hours at room temp.; 1 g. in 50 ml. of methanolic 0.04 M sulfuric acid for one hour at 50–65° and then for two days at room temp.; 1 g. in 15 ml. of glacial acetic acid for one hour at 100° and then two days at room temperature.

Isolation of and Estimation of Products.—The benzene reaction mixture was subjected to exhaustive steam distillation, yielding fractions of 0.26 g. and 0.23 g. after extraction with methylene chloride. A semi-quantitative analysis was made for fluorenone and for 2-benzoylbiphenyl by measurement of the optical absorbance of ethanol solutions of these fractions at 2300, 2570 and 2650 Å. On evaporation of the ethanol the first residue yielded crystals of 2-benzoylbiphenyl, m.p. 83.3–85.3°, m.p. with authentic material[2] 86–87°, and a small amount of yellow crystalline material, m.p. 83–84°. The yellow crystalline material was subjected to microscopic examination and was identical with fluorenone in the following respects: hexagonal plates, highly birefringent, four angles about 148°, two angles about 64°, parallel extinction. The second fraction yielded only 2-benzoylbiphenyl, m.p. 84.3–85.3°, in crystalline form.

The methanol reaction mixture was neutralized with sodium hydroxide, distilled to remove most of the methanol, water was added, and then the resulting mixture was extracted with methylene chloride. The methylene chloride layer was subjected to exhaustive steam distillation and the distillates, after extraction with methylene chloride and evaporation to dryness, yielded 0.95 g. of residue. The infrared spectra of this residue had peaks characteristic of fluorenone, benzophenone, 2-methoxybenzophenone, 2-aminobenzophenone and one or more unidentified other materials. A semi-quantitative analysis based on absorbance at 2150, 2350 and 2570 Å. was made for fluorenone, 2-aminobenzophenone and 2-methoxybenzophenone.

The acetic acid reaction mixture was distilled to remove most of the acetic acid and the residue was treated with methylene chloride and aqueous sodium hydroxide. The methylene chloride layer was subjected to steam distillation and gave 0.59 g. of neutral residue. Semi-quantitative analysis of an ethanol solution using absorbance at 2350, 2570 and 2650 Å. gave estimates of the amounts of fluorene, 2-aminobenzophenone and 2-acetoxybenzophenone. On evaporation of the ethanol, yellow crystals of fluorenone separated, m.p. 78.5–81.5°, mixed m.p. with authentic fluorenone 79–82°. The infrared spectra of the residue obtained by evaporation of the mother liquor had peaks at 5.87, 6.24, 10.90 and 13.54 characteristic of fluorenone; at 5.70, 6.28, 6.95, 7.78, 7.95, 8.43 and 13.25 characteristic of 2-acetoxybenzophenone, and at 3.07 and 3.50 characteristic of 2-aminobenzophenone. In addition to the listed

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[1] Department of Chemistry, University of South Carolina, Columbia, S. C.

[2] D. F. DeTar and S. Sagmanli, THIS JOURNAL, **72**, 965 (1950).

[3] D. F. DeTar, *ibid.*, **73**, 1446 (1951).

[4] D. F. DeTar and H. Scheifele, *Org. Syntheses*, **32**, 8 (1952).

[5] W. C. Lothrop and P. A. Goodwin, THIS JOURNAL, **65**, 363 (1943).

peaks, this residue showed absorption peaks for all of the individual peaks of the respective compounds.

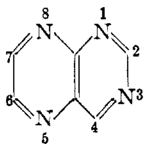
BAKER LABORATORY OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, NEW YORK

Spectrophotometric Determination of the Ionization Constants of Pteridine, 2-Aminopteridine and 4-Aminopteridine

BY DELOS F. DETAR,[1] C. K. CAIN AND B. SPENCER MEEKS, JR.[2]

RECEIVED MAY 5, 1953

Interest in the chemistry of pteridine (I) and its derivatives has been especially great since the discovery that the pteridine nucleus is an important part of the folic acid molecule. Until very recently pteridine itself and its simple monofunctional derivatives were largely unknown, a situation perhaps stemming from the fact that all of the interesting naturally occurring derivatives were tri- and tetra- substituted pteridines.



A few years ago Jones[3] made a preliminary report of the preparation of pteridine. More recently the chemistry of the simple pteridines has been admirably worked out by Albert, Brown and Cheeseman.[4] The present investigation was undertaken before the report of this work was available. Albert, Brown and Cheeseman measured the pK of the acid forms (BH^+) of the pteridines by potentiometric titration. In this work the pK^* values have been measured spectrophotometrically by the general procedure described by Sager, Schooley, Carr and Acree.[5] The results are presented in Table II.

TABLE I

SPECTROPHOTOMETRIC DATA FOR CALCULATION OF THE IONIZATION CONSTANT OF 2-AMINOPTERIDINE

pH of buffer (0.02 M)	Extinction coefficients × 10^{-4} at various wave lengths, mμ 260	265	290	300	305
6.98	0.751	0.681	0.086	0.076	0.080
7.14	.748	.681	.084	.075	.079
7.27	.738	.675	.084	.075	.078
Av. ϵ_B[a]	.746	.679	.085	.075	.079
1.90	0.130	0.176	0.646	0.769	0.745
1.98	.133	.175	.645	.770	.744
2.11	.135	.178	.646	.771	.748
Av. ϵ_i[a]	.133	.177	.645	.770	.746
4.19	0.382	0.383	0.439	0.513	0.500
4.30	.410	.406	.406	.474	.463
4.68	.549	.517	.266	.300	.296

[a] See text for definitions.

TABLE II

CALCULATED VALUES OF pK^*

pH	pK^* calcd. at 275 mμ	285 mμ
Pteridine: av. pK^* 4.15 ± 0.06[a] (4 samples) (4.12 ± 0.05)[b]		
3.85	4.23	4.13
4.21	4.28	4.09
4.30		4.12
4.67		4.07

	305	320	325
4-Aminopteridine: av. pK^* 3.514 ± 0.020[a] (3 samples) (3.56 ± 0.08)[b]			
3.45	3.48	3.48	3.50
3.62	3.49	3.50	3.50
3.93	3.57	3.55	3.56

pH	260	265	290	300	305
2-Aminopteridine: av. pK^* 4.386 ± 0.020[a] (3 samples) (4.29 ± 0.03)[b]					
4.19	4.35	4.35	4.42	4.42	4.42
4.30	4.38	4.38	4.43	4.43	4.43
4.68	4.35	4.36	4.36	4.36	4.36

[a] For error limits see text. [b] pK by titration as reported by Albert, Brown and Cheeseman.[4] Error figures represent maximum deviations from the calculated titration curve and apparently are derived from a single determination.

The agreement between the two sets of pK values is very good.

Experimental Part

Pteridines.—The pteridine and 2-aminopteridine samples were prepared by a method similar to that described by Albert, Brown and Cheeseman[4] but independently worked out in this Laboratory. The samples were sublimed and recrystallized several times until further purification gave no change in the ultraviolet spectra. The 4-aminopteridine was a sample prepared by Mr. N. T. Gehshan.[6]

Buffer Solutions.—The following buffers were used: pH 0.5–1.5, hydrochloric acid; 1.5–3.5, citrate; 3.5–5.5, acetate; 5.5–8.0, phosphate; 8.0–12.0, borate; 12.0, sodium hydroxide. Buffer concentrations were 0.02 M, and pH values were read using a Leeds and Northrup pH meter with calomel and glass electrodes standardized at pH 4 and pH 7 against Bureau of Standards potassium acid phthalate and Leeds and Northrup phosphate buffer.

Spectrophotometric Measurements.—A Beckman model DU spectrophotometer was used in this work. In obtaining the extinction coefficients such as those given in Table I two sets of absorbance readings were taken on each sample, one set of readings with solvent in cell 1 and solution in cell 2, and another set with solvent in cell 2 and solution in cell 1. The two absorbance values were averaged for each wave length. This averaging procedure increases the accuracy by cancelling out bias between the two cells, it provides increased precision, and it eliminates gross errors.

Equations for Calculation of pK^*.—For a compound BH^+, the acid strength that is determined spectrophotometrically is defined by eq. 1

$$K = C_B a_{H_3O^+}/C_{BH^+} \quad (1)$$

The ionization constant is rather insensitive to ionic strength since $a_{H_3O^+}$ and a_{BH^+} tend to be changed to about the same extent by the ionic environment. Since the buffer concentrations used were low (about 0.02 M), the pK^* values reported in Table II are probably equal to pK_a within the experimental error.

The values of pK^* were calculated using eqs. 2 and 3

$$pK^* = pH + \log [\alpha/(1 - \alpha)] \quad (2)$$

α = fraction of the compound which is in the form BH^+. In terms of spectrophotometrically measured quantities α is given by eq. 3

$$\alpha = (\epsilon - \epsilon_B)/(\epsilon_i - \epsilon_B) \quad (3)$$

where ϵ_B is the extinction coefficient of the basic form, ϵ_i of

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[1] Department of Chemistry, University of South Carolina, Columbia, S. C.

[2] From the Ph.D. thesis of B. Spencer Meeks, Jr.

[3] W. G. M. Jones, *Nature*, **162**, 524 (1948).

[4] A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951); 1620, 4219 (1952); A. Albert, *Quart. Rev.*, **6**, 197 (1952).

[5] E. E. Sager, M. R. Schooley, A. S. Carr and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 521 (1945).

[6] N. T. Gehshan, M.S. Thesis, Cornell University, 1948.

the acidic form BH^+ and ϵ the extinction coefficient of the mixture of the two forms.

Procedure.—The first step was to obtain the absorption spectra curves of the compound in a series of buffers in order to ascertain regions in which the acidic and basic forms of the compound differ significantly. The second step was to select suitable wave lengths for a more careful study using a much wider series of buffer solutions. A plot of the extinction coefficients against pH served to locate the pH regions at which the absorption of the pure acidic and basic forms may be obtained. Such plots also showed that multiple ionization was absent in the pH range covered.

Typical spectrophotometric data are given for 2-aminopteridine in Table I in order to illustrate the type of precision attainable. The calculation of pK^* is illustrated in Table II. The variance (s^2) of a single value of pK^* is 0.00114 as estimated from the deviation of the individual values from the average. The expected variance can also be estimated from the data in Table I using the principle of propagation of error. The contribution to the variance of pK^* due to spectrophotometric errors is about 0.0005, and that due to variance of pH determinations is about 0.0009, giving a total variance of 0.0014. The two variance estimates are in excellent agreement. Simple averaging of the pK^* values is permissible since it can be shown that all the values have nearly the same weight. The actual number of independent determinations of pK^* is three, since three samples of 2-aminopteridine were used for each pH range (a separate sample at each pH value of Table I). Thus the variance of the average is 0.00038, corresponding to a standard deviation of the average of 0.020 pK unit.

Pteridine itself offered considerable difficulties. It was found that spectrophotometer readings drifted and it was necessary to obtain a series of readings over a period of about an hour. The zero time reading was obtained by extrapolating a plot of log ϵ against time back to zero time. The instability of the spectral data resulted in rather larger uncertainty in pK^* for this compound. A "weighted" average of 4.17 was calculated, based on variance estimates of individual pK^* values due to spectrophotometric errors. This differs very little from the straight average, and there are an insufficient number of measurements to justify the use of weighting.

DEPARTMENT OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, NEW YORK

The Selective Demethylation of Homoveratrylamine[1]

BY K. E. HAMLIN AND F. E. FISCHER

RECEIVED JULY 2, 1953

During the course of another investigation,[2] substantial quantities of isovanillin or a compound leading to 3-hydroxy-4-methoxyphenethylamine were required. Synthesis of isovanillin by various literature methods including the application of a variety of demethylating agents to veratraldehyde[3] has not been satisfactory. The experiments of Birch[4a,b] involving the demethylating action of sodium and liquid ammonia on various phenol ethers suggested a possible solution to the problem. Significantly, by this reaction, Birch was able to convert 3,4-dimethoxytoluene to 4-methoxy-*m*-cresol in 70% yield.

Accordingly, the action of sodium and liquid ammonia on a group of veratryl compounds was studied. The application of this method to veratraldehyde, veratric acid and homoveratronitrile was singularly unfruitful. In these cases, guaiacol was the only identifiable product and was found only in trace amounts. However, when homoveratrylamine was treated with sodium and liquid ammonia, a selective demethylation occurred, and 3-hydroxy-4-methoxyphenethylamine was obtained in excellent yields. Inasmuch as homoveratrylamine is readily available, it may now serve as a convenient source of isovanillyl derivatives.

Experimental

3-Hydroxy-4-methoxyphenethylamine.—With stirring, 63.4 g. (0.35 mole) of 3,4-dimethoxyphenethylamine was added in a slow stream to a solution of 26.2 g. (1.14 atoms) of sodium in 700 cc. of liquid ammonia. The resulting mixture was allowed to stand for six hours until it reached room temperature and was then decomposed by cautious addition of ice. This material was extracted with ether to remove unreacted amine, and the aqueous phase was aerated to remove excess ammonia and was finally made acidic while cooling. Following ether extraction, the acid layer was treated with excess sodium bicarbonate solution and the amine thus released was extracted by means of butanol. The butanol extract was dried over anhydrous magnesium sulfate and was then treated with ethereal hydrogen chloride. The crystalline material thus formed was recrystallized from methanol–ether. In this manner, 61 g. (85% yield) of 3-hydroxy-4-methoxyphenethylamine hydrochloride was obtained melting at 204–205.5°; reported[5] m.p. 201–203°.

Anal. Calcd. for $C_9H_{13}NO_2 \cdot HCl$: N, 6.88. Found: N, 6.85.

N-Acetyl-3-hydroxy-4-methoxyphenethylamine.—A solution of 20.4 g. (0.1 mole) of 3-hydroxy-4-methoxyphenethylamine hydrochloride in 15.3 g. (0.15 mole) of acetic anhydride was stirred while adding portionwise 27 g. (0.32 mole) of sodium bicarbonate. The mixture was then heated on a steam-bath for one hour. After cooling, the resulting crystalline material was filtered, washed with water and dried. After recrystallization from a mixture of absolute ethanol and heptane, the N-acetyl-3-hydroxy-4-methoxyphenethylamine melted at 124–125°; yield 12.9 g., 53%.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N 6.70. Found: C, 63.30; H, 7.04; N, 6.74.

Acknowledgment.—We are indebted to E. F. Shelberg, Chief Microanalyst, and his staff for the analytical data.

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[1] Presented before the Medicinal Chemistry Division at the 124th Meeting of The American Chemical Society, Chicago, Illinois, 1953.

[2] M. B. Moore, H. B. Wright, M. Freifelder and R. K. Richards, *J. Am. Pharm. Assoc.*, in press.

[3] M. B. Moore, personal communication.

[4] (a) A. J. Birch, *J. Chem. Soc.*, 102 (1947); (b) George W. Watt, *Chem. Revs.*, **46**, 339 (1950).

[5] F. A. Ramirez and A. Burger, THIS JOURNAL, **72**, 2781 (1950).

ABBOTT LABORATORIES
NORTH CHICAGO, ILLINOIS

The Reaction of Cyclohexene with Bromine, Iodine Monobromide and Iodine Monochloride

BY ALEXANDER GERO, JOSEPH J. KERSHNER AND RICHARD E. PERRY

RECEIVED JUNE 21, 1953

As a preliminary to studies on enol titration, we have investigated the relative rates of addition of various halogens to an olefin. Rate studies on such additions have been performed[1] but we know of no comparative studies on the rates of addition of various halogens to the same olefin, under the same conditions.

Cyclohexene was chosen as the standard olefin because it is easily available in good purity, sufficiently high-boiling for easy handling and non-

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[1] For literature, see A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2d ed., John Wiley and Sons, Inc., New York, N. Y., p. 432 ff.

polar. Its reactions with bromine, iodine bromide and iodine chloride were studied, using carbon tetrachloride and acetic acid as solvents. In this way, polarity effects were brought out clearly.

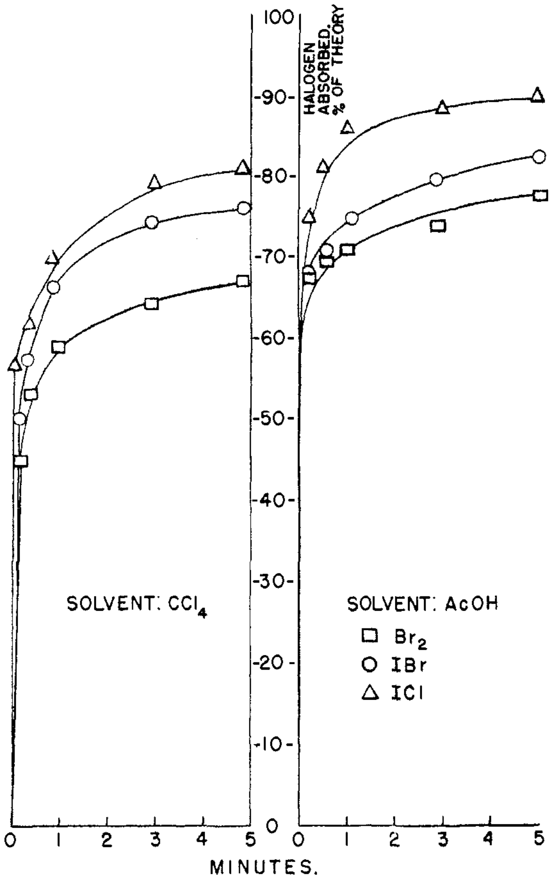

Fig. 1.

Representative results are shown in Figs. 1 and 2. They are in agreement with the accepted polar mechanism of olefin addition reactions,[1] since the most polar halogen (iodine monochloride) adds fastest, the least polar (bromine) slowest, and the more polar solvent (acetic acid) accelerates the addition. It is remarkable that bromine is consumed far beyond the theoretical limit of addition; in carbon tetrachloride in two days 137%, and in three days 152% of the theoretical amount of bromine had disappeared. In acetic acid the bromine absorption was 106% after three days and 118% after five days. No evidence of substitution was found with either of the mixed halogens in any solvent. This seems to indicate that the polarity of an inter-halogen molecule inhibits its break-up into atoms as required for substitution.[2] The inference is that bromine is also somewhat polarized in acetic acid solution.

Solutions of iodine monobromide, which are no more difficult to prepare than those of bromine, might well replace the latter, now generally used, for quantitative unsaturation tests. With iodine monobromide decoloration occurs much more rapidly and substitution is absent.

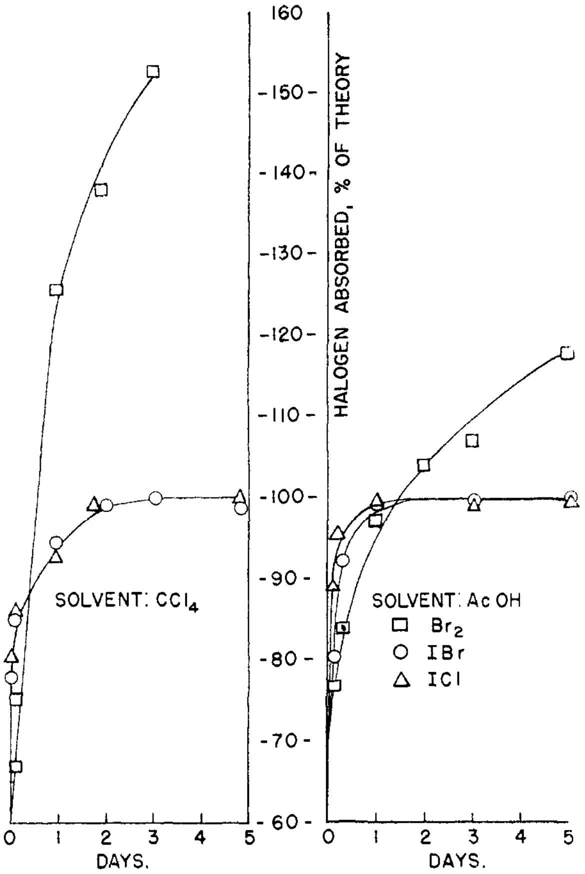

Fig. 2.

Experimental

Ten mg. of cyclohexene was mixed with 5 ml. of 0.05N halogen solution and kept in the dark at 25° for periods ranging from 15 seconds to five days. Then the mixture was stirred mechanically into excess aqueous iodide solution and the liberated iodine titrated. With acetic acid as the solvent, the iodide solution was also buffered with disodium phosphate, for the dihalocyclohexanes are easily dehalogenated by iodide ion at low pH. From the results of the titration the halogen absorbed by the cyclohexene was calculated.

HAHNEMANN MEDICAL COLLEGE
PHILADELPHIA 2, PENNSYLVANIA

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[2] H. C. Brown, M. S. Kharasch and T. H. Chao, THIS JOURNAL, **62**, 3435 (1940).

The Application of the Glass Electrode in Liquid Ammonia Systems[1,2]

BY ARNO H. A. HEYN AND MARTHA J. BERGIN

RECEIVED MARCH 24, 1953

Glass electrodes have been used for measurement of the hydrogen ion activity in some cases in nonaqueous solutions.[3,4] However, a glass electrode which had been thoroughly hydrated by immersion in water was used. It is likely, therefore, that the system measured was "non-aqueous" only with respect to the solution before the electrode had been immersed and that equilibria with the hydrated glass surface established the potentials. Work by

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[1] From a Ph.D. Thesis of Martha J. Bergin, May, 1952.

[2] Supported in part by a Grant-in-aid of the Research Corporation, New York, N. Y.

[3] L. Lykken, *et al.*, *Ind. Eng. Chem.*, *Anal. Ed.*, **16**, 219 (1944).

[4] L. Lykken, ASTM Symposium on pH Measurement, Technical Publication No. 73, p. 71 (1946).

Hubbard and co-workers[5] has shown that the glasses which were more soluble in water, and were therefore more highly hydrated, showed the best *p*H response when used as electrodes. This points out the importance of hydration for glass electrode action.

The question arises, whether glass electrode action exists in liquid ammonia solution. Liquid ammonia ionizes to a very slight extent to form NH_4^+ and NH_2^-, where the ammonium ion, analogous to the hydronium ion, is the solvated proton.[6,7] This suggests that glass electrodes might respond to changes in the ammonium ion activity in liquid ammonia in a similar manner as to changes in the hydronium ion concentration in aqueous solutions.

The following conditions would have to prevail in order to make glass electrode action in liquid ammonia possible: 1. The measuring instrument used must be sufficiently sensitive so that the increase in the resistance of the glass electrode with a decrease in temperature to below the boiling point of ammonia does not interfere. 2. Suitable reference electrodes for liquid ammonia solutions must be used. 3. The glass used must be solvated by liquid ammonia. 4. The ammonium ions in the glass must be in equilibrium with those in the solution.

After initial experiments failed to give evidence for electrode action in liquid ammonia a systematic investigation of points 1, 2, and 3 showed that the failure of glass electrode action is not due to these causes, but is probably due to lack of an equilibrium of the ammonium ion between the glass and the solution.

In order to show that the decrease in temperature necessitated by the low boiling point of ammonia (−33.4°) was not responsible for lack of glass electrode action, the electrical resistance of glass electrodes was measured over the range 6 to 50° in aqueous solutions and over −35 to 45° in alcohol–water solutions. In both cases the resistance was found to follow the relationship known to hold for higher temperatures[8]

$$\log R = A + (B/T)$$

where R is the observed resistance, T the absolute temperature and A and B are constants (Fig. 1). In addition, *p*H measurements could be obtained both at room temperature and at −29° in the water–alcohol system. In liquid ammonia solutions, however, the resistance of the glass electrodes appeared to be infinite (no current could be measured) at −35° or even when the temperature was increased to −1°.

Lead–lead nitrate electrodes were used as reference electrodes in the cell system studied

Lead	$Pb(NO_3)_2$, 0.1 *M*	NH_4NO_3 Varying concn.	Glass membrane	NH_4NO_3, 0.1 *M*	$Pb(NO_3)_2$ 0.1 *M*	Lead
	Liquid ammonia			Liquid ammonia		

The potential of a reference electrode in such a system is unimportant provided it remains constant. Although the lead–lead nitrate electrode is not useful in aqueous work since a reproducible potential cannot be obtained owing to lead hydroxide formation, this electrode has been used in electrochemical measurements in liquid ammonia. In many respects, its significance for electrochemical measurements in liquid ammonia parallels that of the hydrogen electrode in aqueous solutions.[9] Solvation of the glass by ammonia is expected to have a bearing on glass electrode action in liquid ammonia. For all measurements in liquid ammonia solutions the glass electrodes used were left in contact with the liquid ammonia solution for several hours, and in some cases for days. Under these conditions solvation should have occurred. To be perfectly sure, however, that ammonium ions had entered the glass structure, sodium ions were partially replaced by ammonium ions electrolytically by the method of Hurd and co-workers.[10,11] According to nitrogen analyses of the glass, 60% of the sodium ions were thus replaced. Such membranes gave equally negative results.

All of the several glasses tried (Corning 015, Beckman "General Purpose," Beckman "Type E") failed to show glass electrode response in liquid ammonia solution.

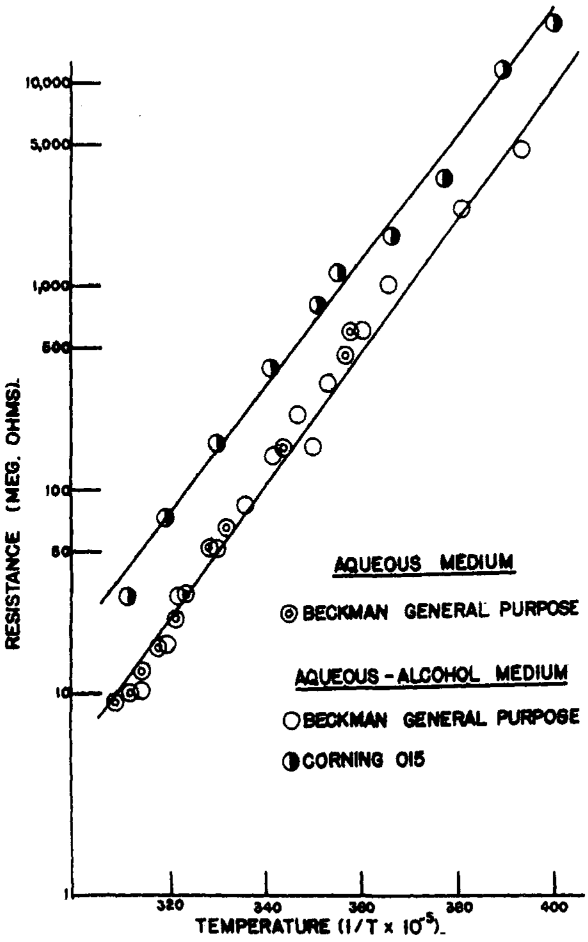

Fig. 1.—Resistance of glass electrodes *vs*. temperature.

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(5) D. Hubbard, *J. Research Natl. Bur. Standards*, **36**, 511 (1946).

(6) V. A. Pleskov and A. M. Monoszon, *Acta Physiochim. U.S.S.R.*, **1**, 725 (1935).

(7) E. C. Franklin, THIS JOURNAL, **27**, 820 (1905).

(8) E. L. Eckfeldt and G. A. Perley, *J. Electrochem. Soc.*, [2] **98**, 37 (1951).

(9) V. A. Pleskov and A. M. Monoszon, *J. Phys. Chem., U.S.S.R.*, **4**, 696 (1933).

(10) C. B. Hurd, E. W. Engel and A. A. Vernon, THIS JOURNAL, **49**, 447 (1927).

(11) J. S. Krudl, A. S. Trumin and C. D. Scott, *J. Ceram. Soc.*, **24**, 225 (1941).

Even changing the nature of the ion produced no electrode action in liquid ammonia. In aqueous solutions at a high *p*H other ions, most frequently sodium ions, will take part in the transport of current, causing the well known "sodium error" of glass electrodes. The presence of a large excess of sodium ion in liquid ammonia solution did not produce an electrode response with any of the glasses tested.

Ammonium ions in liquid ammonia are the counterpart of hydronium ions in water: they change colors of *p*H indicators, catalyze solvolysis reactions, are displaced by certain metals and set up potentials with a hydrogen electrode.[9] Glass electrode action might therefore also be expected in liquid ammonia solutions. Nevertheless, there are differences: the heat of solvation of the proton is 17 kcal./mole lower in liquid ammonia than in water, indicating a more stable system in ammonia. The low mobility of ammonium ions in ammonia as compared with hydronium ions shows that there is no "Grotthuss" conduction in liquid ammonia.

Though complete exchange exists between NH_4^+ and NH_3,[12] the dissociation of NH_4^+ into H^+ and NH_3 is very slight. Even in water ammonium ions have not been found to cause glass electrode "errors" such as sodium ions. In terms of Dole's statistical treatment of glass electrode action,[13] the ammonium ion does not appear to have sufficient energy to exchange with the proton on the glass surface. Therefore, it seems plausible that the ammonium ions in liquid ammonia may not be in equilibrium with ions on the surface of the electrode.

Experimental

The Cell.—A cylindrical cell of 70 mm. diameter provided with a large ground glass joint and several smaller joints in the head for the lead-plated platinum reference electrode and glass electrode was used. The inside of the glass electrode was also filled with liquid ammonia and was provided with another reference electrode. The cell was cooled by immersion in a Dewar flask in acetone and Dry Ice.

Measuring Equipment.—A Beckman model G *p*H meter was used for the purpose of detecting *p*H response. A Precision multirange test meter was used for all current measurements. With this meter 0.1 microampere can be detected. A 2400-volt d.c. power supply was placed in series with the cell and the ammeter. When *p*H measurements were attempted the power supply was removed and the *p*H meter inserted.

***p*H Sensitive Glasses.**—Initial studies were confined entirely to Corning 015 type glass. In all cases the *p*H sensitivity of the membranes was first checked in water. The membranes were then subjected to evacuation followed by long periods of immersion in liquid ammonia. This procedure was adopted to ensure complete replacement of the water in the membrane by liquid ammonia.

Membranes composed of *p*H sensitive glasses of different compositions were similarly tested, *i.e.*, Beckman General Purpose glass and Beckman type E.

Measurements and Results.—A power supply of 300 and 2400 v. d.c., respectively, the cell and the microammeter were connected in series. The resistance of the glass membrane was calculated from Ohm's law. Measurements were made in aqueous solution between 6° and 52° for Corning 015 and Beckman general purpose glass and between 25° and 30° for the Beckman type E glass. The resistance for Corning 015 glass varied between 21 megohms at 52° to 1300 ± 200 megohms at 6°. For Beckman General Purpose glass the resistance varied between 9 megohms at 50° and 600 megohms at 7°.

Similar measurements were performed with aqueous alcohol solutions containing 80% of alcohol and containing a small amount of hydrochloric acid. Measurements could now be carried out to −33°, giving a resistance of 2×10^3 megohms for Corning 015 glass and 1.2×10^3 megohms for Beckman General Purpose glass.

In liquid ammonia solutions no current could be observed in the temperature range investigated, −35 to −1°.

BOSTON UNIVERSITY
DEPARTMENT OF CHEMISTRY
BOSTON 15, MASS.

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(12) C. J. Nyman, S. C. Fung and H. W. Dodgen, THIS JOURNAL, **72**, 1033 (1950).

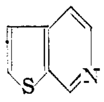
(13) M. Dole, *J. Chem. Phys.*, **2**, 862 (1934).

Sulfur Analogs of Isoquinolines and β-Carbolines. III. The Pomeranz–Fritsch Reaction

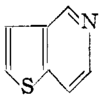
BY WERNER HERZ AND LIN TSAI

RECEIVED JUNE 8, 1953

In a previous paper[1] it was demonstrated that isosteres of substituted isoquinolines may be prepared by applying the Bischler–Napieralski reaction to derivatives of thiophene. This work is being extended in our laboratory. It also seemed desirable to investigate the feasibility of synthesizing the parent substances, thieno[2,3-c]-(I) and thieno-[3,2-c]pyridine (II) by means of the Pomeranz–Fritsch reaction[2] inasmuch as 2- and 3-thiophenealdehyde are readily available. A comparison of the properties of these substances with those of isoquinoline would be of great interest.



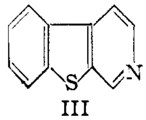
I



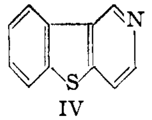
II

Although the condensation of the aldehydes with aminoacetal proceeded with great ease, cyclization of the resulting Schiff bases under the usual conditions gave only small yields of the desired thienopyridines I and II. This seems to be due largely to resinification under the influence of sulfuric acid at the temperatures necessary to effect cyclization. Slightly better yields were achieved by using a mixture of polyphosphoric acid and phosphorus oxychloride as cyclizing agent. To our knowledge this medium has not previously been used in such reactions.

In order to supplement our earlier work on the preparation of sulfur analogs of β-carbolines[3] studies were also carried out which had as their aim the preparation of thianaphtheno[3,2-c]-(III) and thianaphtheno[2,3-c]pyridine (IV) from the aminoacetals derived from 2- and 3-thianaphthenealdehyde. III[4] and IV[5] have since been prepared by different, somewhat less convenient, routes. The cyclization did not proceed in sulfuric acid solution, but using polyphosphoric acid–phosphorus oxychloride the



III



IV

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(1) W. Herz, THIS JOURNAL, **73**, 351 (1951).

(2) W. J. Gensler, *Organic Reactions*, **6**, 191 (1951).

(3) W. Herz, THIS JOURNAL, **72**, 4999 (1950).

(4) H. Kotake and T. Sakan, *J. Inst. Polytech. Osaka City Univ., Ser. C.*, **2**, No. 1, 25 (1951); *C.A.*, **46**, 6121 (1952).

(5) D. B. Capps and C. S. Hamilton, THIS JOURNAL, **75**, 697 (1953).

yields of thianaphthenopyridines were 18 and 12%. This suggests that polyphosphoric acid may be a useful cyclizing agent for other syntheses using the Pomeranz–Fritsch method.

The ultraviolet spectrum of I in isoöctane solution (maxima at 223, 227, shoulder at 242, maxima at 293, 299 and 304 mμ; corresponding log ε's 4.24, 4.23, 3.68, 3.88, 3.76) exhibits marked resemblance to that of isoquinoline,[6] but that of II (maxima at 222, 238, 256, shoulder at 274, maxima at 281, 291 and 337 μ, log ε's 4.55, 3.58, 3.63, 3.45, 3.43, 3.30, 2.35) does not possess this similarity in the longer wave length region. It may be that in the spectrum of II the 290–310 mμ band of I is sufficiently reduced in intensity and displaced toward shorter wave lengths to give rise to the less well pronounced maxima in the region 270–295 mμ. A somewhat similar situation is found in the spectra of the two isomeric thianaphthenopyridines III (maxima at 232, 272, 280, 328 and 338 mμ, log ε's 4.61, 3.88, 4.03, 3.53 and 3.60) and IV (maxima at 230, 252, 305 and 316 mμ, log ε's 4.70, 4.33, 3.15 and 3.21).

Acknowledgment.—This work was supported in part by a grant from the U. S. Public Health Service, Department of Health, Education and Welfare.

Experimental[7]

Diethyl 2-Thenylideneaminoacetal.—A mixture of 11.2 g. of 2-thiophenealdehyde and 14 g. of aminoacetal was heated on the steam-bath. After two hours ether was added and the mixture was dried over sodium sulfate. Removal of ether followed by fractionation *in vacuo* yielded 19.6 g. (86%) of condensation product, b.p. 125–128° (2.5 mm.). The analytical sample boiled at 115–118° (1.9 mm.), $n^{23}\text{D}$ 1.5231.

Anal. Calcd. for $C_{11}H_{17}NSO_2$: C, 58.12; H, 7.54. Found: C, 58.16; H, 7.55.

Diethyl 3-Thenylideneaminoacetal.—Condensation of similar quantities of 3-thiophenealdehyde[8] and amino acetal yielded 20.5 g. of product, b.p. 120–121° (1.8 mm.). The analytical sample boiled at 128° (3 mm.), $n^{23}\text{D}$ 1.5179.

Anal. Calcd. for $C_{11}H_{17}NSO_2$: C, 58.12; H, 7.54. Found: C, 58.24; H, 7.39.

Diethyl 2-Thianaphthenylideneaminoacetal.—The yield of condensation product from 14.4 g. of 2-thianaphthenealdehyde[9] and 12 g. of aminoacetal was 19 g. (78%), b.p. 155–161° (0.2 mm.). The liquid solidified upon standing and was sublimed for analysis at a bath temperature of 110–125° (0.5 mm.), m.p. 45–46°.

Anal. Calcd. for $C_{15}H_{19}O_2NS$: C, 64.95; H, 6.90; N, 5.05. Found: C, 65.05; H, 7.17; N, 5.15.

Diethyl 3-Thianaphthenylideneaminoacetal.—The yield of product, b.p. 155–165° (1.5 mm.), was 20.4 g. (83%). The analytical sample boiled at 162–165° (1.5 mm.), $n^{23}\text{D}$ 1.5711.

Anal. Calcd. for $C_{16}H_{19}NSO_2$: C, 64.95; H, 6.90. Found: C, 64.93; H, 6.82.

Cyclizations. (A) Sulfuric Acid Method.—To 6 g. of ice-cold sulfuric acid was gradually added 3 g. of the aminoacetal, then another 9 g. of sulfuric acid and 2 g. of phosphorus oxychloride. The mixture was kept at 160° for 1.5 hours, in the course of which it resinified, cooled and diluted with water. The filtered solution was extracted with ether (this fraction usually yielded aldehyde formed by hydrolytic cleavage of the acetal), made basic and again extracted with ether. The basic fraction after drying and removal of ether was distilled or dissolved in a little ethanol and treated with 5 ml. of a saturated solution of picric acid in ethanol. The picrate was collected after chilling and recrystallized from ethanol.

(B) Polyphosphoric Acid Method.—A solution of 1 g. of phosphorus oxychloride in 30 g. of polyphosphoric acid was heated to the desired temperature in an oil-bath, the aminoacetal added with stirring, the mixture stirred for 5 to 30 minutes and then poured into ice-water. The aqueous solution was extracted with ether, made basic, saturated with ammonium sulfate and again extracted with ether. The ethereal solution was dried and the solvent removed under reduced pressure. The residue was sublimed *in vacuo*.

Thieno(2,3-c)pyridine (I).—Procedure A yielded 102 mg. of a picrate which decomposed at 207.5–208.5°.

Anal. Calcd. for $C_{13}H_8N_4SO_7$: C, 42.86; H, 2.21; N, 15.38. Found: C, 43.42; H, 2.26; N, 15.26.

Procedure B, using 10 g. of Schiff base in 200 g. of polyphosphoric acid and 10 g. of phosphorus oxychloride at 120° for 30 minutes, yielded 225 mg. of crude thieno(2,3-c)pyridine by fractional sublimation *in vacuo* of the basic residue. Two sublimations at a bath temperature of 70° (0.5 mm.) furnished colorless crystals, m.p. 54–55°.

Anal. Calcd. for C_7H_5NS: C, 62.19; H, 3.73. Found: C, 62.39; H, 3.90.

After collection of the first fraction, the bath temperature was raised to 130–140° and 90 mg. of a higher-melting solid, m.p. 142–144°, was obtained. This material has not yet been identified.

Thieno(3,2-c)pyridine (II).—Two and three-tenths grams of the Schiff base in 15 g. of polyphosphoric acid and 1 g. of phosphorus oxychloride at 120–130° for 10 minutes yielded 150 mg. of crude base. Resublimation at room temperature (0.25 mm.) furnished an analytical sample, m.p. 42–43°.

Anal. Calcd. for C_7H_5NS: C, 62.19; H, 3.73; N, 10.36. Found: C, 61.72; H, 3.69; N, 10.01.

The picrate melted at 224.5°.

Anal. Calcd. for $C_{13}H_8N_4O_7S$: C, 42.86; H, 2.21; N, 15.38. Found: C, 42.88; H, 2.27; N, 14.9.

Procedure A yielded 201 mg. of picrate.

Thianaphtheno(2,3-c)pyridine (III).—From 1.3 g. of the Schiff base in 31 g. of polyphosphoric acid and 1 g. of phosphorus oxychloride at 150–160° for 20 minutes there was obtained 240 mg. of the base. This was purified first by recrystallization from ether–petroleum ether and finally by sublimation at 0.2 mm., m.p. 96–98° (lit.[4] 98–99°). The picrate decomposed at 256° (lit.[4] 258–260°).

No cyclization was effected by means of 96% sulfuric acid at 5° for 10 hours as well as at 100° for two hours with a mixture of phosphorus oxychloride and sulfuric acid.

Thianaphtheno(3,2-c)pyridine (IV).—From 1.6 g. of the Schiff base in 30 g. of polyphosphoric acid and 1 g. of phosphorus oxychloride at 90–100° for 20 minutes there was obtained 0.2 g. of the base. Recrystallization from petroleum ether furnished colorless needles, m.p. 71–71.5° (lit.[5] 69–70.5°). The picrate melted at 248°.

Anal. Calcd. for $C_{17}H_{10}O_7N_4S$: N, 13.39. Found: N, 13.6.

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THE FLORIDA STATE UNIVERSITY
TALLAHASSEE, FLORIDA

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[6] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

[7] Melting points and boiling points are uncorrected. Analyses by Clark Microanalytical Laboratory, Urbana, Illinois, and Drs. Weiler and Strauss, Oxford.

[8] E. Campaigne and W. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

[9] D. A. Shirley and M. J. Danzig, *ibid.*, **74**, 2935 (1952).

Preparation of Normal and Secondary Butyl Hydroperoxides

BY E. G. LINDSTROM

RECEIVED JULY 6, 1953

The classical method of preparing methyl and ethyl hydroperoxides is the reaction of the appropriate alkyl sulfate with hydrogen peroxide in concentrated aqueous potassium hydroxide solution.[1] It appears, however, that the method is not applicable to higher members of the series. Medvedev[2] was

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[1] A. Baeyer and V. Villiger, *Ber.*, **34**, 738 (1901).

[2] S. S. Medvedev and E. N. Alekseeva, *ibid.*, **65B**, 133 (1932).

unable to isolate *n*-propyl hydroperoxide, although he obtained a good yield of isopropyl hydroperoxide. Harris and Egerton[3] succeeded in preparing *n*-propyl hydroperoxide in yields of only 1.3% per pass. Numerous attempts to prepare *s*-butyl hydroperoxide in our own laboratory following the procedures used by these earlier workers were entirely unsuccessful. We have now found that relatively good yields of *n*- and *s*-butyl hydroperoxides can be obtained by the classical procedure if most of the water employed as reaction solvent is replaced with methanol.

Although the reaction has not been extended to alkyl hydroperoxides higher than butyl, there is an excellent prospect that this improved procedure will prove to be a general one, and it is anticipated that this method may result in improved yields for some of the lower hydroperoxides. The success of the method apparently depends on the fact that methanol brings the alkyl sulfate, hydrogen peroxide and potassium hydroxide into solution in the same phase. Other alcohols and similar solvents may also serve as suitable reaction media.

n-, iso and *s*-butyl hydroperoxides have been previously reported,[4] but properties and methods of synthesis were not included.

Preliminary studies on *n*- and *s*-butyl hydroperoxides indicate that they are relatively stable compounds; detonation was not obtained by hammer blows or by heating with a free flame. In this respect primary and secondary butyl hydroperoxides are more similar to *t*-butyl hydroperoxide than to the relatively unstable methyl and ethyl hydroperoxides.

Experimental

s-**Butyl Hydroperoxide.**—The preparative procedure employed was similar to that of Harris and Egerton[3] except that a 25% solution of potassium hydroxide in methanol was used in place of the 50% aqueous potassium hydroxide solution. A solution of 1.88 moles of potassium hydroxide in 400 ml. of methanol, chilled and decanted from solid carbonate, was added dropwise to 200 ml. of 30% hydrogen peroxide (2.3 moles) in a three-neck flask equipped with a stirrer. Then 395 g. (1.88 moles) of chilled *s*-butyl sulfate was added dropwise. The reaction mixture was held at −20 to −10° during these additions and then stirred at +2° (ice-bath) for 20 hours. The reaction mixture was added to 2 l. of ice and water; unreacted butyl sulfate was recovered by ether extraction. The aqueous phase was neutralized with 50% sulfuric acid at 0° and 3 pounds of ammonium sulfate was added. The *s*-butyl hydroperoxide was separated by three 200-ml. extractions with ether. Three hundred grams (1.44 moles) of butyl sulfate was recovered and the ether extract of the hydroperoxide contained 0.45 equiv. of peroxide.

Most of the ether was removed at atmospheric pressure from the hydroperoxide fraction; 200 ml. of water was added producing two phases and the mixture was distilled in a three-foot spinning band column at 20:1 reflux ratio and 35 mm. There was obtained 16.2 g. (40% based on butyl sulfate which reacted) of *s*-butyl hydroperoxide as an azeotrope along with an equal volume of water at 30–31°. In other preparations this azeotrope distilled at 36° at 100 mm. and 47° at 150 mm. The azeotropic mixture was saturated with ammonium sulfate and the hydroperoxide layer was dried with anhydrous cupric sulfate; n^{20}_{D} 1.4052, d^{20}_{4} 0.9094. The active oxygen was determined by reaction with potassium iodide in acetic acid solution.

Anal. Calcd. for $C_4H_{10}O_2$: C, 53.31; H, 11.19; active (O), 17.76. Found: C, 52.13, 52.39; H, 11.26, 10.92; active (O), 16.1, 16.0.

n-**Butyl hydroperoxide** was prepared in an analogous manner. Eleven ml. (20% yield based on 0.78 moles of reacted *n*-butyl sulfate) was obtained as an azeotrope (b.p. 28–29° at 100 mm.). A heart cut of the hydroperoxide was dried and redistilled at 5 mm.; n^{20}_{D} 1.4032, d^{20}_{4} 0.9078.

Anal. Calcd. for $C_4H_{10}O_2$: active (O), 17.76. Found: active (O) 16.4, 15.2.

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RICHMOND 1, CALIF.

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[3] E. J. Harris and A. C. Egerton, *Proc. Roy. Soc.* (*London*), **A173**, 126 (1939).

[4] D. Downs, A. D. Walsh and R. W. Wheeler, *Trans. Royal Soc.* (*London*), **A243**, 463 (1951).

2-Thienol

BY CHARLES D. HURD AND HUGH J. ANDERSON[1]

RECEIVED JUNE 11, 1953

The original synthesis[2] of 2-thienol involved oxidation of a mixture of 2-thienylmagnesium bromide and isopropylmagnesium bromide, the yield being about 25% of the theoretical. The present work describes some new synthetical approaches, but it is interesting to note that none gave yields as high as the original method. These results were obtained.

(a) A 10% yield by treatment of 2-thienyllithium with 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide, which method gave a nearly quantitative yield of phenol[3] from phenyllithium. (b) A 5% yield by treatment of a mixture of 2-thienylmagnesium bromide and isopropylmagnesium bromide with 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide. (c) No 2-thienol following reaction of 2-thienyldimethylcarbinol in glacial acetic acid with 30% hydrogen peroxide and either aluminum chloride, zinc chloride or titanium tetrachloride. This was adapted from Kharasch's procedure[4] for the preparation of phenol from phenyldimethylcarbinol.

Experimental

Oxidation of 2-Thienyllithium.—A solution of 0.1 mole of 2-thienyllithium[5] in 300 ml. of dry ether was forced through a plug of glass wool into a dropping funnel. It was added slowly, with cooling and stirring, into a solution of 0.05 mole of 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide[6] in 100 ml. of dry ether. After standing overnight at −10°, the mixture was poured on Dry Ice and decomposed with dilute sulfuric acid. The ether layer was removed and the aqueous layer was saturated with salt. After two more extractions with ether, the combined ether solutions were washed with three 50-ml. portions of 20% sodium hydroxide solution. The almost black basic solution was cooled and neutralized rapidly with cold dilute sulfuric acid and saturated with salt. This solution was then extracted with four 50-ml. portions of ether, the ether dried and removed to give 1.0 g. of thienol, b.p. 82–87° at 8 mm., a 10% yield. The product was characterized by means of the benzoate, m.p. 43–44°.

The same procedure applied to phenyllithium gave a 75% yield of phenol.

Oxidation of 2-Thienylmagnesium Bromide.—A mixture[2] of 0.1 mole of 2-thienylmagnesium bromide and 0.15 mole of isopropylmagnesium bromide was forced through a plug of glass wool into a dropping funnel. It was then added slowly with stirring and cooling to a solution of 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide in 100 ml. of dry ether. After storing overnight at −10° it was processed

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[1] The Texas Company Fellow, 1952.

[2] C. D. Hurd and K. L. Kreuz, THIS JOURNAL, **72**, 5543 (1950).

[3] E. Müller and T. Töpel, *Ber.*, **72**, 273 (1939).

[4] M. S. Kharasch, A. Fono and W. Nudenberg, *J. Org. Chem.*, **15**, 748 (1950).

[5] H. Gilman and D. A. Shirley, THIS JOURNAL, **71**, 1870 (1949).

[6] H. Hock and W. Susemihl, *Ber.*, **66**, 61 (1933).

in the same manner as described above to give about 5% yield of 2-thienol.

Treatment of 2-Thienyldimethylcarbinol.—A solution of 5 g. of 2-thienyldimethylcarbinol, prepared in 60% yield by adapting the method of Klages,[7] in 75 ml. of glacial acetic acid was placed in a flask and to it was added 10 ml. of 30% hydrogen peroxide and 0.5 g. of freshly fused zinc chloride. The solution immediately became bright red in color and after 24 hours it was nearly opaque. No thienol was obtained on processing the mixture.

The use of aluminum chloride or titanium tetrachloride instead of zinc chloride also was unsatisfactory.

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[7] A. Klages, *Ber.*, **35**, 2633 (1902).

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS

The Distribution of Triterpenes in Rugel's Plantain[1]

BY R. C. HILTIBRAN, C. L. WADKINS AND H. J. NICHOLAS

RECEIVED MAY 18, 1953

In connection with a study of the pentacyclic triterpenes and plant sterols now under way in this Laboratory, it appeared of interest to investigate the simultaneous occurrence of these substances and their distribution within various common plants. Zimmermann[2] has stated that only in the dandelion are triterpenes found in all parts of the plant, and Noller[3] has suggested that other plants will be found having a similar distribution. Rugel's Plantain, or *Plantago rugellii*, one of the most prolific weeds in this country, appears from the data presented here to be another such plant. The specimens employed in the present study were obtained from Missouri and Eastern Kansas and were distinguished from the almost identical species *Plantago major* by inspection of the spike.[4]

A chemical study of the alcoholic extracts of the dried and finely ground plant revealed sitosterol (as the sitosterol mixture[5]) as the only sterol present and ursolic acid and oleanolic acid as the triterpenes. The occurrence of these isomeric triterpenes in the same plant appears to be fairly unique, since only a few plants have been reported to contain ursolic and oleanolic acids together.[6-8]

The quantitative distribution of the substances studied is shown in Table I. Ursolic acid and sitosterol occur in all parts of the plant, whether young (before the appearance of seed stalks) or mature. Oleanolic acid, however, was found only in the aereal portions of the mature plant and not at all in the young plant. It appears to us that this constant association of ursolic acid and sitosterol throughout the plant suggests some close metabolic relationship.

TABLE I

RECOVERY OF URSOLIC ACID, OLEANOLIC ACID AND SITOSTEROL FROM *Plantago rugelli*

Plant part	Plant part wt., g.	Yield, g. Ursolic acid	Oleanolic acid	Sito-sterol
	Young Plant			
Roots	565	0.9	...	0.8
Leaves	3819	2.3	...	3.8
	Mature Plant			
Roots	1004	0.9	...	1.2
Leaves	2625	5.0	2.0	2.9
Seed stalks	3363	0.5	1.0	0.9
Flower parts	4016	6.0	1.5	4.3

The steroid and triterpenes were isolated by procedures generally used for isolation of sapogenins,[9] and were identified by chemical methods. The absence of oleanolic acid in the young plant was substantiated by a paper chromatographic procedure which will be published at a later date.

Experimental[10]

Preparation and Fractionation of Extracts.—Large quantities of the plant were carefully washed, then dried in air. After sectioning, each part was finely ground and exhaustively extracted with hot, 95% ethanol. The individual extracts were concentrated to low volume and refluxed for two hours in approximately 2 *N* alcoholic HCl. The cooled mixture was diluted with water, extracted with 5% $NaHCO_3$ until the latter was practically colorless, and then with 5% KOH. Oleanolic acid and ursolic acid precipitated out as the K salts during the latter operation. After removal of the precipitate, extraction with 5% KOH was continued until acidification of the extract gave no precipitate. This was essential for complete separation of the carboxylated triterpenes, which tend to remain in the ether at this point.

Isolation of Sitosterol.—The neutral ether fraction was washed with distilled water and evaporated to dryness. It consisted, in each case, principally of orange pigment, a waxy hydrocarbon melting at 72-72.5° (after several crystallizations from methanol) and sitosterol in the form of the sitosterol mixture.[5] Fractionation of this crude product was best effected by chromatography on silica gel prepared according to the method of Gordon, *et al.*[11] The crude product was placed on the column with the help of a little benzene (keeping a ratio of $^1/_5$ of crude product to silica gel) and the column was washed down with low boiling petroleum ether. The first few fractions contained the orange pigment and waxy hydrocarbon. Continued elution with petroleum ether slowly removed the sitosterol; more rapid removal was effected by elution with 2% ethanol in petroleum ether. Two to four crystallizations from methanol served to bring the sitosterol to m.p. 138-140°, not depressed by admixture with an authentic sample of sitosterol mixture from soybean. It gave a characteristic color in the Liebermann-Burchard test. An acetate was prepared from a composite sample from all plant parts by refluxing with acetic anhydride in pyridine; m.p. 127°, not depressed by admixture with an authentic sample of acetate prepared from soybean sitosterol mixture.

Separation of Oleanolic and Ursolic Acids.—The KOH precipitate and KOH extracts were acidified, then extracted with ether. The latter was washed with water and distilled off, leaving a greenish, amorphous mass. The material was placed on a silica gel column ($^1/_5$ ratio of crude product to silica gel) with the help of a little warm benzene and eluted with low boiling petroleum ether until waxy solid no longer

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[1] Presented before the Division of Biological Chemistry of the American Chemical Society at the autumn meeting held in Atlantic City, N. J., 1952.

[2] J. Zimmermann, *Helv. Chim. Acta*, **26**, 642 (1943).

[3] C. R. Noller, *Ann. Rev. Biochem.*, **14**, 383 (1945).

[4] J. M. Fogg, Jr., "Weeds of Lawn and Garden," Univ. of Penn. Press, Philadelphia, Pa., 1945, p. 159.

[5] L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd. Ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 285.

[6] E. J. Rowe, J. E. Orr, A. H. Uhl and L. M. Parks, *J. Am. Pharm. Assoc.*, **38**, 122 (1949).

[7] T. Bersin and A. Muller, *Helv. Chim. Acta*, **35**, 1891 (1952).

[8] C. Djerassi, *et al.*, THIS JOURNAL, **75**, 2254 (1953), in compiling a list of plant sources of oleanolic acid, were apparently unaware of our Abstract.[1]

[9] R. E. Marker, *et al.*, *ibid.*, **69**, 2167 (1947).

[10] Melting points are uncorrected and were obtained on the Fisher-Johns block.

[11] A. H. Gordon, A. J. P. Martin and R. L. M. Synge, *Biochem. J.*, **37**, 79 (1943).

came off. Continued elution with 2% ethanol in petroleum ether slowly removed the oleanolic and ursolic acids as a mixture. The isomers were readily separated in crude form at this point by boiling in methanol and filtering or decanting the partially cooled methanol solution. The supernatant or filtrate contained the oleanolic acid, since ursolic acid is only slightly soluble in hot methanol.

Isolation of Oleanolic Acid as the Acetate.—Oleanolic acid, obtained in amorphous form by evaporation of the methanol solution, was converted to the acetate for preliminary identification by boiling with acetic anhydride in pyridine. Samples of the acetate from each plant part melted sharply between 258 and 261° after several crystallizations from methanol. A composite sample from all plant parts containing oleanolic acid consisted of needles, m.p. 259–261° after two crystallizations from methanol.[12]

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 76.80; H, 9.88.

Oleanolic Acid.—Each of the oleanolic acid acetate samples was saponified with 5% alcoholic KOH to the free acid. After several crystallizations from methanol, needles melting sharply between 295 and 302° were obtained in each case. None of the samples depressed the melting point of an authentic sample of free oleanolic acid.[13] A composite sample of all of the free acid fractions, after two crystallizations from acetone, consisted of needles, m.p. 302–303°.[12] It gave a characteristic color in the Liebermann–Burchard test.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.58. Found: C, 78.66; H, 10.38.

Oleanolic Acid Benzoate.—A composite sample of the free acid was boiled with benzoyl chloride in pyridine, yielding a benzoate, m.p. 259–261°, after several crystallizations from methanol.[14]

Isolation of Ursolic Acid as the Acetate.—Crude ursolic acid obtained as outlined above consisted of an amorphous, green powder which resisted all attempts to purify it by crystallization from various solvents. Samples from each plant part, however, were readily converted to the crystalline acetate by boiling in acetic anhydride–pyridine mixture. Each preparation melted sharply between 284 and 287° after several crystallizations from acetone or methanol. A composite sample from all plant parts, after two crystallizations from acetone, consisted of needles, m.p. 286–287°.[15]

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 77.04; H, 10.12.

Ursolic Acid.—Saponification of each of the acetate samples with 5% alcoholic KOH gave an amorphous white powder, m.p. 260–285°, which also resisted numerous attempts at crystallization from various solvents. Except in one case (mature roots) the acid was finally obtained in crystalline form by treating the saponified product according to the procedure of King, *et al.*[16] A composite sample from all plant parts, after two crystallizations from ethanol, consisted of needles, m.p. 283–285°,[15] undepressed by admixture with an authentic sample of ursolic acid.[13] It gave a characteristic color in the Liebermann–Burchard test.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 78.89; H, 10.58. Found: C, 78.62, H, 10.80.

Ursolic acid monoacetyl methyl ester, prepared according to the procedure of Rowe, *et al.*,[6] melted at 247°, in agreement with the recorded value.

Ursolic acid acetate acid chloride, prepared according to the procedure of Sando,[17] melted at 221°, in agreement with the recorded value.

Acknowledgments.—We wish to thank Mr. Albert Kihm and Mr. Robert Manning for technical assistance, and the General Appropriations Fund of the University of Kansas for financial support during this investigation.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF KANSAS
LAWRENCE, KANSAS

The Reaction of Ethyl Trichloroacetate with Aromatic Grignard Compounds

BY A. KALUSZYNER AND S. REUTER

RECEIVED MAY 18, 1953

Henry[1] has described the reaction between methylmagnesium bromide and ethyl trichloroacetate (I) as leading to the expected trichloro-*t*-butyl alcohol, without indicating the yield. Experiments with aromatic Grignard compounds, undertaken in an attempt to synthesize substances of the general formula CCl_3CAr_2OH, have led to unexpected results.

The reaction of I with phenylmagnesium bromide (4 moles per mole ester) did not yield the chlorinated tertiary alcohol in isolable quantities. Apart from about 0.4 mole of biphenyl, a yield of 1 mole of chlorobenzene was obtained, identified by boiling point, density and refractive index. In the aqueous layer obtained in the decomposition of the reaction product, one third of the chlorine of the ester I was recovered in form of chloride ion. Phenyllithium reacts with I in the same manner.

The analogous reaction with *p*-tolylmagnesium bromide gave 0.6 mole of *p*-chlorotoluene, 0.8 mole of 4,4′-dimethylbiphenyl and in the aqueous layer, 80% of the chlorine of I as chloride ion. The reaction with *p*-chlorophenylmagnesium bromide yielded 0.2 mole of *p*-dichlorobenzene, 0.8 mole of 4,4′-dichlorobiphenyl and 72% of the chlorine atoms of I in ionic form.

It appears, therefore, that ethyl trichloroacetate reacts with arylmagnesium bromides according to the following equation to give the corresponding aryl chloride

$$\mathrm{ROOC{\cdot}CCl_3 + ArMg\,Br \longrightarrow ArCl + (ROOC{\cdot}CCl_2)^{-}MgBr^{+}} \quad (1)$$

In the case of phenylmagnesium bromide, all of the trichloroacetate reacts in that manner, in that of *p*-tolylmagnesium and of *p*-chlorophenylmagnesium bromide, only 60 and 10%, respectively.

Replacement of MgX in Grignard compounds by chlorine has been known to occur with substances containing "positive chlorine," such as aryliodonium chloride,[2] ethyl hypochlorite,[3] N-chloropiperidine[4] and benzene sulfochloride.[5] One has, therefore, to conclude that in ethyl trichloroacetate (I), the accumulation of chlorine atoms gives them an electropositive character.

For the formation of chloride ion and the biaryl compound in the reaction between an arylmagnesium bromide and ethyl trichloroacetate, a number of possibilities exist. In this respect, it is re-

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[12] A. Winterstein and G. Stein, *Z. physiol. Chem.*, **199**, 64 (1931), give m.p. 259–264° for oleanolic acid acetate and m.p. 305–308° for free oleanolic acid.

[13] Kindly supplied from the collection of Dr. C. E. Sando at the U. S. Department of Agriculture.

[14] Y. Obata, *J. Agr. Chem. Soc. Japan*, **17**, 219 (1941), gives m.p. 260–262° for oleanolic acid benzoate. See *C. A.*, **45**, 3912c (1951).

[15] Rowe, *et al.*, ref. 6, give m.p. 288–289° for ursolic acid acetate and m.p. 282–284° for free ursolic acid.

[16] N. M. King, A. Chatterjee and L. M. Parks, *J. Am. Pharm. Assoc.*, **39**, 595 (1950).

[17] C. E. Sando, *J. Biol. Chem.*, **90**, 477 (1931).

[1] L. Henry, *Bull. soc. chim. Belg.*, **20**, 152 (1906); *Chem. Zentr.*, **77**, 1178 (1906).

[2] H. Hepworth, *J. Chem. Soc.*, **119**, 1244 (1921).

[3] N. N. Melnikow, *Chem. Zentr.*, **107**, II, 2896 (1936).

[4] R. I. W. Le Fèvre and P. I. Markham, *J. Chem. Soc.*, 703 (1934).

[5] R. I. W. Le Fèvre, *J. Chem. Soc.*, 1245 (1932); *cf.* H. Gilman and R. E. Fothergill, THIS JOURNAL, **51**, 3501 (1929).

called[6] that DDT and its analogs react with Grignard compounds to give substances of the formulas: $(RC_6H_4)_2CHCHCl_2$, $(RC_6H_4)_2CHCCl{=}CClCH(C_6H_4R)_2$ and $(RC_6H_4)_2CHCH{=}CHCH(C_6H_4R)_2$. Although we have not succeeded in elucidating the fate of the trichloroacetate molecule, the following conclusions can be drawn from the experimental material. In the reaction of I with phenylmagnesium bromide, all of the chloride ion and of the biphenyl must derive from an interaction of the Grignard compound with $(ROOCCCl_2)^-MgBr^+$. In the other two cases, both this type of reaction can occur, but equally a direct interaction of the Grignard compound with I, *e.g.*, according to the equation

$$ROOCCCl_3 + 2ArMgBr \longrightarrow ArAr + (ROOCCCl_2)^-MgBr^+ + MgBrCl$$

In all three instances, for each mole of biaryl isolated, approximately three equivalents of chloride ion are found.

The reductive dehalogenation of trichloroacetic acid has been observed in other reactions.[7,8]

It is interesting that according to Pepper and Kulka[9] *p*,ω,ω,ω-tetrachloroacetophenone and *p*-chlorophenylmagnesium bromide give *p*,ω,ω-trichloroacetophenone. It could be shown that also in the reaction between ω-trichloroacetophenone and phenylmagnesium bromide (4 moles per mole), 43% of the chlorine reappears in the form of chloride ions; apart from biphenyl (1.7 moles per mole ketone), no defined organic material could, however, be isolated in this case.

In contradistinction to I, ethyl trifluoroacetate reacts normally with Grignard compounds. This reaction will be described in a forthcoming communication.

Experimental

Ethyl trichloroacetate (I) had b.p. 167°, n^{20}_D 1.4505. **ω-Trichloroacetophenone**, b.p. 254–255°, was prepared from trichloroacetyl chloride and benzene[10] and ***p*-chlorobromobenzene**, m.p. 67°, according to Mouneyrat and Pouret.[11]

General Procedure.—A quantity of 0.1 mole of ethyl trichloroacetate (or trichloroacetophenone) and 0.4 mole of the Grignard compound in ether was employed. The second component was added at 0° to the Grignard solution and the reaction completed by refluxing for 90 minutes. (In one experiment, the mixture was kept at 0° for 12 hours, but the result was the same.) The product was decomposed with ice-cold distilled water and dilute sulfuric acid. In the aqueous layer, chloride ion was determined in the usual manner. The ethereal layer was washed with 5% sodium carbonate solution, dried and concentrated and the residue subjected to fractional distillation.

Reaction of I with Phenylmagnesium Bromide.—In two experiments, 11.3 and 10.0 g. of chlorobenzene was isolated (0.1 and 0.09 mole, respectively); b.p. 132°, d^{28}_4 1.104, n^{20}_D 0.5252. The quantities of biphenyl were 5.7 g. (0.037 mole) and 8.0 g. (0.050 mole), respectively. Thirty-five and thirty-seven per cent. of the total chlorine of I were found in the aqueous layer.

Reaction of I with *p*-Tolylmagnesium Bromide.—*p*-Chlorotoluene (7.5 g., 0.06 mole) was identified by permanganate oxidation to *p*-chlorobenzoic acid, m.p. 238°; **4,4′-dimethylbiphenyl** (11.0 g., 0.076 mole) by melting point (120°) and mixed m.p. Eighty per cent. of the total chlorine of I was recovered in the aqueous layer.

Reaction of I with *p*-Chlorophenylmagnesium Bromide.—Both ***p*-dichlorobenzene** (2.5 g., 0.017 mole) and **4,4′-dichlorobiphenyl** (9.0 g., 0.04 mole) were identified by m.p. (52–53°, 146–147°) and comparison with authentic specimens. Seventy-five per cent. of the total chlorine had been converted into ionic form.

Reaction of I with Phenyllithium.—The reaction between I (0.05 mole) and phenyllithium (0.2 mole, 31.5 g. of bromobenzene and 2.8 g. of lithium) was carried out as described above, but in an atmosphere of nitrogen. The products obtained were: chlorobenzene (6.3 g., 0.06 mole); biphenyl (2.5 g., 0.016 mole) and chloride ion (31% of the total chlorine in the quantity of the ester employed).

Laboratories, Medical Corps
Israel Defense Forces
Tel-Aviv, Israel

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(6) W. Awe and J. Reinecke, *Experientia*, **6**, 185 (1950).

(7) H. W. Doughty and D. A. Lacoss, This Journal, **51**, 853 (1929).

(8) Rathke, *Ann.*, **161**, 166 (1872).

(9) J. M. Pepper and M. Kulka, This Journal, **72**, 1417 (1950).

(10) H. Biltz, *J. prakt. Chem.*, [2] **142**, 196 (1937).

(11) A. Mouneyrat and Ch. Pouret, *Bull. soc. chim. France*, **19**, 801 (1898).

2,3-Bis-(*p*-aminophenyl)-2,3-butanediol

By Nelson J. Leonard, Sherlock Swann, Jr., and Glenn Fuller

Received June 10, 1953

Because of increasing interest in 2,3-bis-(*p*-aminophenyl)-2,3-butanediol (I)[1] as an immediate precursor of compounds having pronounced physiological activity,[2] we wished to provide a method for the synthesis of I by the electrolytic reduction of *p*-aminoacetophenone which would require only readily available apparatus. The electrolytic reduction has been carried out under the following conditions to give acceptable yields of 2,3-bis-(*p*-aminophenyl)-2,3-butanediol dihydrochloride (55–59%): the cathode used was tin,[3] the anode, platinum,[4] both anolyte and catholyte were 1.6 *N* hydrochloric acid, the temperature was maintained at 24–30°, and the initial cathode current density was in the range 0.01–0.02 amp. per cm.².

Experimental

Electrolytic Reduction of *p*-Aminoacetophenone.—The tin cathode (of 99.9% purity or better), with a surface area of 100 cm.², was cast in a graphite mold initially at a temperature of 70°. It was prepared prior to use by the customary procedure.[5] The anode was of smooth platinum. A porous alundum diaphragm was first cleaned in 20% nitric acid, soaked in 20% aqueous sodium silicate, then in 20% sulfuric acid and finally in 20% hydrochloric acid.[5] The catholyte was prepared by dissolving 13.5 g. (0.1 mole) of *p*-aminoacetophenone (Eastman Kodak Co. material recrystallized) in 100 ml. of 1.6 *N* hydrochloric acid. The anolyte was 1.6 *N* hydrochloric acid. The electrolysis cell was assembled in the usual manner,[5] and stirring was effected by a magnetic stirrer. The line potential was 6 v. The temperature of the cell was maintained at 24–30° while a current of 1 amp. was allowed to flow through the solution (100 ml. of 1 *M* *p*-aminoacetophenone hydrochloride). The initial cathode current density was therefore 0.01 amp. per cm.². During the course of the reduction, the current diminished to 0.84 amp. after 4 hours. Approximately 1.5 l. of hydrogen was evolved, the rate of evolution increasing toward the end of the reaction. After 5.3 hours

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(1) M. J. Allen and A. H. Corwin, This Journal, **72**, 114 (1950).

(2) *E.g.*, Amphenone "B": A. E. Heming, D. E. Holtkamp, J. F. Kerwin, L. F. Mansor and J. G. Dacanay, *Proc. Soc. Exptl. Biol. Med.*, **80**, 154 (1952).

(3) S. Swann, Jr., P. E. Ambrose, R. C. Dale, R. C. Rowe, H. M. Ward, H. D. Kerfman and S. Axelrod, *Trans. Electrochem. Soc.*, **85**, 231 (1944).

(4) Past experience indicates that an anode of carbon or graphite would be equally satisfactory.

(5) S. Swann, Jr., "Electrolytic Reductions" in A. Weissberger, editor, "Technique of Organic Reactions," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1948.

(twice the time theoretically required), the electrodes were removed and the catholyte and washings were collected. The isolation of the 2,3-bis-(*p*-aminophenyl)-2,3-butanediol dihydrochloride was accomplished by the method of Allen and Corwin,[1] with the exception that the temperature was kept under 50° (rather than 25°) in the evaporation of the final catholyte solution *in vacuo;* yield 10.2 g. (59%) of yellow-brown solid which decomposed slowly above 230°.

2,3-Bis-(*p*-aminophenyl)-2,3-butanediol.—Saturated aqueous potassium carbonate solution was added to a solution of 51.5 g. of the pinacol dihydrochloride in 300 ml. of water until the mixture was strongly alkaline. The solid precipitate was filtered and treated with hot acetone. The 2,3-bis-(*p*-aminophenyl)-2,3-butanediol separated from acetone as faintly yellow platelets, m.p. 239-242° dec. (reported[1] 248–249°), of analytical purity; yield 16.3 g. (40%).

THE CHEMICAL LABORATORIES
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

The Preparation of Samarium Metal[1]

BY E. I. ONSTOTT

RECEIVED JUNE 8, 1953

In a recent communication to the editor, Daane, Dennison and Spedding[2] described the preparation of samarium metal of at least 98% purity by reaction of samarium oxide with lanthanum metal. They also mentioned that barium had been tried as a reductant with little success. In this Laboratory relatively pure samarium metal has been produced by reaction of barium with anhydrous samarium(III) bromide. The reaction is carried out in a tantalum crucible[3] in an argon atmosphere by heating the mixture to a temperature of 1650–1700° for a period of about 20 minutes. During this heating period the samarium metal is collected in the bottom of the crucible and the excess barium is distilled out. The yield of metal is about 10 g. or 50% for a 50-g. batch of bromide. This technique of heating the charge to a high temperature to facilitate separation of the metal in the massive state has been used previously by Spedding, *et al.*, in the preparation of other rare earth metals.[4]

The purity of samarium metal prepared in this manner is believed to be greater than 99.5%. Spectrographic analysis showed the metal to contain: Li, Na, Mg, Ca, Mn, Fe, Cu, each less than 0.001%; Ba, Si, Sn, each less than 0.01%; Bi, 0.001–0.1%. Europium content was about 0.08%, since the samarium oxide used to make the anhydrous bromide contained this amount of europium oxide, as determined by a combination of gravimetric, colorimetric[5] and tracer analysis. No other rare earths were detected by spectrographic analysis. The samarium oxide as received from the Société de Produits Chimique des Terres Rares contained 1.5% calcium and 1.5% europium oxide. Purification was made by two electrolyses according to the method of McCoy,[6] followed by two oxalate precipitations and ignition to the oxide.

An experiment in this Laboratory confirms the report of Daane, Dennison and Spedding[2] that samarium metal is relatively volatile. When recasting samarium metal at about 1700° in an atmosphere of argon, approximately 1 g. of metal distilled to the lid of the crucible in a period of 5–10 minutes.

The density of three samples of samarium metal was determined by weighing in air, then weighing while suspended in acetylene tetrabromide. Density data are as follows: massive metal as made, 7.499 g./cc.; recast metal, 7.509 g./cc.; distilled metal, 7.495 g./cc. Accuracy of these data, which compare favorably to the value of 7.53 g./cc. obtained by Daane, Dennison and Spedding,[2] is believed to be ±0.005 g./cc.

Acknowledgment.—Some of the analyses were performed by Richard Wilhelm, O. R. Simi and F. H. Ellinger. Valuable suggestions were made by Dr. Henry Taube, Dr. E. R. Jette, Dr. R. D Fowler and Dr. R. P. Hammond.

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

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[1] This work is a contribution from the Chemical and Metallurgical Research Division of the Los Alamos Scientific Laboratory, Los Alamos, New Mexico, under the auspices of the Atomic Energy Commission.

[2] A. H. Daane, D. H. Dennison and F. H. Spedding, THIS JOURNAL, **75**, 2272 (1953).

[3] A. H. Daane, *Rev. Sci. Instruments*, **23**, 245 (1952).

[4] F. H. Spedding and A. H. Daane, THIS JOURNAL, **74**, 2783 (1952).

[5] T. Mneller and J. C. Brantley, *Anal. Chem.*, **22**, 433 (1950).

[6] H. N. McCoy, THIS JOURNAL, **63**, 3432 (1941).

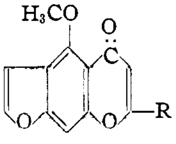
Furochromones and -Coumarins. VIII. Action of Hydrazine Hydrate and Hydroxylamine on Khellin, Khellol and Visnagin

BY ALEXANDER SCHÖNBERG AND MAHMOUD MOHAMED SIDKY

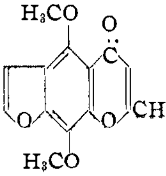
RECEIVED APRIL 10, 1953

The action of hydrazine hydrate on 2-methylchromone has been studied by Koenigs and Freund,[1] and on chromone itself by Baker, Harborne and Ollis.[2] Both groups of researches agree that the reaction products are pyrazole derivatives and not hydrazones of the chromones in question as previously believed. In the case of chromone itself, the product is 5(3)-*o*-hydroxyphenylpyrazole (IIId or IVd).

We have investigated the action of hydrazine hydrate on visnagin (Ia), khellol (Ib) and khellin (II), and believe that the reaction products are the pyrazole derivatives IIIa, IIIb and IIIc or IVa, IVb and IVc, respectively.



Ia, R = CH_3
Ib, R = CH_2OH



II

These substances are soluble in aqueous alkali, and their alcoholic solutions give a blue color with aqueous ferric chloride solution, and with titanium chloride a deep orange color is developed. From IIIa and IIIc—each containing one active hydrogen in the phenolic hydroxy group and one active hydrogen atom attached to a nitrogen atom—dibenzoyl derivatives were obtained when they were treated with benzoyl chloride (Schotten–Baumann).

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[1] E. Koenigs and J. Freund, *Ber.*, **80**, 143 (1947).

[2] W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, 1303 (1952).

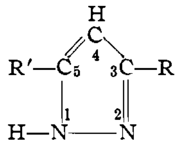
TABLE I

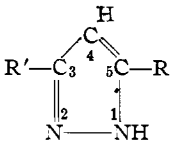
Reactants	Reacn.[a,b] prod.[a]	M.p., °C.	Color test, a, $FeCl_3$ b, $TiCl_3$	Formula of the reacn. prod.		Analyses, %
Hydrazine + Ib	[c]	181[i]	a, Blue	$C_{13}H_{12}O_4N_2$	Found	C, 59.8; H, 4.3; N, 10.7
			b, Deep orange		Calcd.	C, 60.0; H, 4.6; N, 10.8
Hydroxylamine + Ib	[d]	146	....	$C_{13}H_{11}O_5N$	Found	C, 60.0; H, 4.5
					Calcd.	C, 59.8; H, 4.2
Hydrazine + Ic	[e]	157[i]	a, Blue	$C_{14}H_{14}O_4N_2$[h]	Found	C, 61.4; H, 5.2; N, 10.6; $-OCH_3$, 22.4
			b, Deep orange		Calcd.	C, 61.3; H, 5.1; N, 10.2; $-OCH_3$, 22.6
Hydroxylamine + Ic	[f,g]	120–121	....	$C_{14}H_{13}O_5N$	Found	C, 61.2; H, 4.5; N, 4.8
					Calcd.	C, 61.1; H, 4.7; N, 5.1

[a] Solvent for crystallization, dil. alcohol; yield above 85% in all reactions given. [b] The reaction products are colorless, soluble in aqueous sodium hydroxide (10%). [c] IIIb or IVb, 4-methoxy-5-[3(or 5)-hydroxymethyl-5(or 3)-pyrazolyl]-6-benzofuranol. [d] Vb or VIb, 4-methoxy-5-[5(or 3)-hydroxymethyl-3(or 5)-isoxazolyl]-6-benzofuranol. [e] IIIc or IVc, 4,7-dimethoxy-5-[3(or 5)-methyl-5(or 3)-pyrazolyl]-6-benzofuranol. [f] Vc or VIc, 4,7-dimethoxy-5-[5(or 3)-methyl-3(or 5)-isoxazolyl]-6-benzofuranol. [g] It is easily soluble in ethyl alcohol, but difficultly, soluble in light petroleum (b.p. 70–80°). [h] Active hydrogen, 0.7; calcd.; 0.7 (two active hydrogens). [i] Reaction with concd. sulfuric acid, yellow orange.

IIIb, differing from IIIa in having one more hydroxyl, furnished a tribenzoyl derivative.

In contrast to the stability of visnagin (Ia), to hydroxylamine hydrochloride in acetic acid at room temperature,[3] we found that visnagin, khellol and khellin react rapidly with hydroxylamine hydrochloride in pyridine at the boiling point of the mixture. Flavone yields, under similar conditions, 3-*o*-hydroxyphenyl-5-phenylisoxazole[2] (V, R = phenyl, R′ = *o*-hydroxyphenyl).[2] By analogy, we give the reaction products obtained from Ia, Ib and II, the formulas Va, Vb and Vc, respectively, but do not wish to exclude the corresponding formulas VIa–c. The reaction products are soluble in aqueous alkali, their alcoholic solutions give a color reaction with aqueous ferric chloride solution. From Va (or VIa) and Vc (or VIc) monobenzoyl derivatives were obtained; Vb (or VIb) yields a dibenzoyl derivative (Schotten–Baumann). Va (or VIa) was recovered unchanged when boiled with 10% sodium hydroxide solution for one hour, followed by acidification. This stability toward alkali was to be expected, as according to Claisen,[4] 3,5-substituted isoxazoles are very resistant to alkali. The benzoyl derivative of Va (or VIa) was hydrolyzed to V or (VI) by the action of alkali.


III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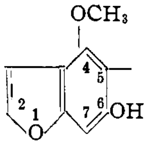
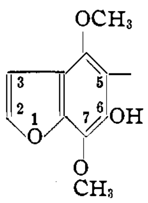

A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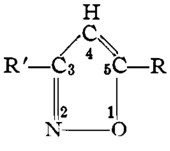
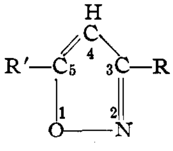

V


VI

IIIa, IVa, Va, VIa, R′ = A, R = CH_3
IIIb, IVb, Vb, VIb, R′ = A, R = CH_2OH
IIIc, IV, Vc, VIc, R′ = B, R = CH_3
IIId, IVd, R′ = *o*-HOC_6H_4, R = H

TABLE II

BENZOYL DERIVATIVES OF THE REACTION PRODUCTS MENTIONED IN TABLE I

Benzoyl deriv.[a] of	M.p., °C.	Solvent for cryst.	Formula of the benzoyl deriv.		Analyses, %
IIIb or IVb	129	MeOH	$C_{34}H_{24}O_7N_2$	Found	C, 71.7; H, 4.3; N, 5.0
				Calcd.	C, 71.3; H, 4.2; N, 4.9
Vb or VIb	132	MeOH	$C_{27}H_{19}O_7N$	Found	C, 69.0; H, 4.1; N, 3.1
				Calcd.	C, 69.1; H, 4.1; N, 3.0
IIIc or IVc	179	EtOH	$C_{28}H_{22}O_6N_2$	Found	C, 69.7; H, 4.5; N, 5.6
				Calcd.	C, 69.7; H, 4.6; N, 5.8
Vc or VIc	150	EtOH	$C_{21}H_{17}O_6N$	Found	C, 66.4; H, 4.3; N, 3.4
				Calcd.	C, 66.5; H, 4.5; N, 3.7

[a] The benzoyl derivatives obtained are colorless, insoluble in aqueous sodium hydroxide (10%).

Experimental[5]

Experiments with Hydrazine Hydrate. Visnagin (taken as an example).—Five grams of hydrazine hydrate in 10 ml. of warm alcohol was added to a solution of 1.2 g. of visnagin in 10 ml. of alcohol, and the mixture warmed for 15 minutes. The cooled mixture was diluted with water, the formed deposit was filtered and crystallized from benzene–light petroleum mixture, as colorless crystals, m.p. 142°. 4-Methyl-5-[3(or 5)-methyl-5(or 3)-pyrazolyl]-6-benzofuranol (IIIa or IVa) gives a blue color with ferric chloride, and a deep orange color with titanium chloride, dissolves in aqueous sodium hydroxide (10%), but is insoluble in hydrochloric acid (12%). It gives a yellow orange color reaction with concentrated sulfuric acid (Found: C, 64.3; H, 4.9; N, 12.3; $-OCH_3$, 12.7. $C_{13}H_{12}O_3N_2$ requires C, 63.9; H, 4.9; N, 11.5; $-OCH_3$, 12.7); yield about 85%.

Benzoylation.—The general procedure for carrying out a Schotten–Baumann reaction has been followed. The dibenzoyl derivative crystallizes slowly from alcohol as colorless crystals, m.p. 150°. It is insoluble in aqueous sodium hydroxide (10%) (Found: C, 71.2; H, 4.5; N, 6.0. $C_{27}H_{20}O_5N_2$ requires C, 71.1; H, 4.4; N, 6.2).

Experiments with Hydroxylamine Hydrochloride. Visnagin (taken as an example).—A mixture of 0.15 g. of hydroxylamine hydrochloride in 0.5 ml. of water, and 0.1 g. of visnagin in 1 ml. of pyridine was refluxed for 4 hours. The cooled mixture was acidified with dilute acetic acid; the deposit formed was filtered and crystallized from benzene–light-petroleum mixture, as colorless crystals, m.p. 146°. 4-Methoxy-5-[5(or 3)-methyl-3(or 5)-isoxazolyl]-6-benzofuranol (Va or VIa) is insoluble in water and soluble in aqueous sodium hydroxide (10%). The yield is *ca.* 85% (Found: C, 63.5; H, 4.8; N, 5.2. $C_{13}H_{11}O_4N$ requires C, 63.7; H, 4.5; N, 5.7.). It was recovered unchanged or almost unchanged when its solution in aqueous sodium hy-

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(3) *Cf.* preceding page 4992.

(4) L. Claisen, *Ber.*, **36**, 3672 (1903).

(5) The color reactions with ferric chloride were carried out by dissolving the substance in alcohol and adding a small amount of dilute aqueous ferric chloride solution. The color reactions with titanium trichloride were carried out similarly. The reagent was titanium trichloride (15%), free from iron (E, Merck, Darmstadt, Germany). The hydrazine hydrate was 50%.

droxide (10%) was refluxed for one hour followed by cooling and acidification with dilute hydrochloric acid.

Benzoylation.—The benzoyl derivative (Schotten–Baumann method) was crystallized slowly from alcohol, as colorless crystals, m.p. 111°. It is insoluble in aqueous sodium hydroxide solution (10%) (Found: C, 68.3; H, 4.3; N, 3.5. $C_{20}H_{15}O_5N$ requires C, 68.8; H, 4.3; N, 4.0.). The benzoyl derivative was refluxed with aqueous sodium hydroxide solution (10%) for one hour, allowed to cool and acidified with dilute hydrochloric acid, the deposit was crystallized from benzene–petroleum-ether mixture and proved to be (Va or VIa) (m.p. and mixed m.p.).

The syntheses of the other substances mentioned in the theoretical part are listed in the Tables I and II.

FOUAD I UNIVERSITY
GIZA, CAIRO, EGYPT

The Osmotic and Activity Coefficients of Calcium, Strontium and Barium Perchlorate at 25°

BY R. A. ROBINSON, C. K. LIM AND K. P. ANG

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Nicholson[1] has deduced the activity coefficients of magnesium, calcium, strontium and barium perchlorate from freezing point measurements; his results for the magnesium salt are in good agreement with those derived[2] from isopiestic vapor pressure measurements at 25°, the latter being higher by 0.003 in γ at 0.1 *m*. If the two sets of data are adjusted relative to the same value of $\gamma = 0.587$ at 0.1 *m*, the isopiestic values at other concentrations are higher, the difference rising to 0.043 at 1 *m*. Some time ago we made isopiestic measurements on calcium perchlorate and we have recently made measurements on the strontium and barium salts which can be compared with the data of Nicholson.

The stock solutions were prepared by adding a slight excess of the carbonate to perchloric acid (of "analytical" purity), filtering off the excess of carbonate and analyzing for the metal. Isopiestic measurements were made with calcium chloride as reference salt (Table I) and the osmotic and activity coefficients (Table II) calculated in the usual way. It proved very difficult to get reproducible results with the barium salt at concentrations less than 1 *m* and the results in this region should be accepted with caution. These solutions seemed to have a very low rate of evaporation and gave a degree of difficulty we have not experienced with any other solutions. The activity coefficients are of the magnitude we would expect for highly dissociated and hydrated salts. The curves for the calcium and strontium salts resemble those plotted from Nicholson's data at the freezing point but the barium salt exhibits a large temperature variation. For example, recalculating the freezing point data to refer to $\gamma = 0.523$ at 0.1 *m*, the activity coefficient of 0.512 at 1 *m* and 25° contrasts with 0.434 at the freezing point.

TABLE I

MOLALITIES OF ISOPIESTIC SOLUTIONS AT 25°

$CaCl_2$	Ca-$(ClO_4)_2$	$CaCl_2$	Ca-$(ClO_4)_2$	$CaCl_2$	Ca-$(ClO_4)_2$	$CaCl_2$	Ca-$(ClO_4)_2$
0.1176	0.1133	1.584	1.392	3.135	2.722	6.074	5.270
.2879	.2695	1.968	1.717	3.210	2.784	6.795	5.799
.3879	.3587	2.017	1.760	3.656	3.176	6.810	5.812
.5528	.5047	2.202	1.916	4.118	3.584	7.385	6.181
.6407	.5807	2.471	2.148	4.330	3.771	7.970	6.540
.8038	.7236	2.483	2.159	4.771	4.163	8.658	6.919
1.121	.9933	2.795	2.427	5.321	4.651		

$CaCl_2$	Sr-$(ClO_4)_2$	$CaCl_2$	Sr-$(ClO_4)_2$	$CaCl_2$	Sr-$(ClO_4)_2$	$CaCl_2$	Sr.$(ClO_4)_2$
0.1051	0.1038	1.066	0.9794	3.817	3.602	6.968	6.833
.1692	.1645	1.233	1.128	4.199	4.000	7.475	7.279
.2429	.2346	1.722	1.569	4.801	4.642	8.468	8.071
.3177	.3044	2.444	2.244	5.377	5.258	8.561	8.139
.4637	.4388	2.804	2.594	6.269	6.174	8.705	8.250
.8449	.7804	3.362	3.143				

$CaCl_2$	Ba-$(ClO_4)_2$	$CaCl_2$	Ba-$(ClO_4)_2$	$CaCl_2$	Ba-$(ClO_4)_2$	$CaCl_2$	Ba-$(ClO_4)_2$
0.2429	0.2409	1.611	1.665	2.437	2.641	3.828	4.502
.5100	.5041	1.917	2.017	2.757	3.053	4.462	5.462
.8711	.8651	2.163	2.319	3.303	3.766	4.629	5.694
1.270	1.292						

TABLE II

OSMOTIC AND ACTIVITY COEFFICIENTS AT 25°

	$Ca(ClO_4)_2$		$Sr(ClO_4)_2$		$Ba(ClO_4)_2$	
m	φ	γ	φ	γ	φ	γ
0.1	0.883	(0.565)	0.864	(0.532)	0.857	(0.523)
.2	.911	.540	.886	.497	.868	.480
.3	.942	.540	.915	.491	.884	.463
.4	.976	.552	.947	.497	.905	.458
.5	1.014	.573	.982	.511	.929	.461
.6	1.051	.598	1.017	.529	.954	.468
.7	1.089	.627	1.052	.550	.977	.476
.8	1.131	.664	1.090	.577	1.000	.486
.9	1.175	.706	1.130	.608	1.024	.499
1.0	1.219	.754	1.170	.643	1.046	.512
1.2	1.310	.866	1.249	.723	1.094	.544
1.4	1.405	1.007	1.329	.818	1.141	.580
1.6	1.503	1.179	1.413	.935	1.188	.621
1.8	1.605	1.393	1.492	1.067	1.233	.673
2.0	1.710	1.659	1.577	1.229	1.279	.717
2.5	1.992	2.66	1.789	1.767	1.394	.866
3.0	2.261	4.27	2.008	2.59	1.509	1.045
3.5	2.521	6.86	2.196	3.71	1.619	1.284
4.0	2.769	10.93	2.372	5.24	1.713	1.542
4.5	3.005	17.28	2.538	7.35	1.791	1.822
5.0	3.233	27.1	2.693	10.16	1.862	2.13
5.5	3.454	42.3	2.834	13.83	1.945	2.53
6.0	3.655	64.7	2.962	18.56	...	...
6.5	3.828	95.7	3.074	24.4	...	...
7.0	3.989	139.3	3.166	31.3	...	...
7.5	...	...	3.241	39.3	...	...
8.0	...	...	3.308	48.6	...	...

UNIVERSITY OF MALAYA
SINGAPORE

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(1) D. E. Nicholson (with W. A. Felsing), THIS JOURNAL, **72**, 4469 (1950); **73**, 3520 (1951).

(2) R. H. Stokes and B. J. Levien, *ibid.*, **68**, 333 (1946).