linear concentration gradient, which leads to the parabolic law, the concentration of diffusion species would decrease exponentially along the diffusion paths, or

$$c = c_0 e^{-\alpha x}$$

where c is the concentration of the diffusion species at a distance x from its starting point. Thus, the concentration gradient would be

$$\partial c/\partial x = -c_0 k e^{-\alpha x}$$

Since the total thickness of oxide, x, is related to the amount of substance that has diffused, w, by a gravimetric factor $w = gx$, then

$$dw/dt = -Dc_0\alpha e^{-w\alpha/g}$$

Integrating

$$w = k \log(1 + at)$$

which is the logarithmic law for oxidation.

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CHICAGO 16, ILL. RECEIVED NOVEMBER 20, 1950

NOTES

Quaternary Salts of Halogenated Pyridines and Quinolines[1]

BY CARL T. BAHNER, WM. K. EASLEY, MADGE D. PICKENS, HAROLD D. LYONS, LILBURN L. NORTON, BETTY GAY WALDEN AND GEORGE E. BIGGERSTAFF

Since certain quaternary salts of pyridine and quinoline have been reported to damage sarcoma cells *in vivo*[2] we have prepared similar salts of several halogenated pyridines and quinolines for screening against sarcoma in mice[3] and for correlation of biological effects and other properties with structure.

The quaternary salts listed in Tables I and II were prepared by reaction of a halogenated heterocyclic base with the appropriate organic halide at 30–40°. When the reactants alone did not form a homogeneous solution a small amount of chloroform was added to bring them into solution. The products usually precipitated as they were formed and the mixture was allowed to stand as long as seemed necessary to obtain a good yield. The rates of reaction varied greatly. For 6-chloroquinoline the reaction periods were: with glycerol-

TABLE I

HALOPYRIDINE DERIVATIVES

Salt from 2-Chloropyridine and	Empirical formula	M.p., °C.[a]	Analyses, % Ionic Halogen Calcd.	Found[b]
β-Phenylethyl bromide	$C_{13}H_{13}BrClN$	193	26.76	26.50
Styrene bromohydrin	$C_{13}H_{13}BrClNO$	182	25.40	25.30
Phenacyl bromide	$C_{13}H_{11}BrClNO$	187	25.57	25.30
p-*t*-Butylphenacyl bromide	$C_{17}H_{19}BrClNO$	192	21.68	21.40
p-Fluorophenacyl bromide	$C_{13}H_{10}BrClFNO$	185–187	24.17	24.03
p-Chlorophenacyl bromide	$C_{13}H_{10}BrCl_2NO$	188–189	23.03	23.01
p-Bromophenacyl bromide	$C_{13}H_{10}Br_2ClNO$	194	20.41	20.42
p-Iodophenacyl bromide	$C_{13}H_{10}BrClINO$	193	18.23	18.00
m-Nitrophenacyl bromide	$C_{13}H_{10}BrClN_2O_3$	172	22.35	22.42
2-Bromopyridine and				
p-Fluorophenacyl bromide	$C_{13}H_{10}Br_2FNO$	174–175	21.30	21.08
p-Chlorophenacyl bromide	$C_{13}H_{10}Br_2ClNO$	201	20.41	20.44
p-Iodophenacyl bromide	$C_{13}H_{10}Br_2INO$	189	16.55	16.40
p-Phenylphenacyl bromide	$C_{19}H_{15}Br_2NO$	160–161	18.45	18.54
5,6,7,8-Tetrahydro-β-naphthacyl bromide	$C_{17}H_{17}Br_2NO$	207	19.44	19.54
3-Fluoropyridine and				
p-Fluorophenacyl bromide	$C_{13}H_{10}BrF_2NO$	189	25.36	25.29
3-Chloropyridine and				
p-Fluorophenacyl bromide	$C_{13}H_{10}BrClNO$	169–170	24.17	24.33

(1) This investigation was supported in part by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

(2) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.; *cf.* J. L. Hartwell and S. R. L. Kornberg, THIS JOURNAL, **68**, 1131 (1946).

(3) Results of screening tests at the National Cancer Institute are to be reported elsewhere.

TABLE I (*Continued*)

	Empirical formula	M.p., °C.[a]	Analyses, % Ionic Halogen Calcd.	Found[b]
3-Bromopyridine and				
Decyl iodide	$C_{15}H_{25}BrIN$	80	29.77	29.92
2,5-Diiodohexane (bis-salt)	$C_{16}H_{20}I_4N_2$	244–245	38.93	38.83
Glycerol-α,γ-dibromohydrin	$C_{13}H_{14}Br_4N_2O$	330	29.93	29.83
Ethyl iodoacetate	$C_9H_{11}BrINO_2$	178–179	34.12	34.53
Cyclohexylethyl bromide	$C_{13}H_{19}Br_2N$	123–125	22.90	22.96
Styrene bromohydrin	$C_{13}H_{13}Br_2NO$	216–217	22.25	22.51
p-*t*-Butylphenacyl bromide	$C_{17}H_{19}Br_2NO$	210–211	19.34	19.64
2,5-Dimethylphenacyl bromide	$C_{15}H_{15}Br_2NO$	254	20.75	20.73
p-Fluorophenacyl bromide	$C_{13}H_{10}Br_2FNO$	112	21.28	20.97
p-Chlorophenacyl bromide	$C_{13}H_{10}Br_2ClNO$	236–240	20.40	20.41
p-Iodophenacyl bromide	$C_{13}H_{10}Br_2INO$	268–270	16.55	16.57
2,5-Dichlorophenacyl bromide	$C_{13}H_9Br_2Cl_2NO$	238–239	18.76	18.74
m-Nitrophenacyl bromide	$C_{13}H_{10}Br_2N_2O_3$	207–209	19.87	19.73
3,4-Dihydroxyphenacyl bromide	$C_{18}H_{11}BrClNO_3$	252	[c]	
p-Methoxyphenacyl bromide	$C_{14}H_{13}Br_2NO_2$	243	20.64	20.64
β-Naphthacyl bromide	$C_{17}H_{13}Br_2NO$	234–235	19.63	19.29
β-Naphthacyl iodide	$C_{17}H_{13}BrINO$	214–215	27.95	27.76
anti-β-Naphthacyl iodide oxime	$C_{17}H_{14}BrIN_2O$	202–203	[d]	
4-Fluoro-α-naphthacyl bromide	$C_{17}H_{12}Br_2FNO$	214	18.80	18.52
5,6,7,8-Tetrahydro-β-naphthacyl bromide	$C_{17}H_{17}Br_2NO$	220–221	19.44	19.24
α-Bromo-β-propionaphthone	$C_{13}H_{13}Br_2NO$	234–235	18.98	18.83
p-Chlorophenyl-α-bromoethyl ketone	$C_{14}H_{12}Br_2ClNO$	203–204	19.71	19.57
3-Iodopyridine and				
2,5-Diiodohexane	$C_{16}H_{20}I_4N_2$	261–264	34.02	34.03
p-Fluorophenacyl bromide	$C_{13}H_{10}BrFINO$	202–204	18.98	19.08
3,5-Dibromopyridine and				
Decyl iodide	$C_{15}H_{24}Br_2IN$	208–209	15.82	15.95
β-Phenylethyl iodide	$C_{13}H_{13}Br_2IN$	206–207	27.01	27.13
p-*t*-Butylphenacyl bromide	$C_{17}H_{18}Br_3NO$	190–191	16.24	15.93
p-Fluorophenacyl bromide	$C_{13}H_9Br_3FNO$	220	17.60	17.36
p-Chlorophenacyl bromide	$C_{13}H_9Br_3ClNO$	225–226	16.98	17.21
p-Bromophenacyl bromide	$C_{13}H_9Br_4NO$	227–228	15.52	15.64
p-Iodophenacyl bromide	$C_{13}H_9Br_3INO$	237	14.22	14.48
m-Nitrophenacyl bromide	$C_{13}H_9Br_3N_2O_3$	238	16.62	16.40
p-Methoxyphenacyl bromide	$C_{14}H_{12}Br_3NO_2$	251	17.15	17.15
p-Chlorophenyl-α-bromoethyl ketone	$C_{14}H_{11}Br_3ClNO$	192	16.50	16.51
p-Phenylphenacyl bromide	$C_{19}H_{14}Br_3NO$	216–217	15.60	15.80
β-Naphthacyl bromide	$C_{17}H_{12}Br_3NO$	203–204	16.44	16.19
β-Naphthacyl iodide	$C_{17}H_{12}Br_2INO$	180–181	23.81	23.99
5,6,7,8-Tetrahydro-β-naphthacyl bromide	$C_{17}H_{16}Br_3NO$	231–232	16.30	16.40
5,6,7,8-Tetrahydro-β-naphthacyl iodide	$C_{17}H_{16}Br_2INO$	205	23.62	23.78

[a] Salts melted with decomposition. [b] Average of two Volhard analyses, unless otherwise indicated. [c] Calcd.: C, 45.32; H, 3.22. Found: C, 45.26; H, 3.48. [d] Calcd.: C, 43.53; H, 3.01. Found: C, 43.46; H, 3.12.

α,γ-dibromohydrin[4] 60 days, with decyl iodide[4] 14 days, with β-phenylethyl bromide[4] 18 days, with β-phenylethyl iodide[4] 18 hours, with phenacyl bromide[5] 14 days, with *p*-methoxyphenacyl bromide[5] 4 days, with *p*-iodophenacyl bromide[5] 24 hours and with β-naphthacyl bromide[5] 24 hours. Among the bases, 3,5-dibromopyridine and 3-bromopyridine reacted more rapidly than 2-chloropyridine and 2-bromopyridine, while 4,7-dichloroquinoline reacted much less rapidly than 6-chloroquinoline. The results observed were in line with the expected deactivating effect of a negative atom attached at the 2- or 4- position on the heterocyclic ring and the steric hindering by a large atom or group attached to the carbon adjacent to the nitrogen.

The bromide salts were white or cream solids while the iodides were yellow. Some of those with low molecular weights were very soluble in water, while others were only slightly soluble. Most of the salts were recrystallized by dissolving in warm methanol, ethanol or ethyl acetate and adding isopropyl ether, but some were recrystallized from water, alcohol or acetone without the aid of isopropyl ether.

Acknowledgments.—The authors wish to express their appreciation to Dr. M. J. Shear and Dr. J. L. Hartwell for arranging screening tests against mouse tumors and securing carbon and hydrogen analyses on some of the compounds, to Miss Marguerite Close for part of the Volhard analyses, to Mr. Hugh Jenkins, Mr. Clifford Myers, Mr. Jack Brasher, Mr. Gene Moore and Mr. Paul Scott for preparation of some of the organic halides used, to Dr. Arthur Roe for

(4) Without solvent.
(5) In chloroform.

TABLE II

HALOQUINOLINE DERIVATIVES

Salt from 6-chloroquinoline and	Empirical formula	M.p., °C.	Analyses, % Ionic halogen Calcd.	Found
Decyl iodide	$C_{19}H_{27}ClIN$	113	29.39	29.33
Glycerol-α,γ-dibromohydrin	$C_{12}H_{12}Br_2ClNO$	234	20.95	21.22
β-Cyclohexylethyl bromide	$C_{17}H_{21}BrClN$	102	22.52	22.33
β-Phenylethyl bromide	$C_{17}H_{15}BrClN$	108–111	22.92	22.83
β-Phenylethyl iodide	$C_{17}H_{15}ClIN$	164	32.09	31.90
Phenacyl bromide	$C_{17}H_{13}BrClNO$	215	22.04	21.78
p-*t*-Butylphenacyl bromide	$C_{21}H_{21}BrClNO$	232	19.08	18.98
p-Chlorophenacyl bromide	$C_{17}H_{12}BrCl_2NO$	205	20.12	20.12
p-Bromophenacyl bromide	$C_{17}H_{12}Br_2ClNO$	207	18.09	18.11
m-Nitrophenacyl bromide	$C_{17}H_{12}BrClNO_3$	215	19.60	19.52
p-Methoxyphenacyl bromide	$C_{18}H_{15}BrClNO$	211	20.34	30.33
β-Naphthacyl bromide	$C_{21}H_{15}BrClNO$	236.5	19.37	19.43
5,6,7,8-Tetrahydro-β-naphthacyl bromide	$C_{21}H_{19}BrClNO$	252	19.17	18.95
3-Bromoquinoline and				
p-Fluorophenacyl bromide	$C_{17}H_{12}Br_2FNO$	258	18.80	18.84

samples of 3-fluoro, 3-chloro and 3-iodopyridine, and to Miss Emogene Stephen, Miss Carolyn Cate, Mr. Tom Fuller and Mr. Lynn Easley for assistance in the purification of the products.

DEPARTMENT OF CHEMISTRY
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN. RECEIVED FEBRUARY 21, 1951

Color Reactions of Human Antibody and Normal Human Gamma Globulin[1]

BY SAM M. BEISER AND ELVIN A. KABAT

As a criterion of purity of the blood group A substances[2,3,4,5] determinations were carried out of the proportions of two characteristic constituents of these antigens, hexosamine and methylpentose, specifically precipitated by an excess of antibodies to A substance. Since such specific precipitates consist of both antigen and antibody, total color values for hexosamine[6] and methylpentose[7] in specific precipitates must be corrected for any color given in these reactions by the antibody. The equivalent color values of normal human γ-globulin were used for this purpose although the possibility was recognized[2] and commented upon[8] that human antibody and normal human gamma globulin may not give identical color values. This report shows that human antipneumococcal antibodies give color values identical with those for human gamma globulin in the reactions for hexosamine and methylpentose as well as with Folin–Ciocalteu tyrosine reagent.[9]

Experimental

Antipneumococcal antibodies were produced by injection into a human being of a mixture of pneumococcal polysaccharides.[10] A large sample of serum was obtained and found to contain 38 μg. anti-C[11], 23 μg. anti-SII[11] and 9 μg. anti-SIII[11] N per ml. Specific precipitates of C-anti-C, SIII-anti-SIII and SII-anti-SII were obtained from about 100-ml. portions of serum, which had been in the refrigerator until the complement was destroyed, washed free from excess serum protein[9,10,12] dissolved in water with 0.5 ml. of 0.1 *M* NaOH, and made up to a known volume. Four samples of normal human gamma globulin were available for comparison with the human antibodies.[13]

Hexosamine/Total N Ratio.—Aliquots of the dissolved SII-anti-SII and SIII-anti-SIII specific precipitates were analyzed for nitrogen by the Markham micro-Kjeldahl method[14,12] and for hexosamine by a modification[15] of the Elson-Morgan procedure.[6] The hexosamine values were corrected for the color given in this reaction by the SII and SIII in the dissolved precipitates; these samples of polysaccharide gave color values equivalent to 3.3 and 0.9% hexosamine, respectively. Two lots of normal human gamma globulin were analyzed for nitrogen and hexosamine. C-anti-C precipitates were not suitable for determining the hexosamine/total N ratio since the C substance has a high (22%) hexosamine content.

Methylpentose/Total N Ratio.—SIII-anti-SIII and C-anti-C specific precipitates and three gamma globulin samples were analyzed for methylpentose and nitrogen,[14] and the values for the specific precipitates corrected for the methylpentose color given by these polysaccharides; SIII and C gave color values equivalent to 1.4 and 0.8% methylpentose, respectively. SII-anti-SII specific precipitates were not used in determining the methylpentose/N ratios since the SII sample contained 40% of methylpentose.

Folin–Ciocalteu Color Equivalent.—SII-anti-SII and SIII-anti-SIII specific precipitates and two gamma globulin samples were used. SII and SIII contain no nitrogen and give no color with the Folin–Ciocalteu tyrosine reagent and no correction for their presence in the precipitates was necessary. Appropriate dilutions of known nitrogen content were analyzed as described by Heidelberger and MacPherson.[9,12] Color development at 7500 Å. was proportional to N up to about 25 μg. N.

The values of hexosamine/N, methylpentose/N and mean

(1) The work reported in this paper was carried out under a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service and in part under the William J. Matheson Commission.

(2) A. Bendich, E. A. Kabat and A. E. Bezer, *J. Exp. Med.*, **83**, 485 (1946).

(3) E. A. Kabat, A. Bendich, A. E. Bezer and S. M. Beiser, *ibid.*, **85**, 685 (1947).

(4) E. A. Kabat, H. Baer and V. Knaub, *ibid.*, **89**, 1 (1949).

(5) E. A. Kabat, *Bact. Revs.*, **13**, 189 (1949).

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(7) Z. Dische and L. B. Shettles, *J. Biol. Chem.*, **175**, 595 (1948).

(8) G. Holzman and C. Niemann, THIS JOURNAL, **72**, 2048 (1950).

(9) M. Heidelberger and C. F. C. MacPherson, *Science*, **97**, 405 (1943); **98**, 63 (1943).

(10) M. Heidelberger, C. M. MacLeod, S. J. Kaiser and B. Robinson, *J. Exp. Med.*, **83**, 303 (1946).

(11) C denotes the group specific polysaccharide of pneumococcus and SII and SIII the type-specific capsular polysaccharides of types II and III pneumococci.

(12) E. A. Kabat and M. M. Mayer, "Experimental Immunochemistry," C. C. Thomas, Springfield, Ill., 1948.

(13) E. A. Kabat and J. P. Murray, *J. Biol. Chem.*, **182**, 251 (1950).

(14) R. Markham, *Biochem. J.*, **36**, 790 (1942).

(15) K. Meyer, E. M. Smyth and J. W. Palmer, *J. Biol. Chem.*, **119**, 491 (1937).

values for Folin color per 10 μg. N are given in Table I. Within experimental error antipneumococcal antibodies and human gamma globulin give identical results.

TABLE I

COLOR EQUIVALENTS OF HUMAN ANTIBODY AND NORMAL HUMAN GAMMA GLOBULIN

	Hexosamine[a,b] / Total N	Methylpentose[b] / Total N	Folin-Ciocalteu color D 7500 / 10 μg. N
Anti-C		0.032[e]	
Anti-SII	0.07[c]		0.155
Anti-SIII	.07[d]	.030[f]	.150
Gamma globulin			
Fraction II-1, 2[13]	.07		.149
Fraction II-3[13]	.07	.034	.146
Sample B[13]		.032	
Sample S[13]		.026	

[a] Hexosamine was determined after hydrolysis with 2 *N* HCl at 100° for 2 hours. [b] The color values, while reproducible, are not assumed to be specific for either hexosamine or methylpentose.[15,16] [c] Correction for hexosamine color value of SII-14%. [d] Correction for hexosamine color value of SIII-7%. [e] Correction for methylpentose color value of "C" substance-8%. [f] Correction for methylpentose color value of SIII-14%.

(15) E. Vasseur and J. Immers, *Arkiv Kemi*, **1**, 253 (1949).

(16) H. N. Horowitz, M. Ikawa and M. Fling, *Arch. Biochem.*, **25**, 226 (1950).

DEPARTMENTS OF NEUROLOGY AND BACTERIOLOGY
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RECEIVED FEBRUARY 28, 1951

The Attempted Rosenmund Reduction of Diphenylacetyl Chloride[1]

BY JOHN G. BURR, JR.

Recently a supply of diphenylacetaldehyde was desired in this Laboratory, and since diphenylacetyl chloride was available, the Rosenmund reduction of this compound was investigated. The products which were obtained are

$$(C_6H_5)_2CHCOCl \longrightarrow \underset{47\%}{(C_6H_5)_2CHCH(C_6H_5)_2} + \underset{13.5\%}{(C_6H_5)_2CH_2} + \underset{13.5\%}{(C_6H_5)_2CHCOOH} + \underset{75\%}{HCl}$$

The occurrence of a product of the nature of tetraphenylethane as a product of a Rosenmund reduction has not been previously reported. Triphenylacetyl chloride also loses carbon monoxide and hydrogen chloride under Rosenmund conditions; the product in this case is triphenylmethane.[2]

The more usual products and by-products of this reaction were accounted for by Rosenmund[3] as

$$R\text{—}COCl \begin{cases} \longrightarrow RCOCH_2R \longrightarrow RCH_3 + RCOOH + RCH_2CH_2R \\ \longrightarrow RCHO \longrightarrow RCH_2OH \longrightarrow (RCH_2)_2O \end{cases}$$

This scheme does not predict products of the nature of tetraphenylethane or triphenylmethane.

A possible explanation of these two products may be found in the temperature at which these reactions were carried out. It is known, for example, that diphenylacetyl chloride decomposes at temperatures of around 200–250° into carbon monoxide, hydrogen chloride, tetraphenylethylene and diphenylketene.[4,5] Staudinger[4] explains the formation of tetraphenylethylene through an intermediate diphenylchloromethane which is known to decompose upon heating to tetraphenylethylene[6,7] and tetraphenylethane.[7] The moderate

$$(C_6H_5)_2CHCOCl \longrightarrow [(C_6H_5)_2CHCl] + CO$$

$$[(C_6H_5)_2CHCl] \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2 + (C_6H_5)_2CHCH(C_6H_5)_3 + HCl$$

temperature of the reaction observed here (boiling xylene solution) with its long duration might well be sufficient for a smooth production of diphenylchloromethane (but little diphenylketene), and the thermal conversion of this to tetraphenylethylene and tetraphenylethane. The tetraphenylethylene, in the reductive atmosphere, might be converted to tetraphenylethane.

Similarly, triphenylacetylchloride is known[5] to be converted at 170–180° quantitatively to triphenylchloromethane and carbon monoxide. Under the conditions of the Rosenmund reduction, the triphenylchloromethane would probably be converted to triphenylmethane.

Experimental[8]

Attempted Rosenmund Reduction of Diphenylacetyl Chloride.—A suspension of 4 g. of 5% palladium-barium sulfate catalyst, poisoned with 0.6 ml. of quinoline-S solution, in 200 ml. of toluene was prepared, heated to boiling, and a small amount of solvent distilled to dry the remainder. To the cooled solution was added 44.6 g. of diphenylacetyl chloride. A moderately fast stream of hydrogen was passed through the stirred, refluxing mixture. The effluent gases were passed into water, and the absorbed hydrogen chloride titrated with 5 *N* sodium hydroxide. After overnight reaction, 28 ml. of NaOH had been consumed (75% of theory). The cooled solution was filtered from the catalyst, and the solvent was removed under vacuum. The residual pasty solid was heated with aqueous sodium bicarbonate. The undissolved material was filtered off, and the filtrate, after extraction with ether, acidified to give 5.5 g. (13.5%) of diphenylacetic acid (m.p. 145°). The neutral organic substances were stirred with ether. The ether-soluble material was obtained by filtration. It was evaporated, and the residue distilled at high vacuum. The distillate, 4.4 g. (13.5%), b.p. 87–89° (0.1 mm.), $n^{28}D$ 1.5788, was diphenylmethane. The residue was about 5 g. of a semisolid.

The ether-insoluble material weighed 15 g. (47% yield), and after several crystallizations from benzene formed a white microcrystalline powder melting at 211–212°. This material conforms in analysis, melting point, and general solubilities to tetraphenylethane. A mixture melting point with authentic tetraphenylethane (prepared from diphenylchloromethane and zinc, and melting at 211–212°) showed no depression.

(1) This document is based upon work performed under Contract Number W-7405, eng. 26 for the Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) S. Daniloff and E. Venus-Danilova, *Ber.*, **59**, 377 (1926).

(3) K. W. Rosenmund and F. Zetzche, *ibid.*, **54**, 642, 2038 (1921).

(4) H. Staudinger, *ibid.*, **44**, 1619 (1911).

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(7) C. Engler and H. Bethge, *Ber.*, **7**, 1128 (1886).

(8) All melting points were taken on a Fisher-Johns block and are uncorrected. Microanalyses are by Dr. H. W. Galbraith, Knoxville, Tenn.

OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENN.
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Phenylalanine Analogs

BY J. H. BURCKHALTER AND VERLIN C. STEPHENS

The following new compounds related to phenyl-

alanine were prepared in addition to the group already published.[1]

Ethyl (2,4-Dichlorobenzyl)-acetamidomalonate (I).—By the process previously reported,[1] 39.2 g. (0.2 mole) of 2,4-dichlorobenzyl chloride[2] and the sodium salt of 43.4 g. (0.2 mole) of ethyl acetamidomalonate, gave 60 g. of product (80%), m.p. 159–160°. Subsequent recrystallizations from aqueous alcohol did not significantly alter the melting point.

Anal.[3] Calcd. for $C_{16}H_{19}Cl_2NO_5$: C, 51.08; H, 5.09. Found: C, 51.40; H, 5.02.

β-(2,4-Dichlorophenyl)-alanine.—Hydrolysis of 37.6 g. (0.1 mole) of I by refluxing for 14 hours in 150 ml. of 48% hydrobromic acid, gave 24 g. (theoretical yield) of product, m.p. 237–239° dec. Two recrystallizations from water raised the melting point to 238–240° dec.

Anal. Calcd. for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.88. Found: C, 45.92; H, 4.22.

β-(3-Nitro-*p*-tolyl)-alanine.—3-Nitro-*p*-xylyl chloride was prepared by the method of Stephen, Short and Gladding.[4] By treatment of 25 g. (0.13 mole) of this material with 23 g. (0.13 mole) of ethyl acetamidocyanoacetate in the usual manner,[1] there was obtained a brown oil which could not be crystallized. The oil was hydrolyzed by heating at reflux temperature for four and a half hours in hydrochloric acid as described previously.[1] A solid formed in the neutralized solution after it had stood for several days; weight 17 g., m.p. 219° dec. (bath preheated to 210°). Recrystallization from aqueous alcohol gave 10 g. (34%) of product, m.p. 230° dec.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40. Found: C, 53.77; H, 5.60.

(1) Burckhalter and Stephens, THIS JOURNAL, **73**, 56 (1951).
(2) Supplied by Heyden Chemical Corp., Garfield, N. J.
(3) Analyses by Mr. C. W. Beazley, Skokie, Illinois.
(4) Stephen, Short and Gladding, *J. Chem. Soc.*, **117**, 510 (1920).

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
UNIVERSITY OF KANSAS SCHOOL OF PHARMACY
LAWRENCE, KANSAS RECEIVED MARCH 26, 1951

The Synthesis of 2,3-Bis-(*p*-carbethoxyphenyl)-2,3-butanediol by Electrolytic Reduction

BY MILTON J. ALLEN

It recently became necessary to prepare large quantities of 2,3-bis-(*p*-carbethoxyphenyl)-2,3-butanediol. A survey of the electrochemical literature[1] indicated that in acid medium an ester of an aromatic acid is readily reduced to an ether and aromatic acid reduced to an alcohol.

In view of the possibility of saponification of the *p*-carbethoxyacetophenone during reduction in alkaline medium, the free acid was reduced in alkaline medium at a constant reference potential with the resultant excellent yield of the pinacol. Treatment of the pinacol with ethanol and sulfuric acid yielded 2,3-bis-(*p*-carbethoxyphenyl)-2,3-butanediol.

Figure 1 illustrates the cell used in the electrolytic reduction. The instrument used for maintaining a constant reference potential has been previously described.[2]

Experimental[3]

2,3-Bis-(*p*-carbethoxyphenyl)-2,3-butanediol.—The catholyte consisted of 300 g. of *p*-carboxyacetophenone dissolved in 2500 ml. of distilled water containing 280.5 g. of potassium hydroxide (Baker reagent). The anolyte contained 56.1 g. of potassium hydroxide in 500 ml. of aqueous solution. At a reference potential of −2.0 volts the initial current was 4.2 amperes. After 937 minutes a current plateau of 0.9 ampere was reached. The catholyte was filtered, acidified with hydrochloric acid, refrigerated overnight and filtered. The residue was washed with water and dried in a vacuum oven; yield 290 g. (96.2%), m.p. 268–278°. Recrystallization from water gave platelets m.p. 272–273.5°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.09; H, 5.85.

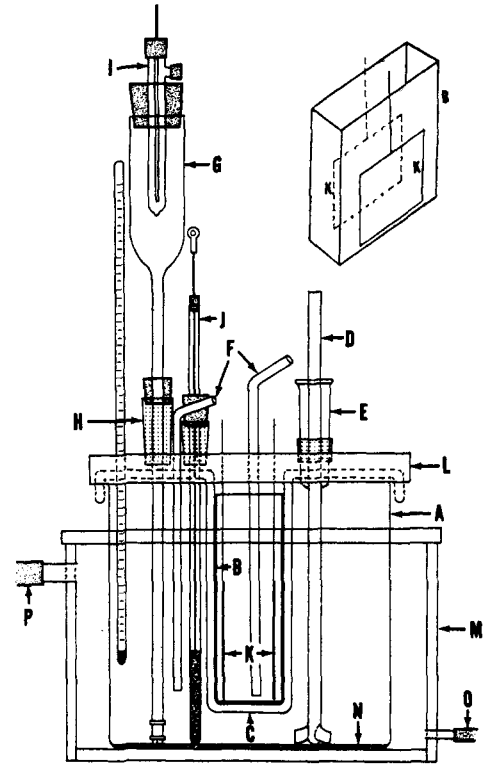

Fig. 1.—Electrolysis cell: A, glass electrolysis cell $8^1/_4$" i.d. × $8^3/_4$" high; B, alundum membrane 2" wide × 6" long × 6" deep, $^1/_8$" wall mix RA 1143 (Norton Company); C, membrane support $^1/_4$" diameter rod; D, paddle stirrer 16" long × $^3/_8$" diameter; E, mercury seal type bearing with 29/42 joint; F, nitrogen inlet tubes to cathode and anode chambers; G, salt bridge, top portion 2" diam. × 4" high narrowing to $^7/_{16}$" × 12" long at end of which is sealed a 14/35 male joint, $^3/_8$" up from the bottom on one side of joint is a $^1/_{64}$" hole, over the male end of the joint is a female collar $^5/_8$" in lengh; H, support for salt bridge 24/40 joint extended 1.5 inches; I, standard Beckman calomel electrode; J, contact to mercury cathode consisting of tube $^1/_{16}$" o.d. × 14" long at bottom of which is sealed a piece of platinum wire. The tube is filled part way with mercury and copper wire inserted for connection to cathode lead. The entire tube passes through a rubber stoppered 24/40 joint; K, platinum anode 4" × 4" × $^1/_{64}$"; L, Plexiglas cover; M, cooling chamber 11" × 11" × $7^1/_4$" high o.d. $^1/_4$" thick Plexiglas; N, mercury cathode; O, one water inlet to cooling chamber, $^1/_4$" i.d. P; two water outlet from cooling chamber, $^1/_4$" i.d.

2,3-Bis-(*p*-carbethoxyphenyl)-2,3-butanediol.—Fifty grams of the pinacol was mixed with 1000 ml. of absolute ethanol and 200 ml. of sulfuric acid. The solution was refluxed for eight hours and diluted with an equal volume of water. After neutralization with aqueous sodium carbonate, most of the alcohol was evaporated on a steam-bath. The cooled solution was extracted a number of times with ether. The combined ether extracts were evaporated to a small volume and refrigerated; yield 48 g. (82%), m.p. 167–168°. Recrystallization from 61.5% methanol gave a crystalline compound m.p. 169.5–170.5°.

(1) "Organische Elektrochemie," Fr. Fichter, Verlag von Theodor Steinkopf, Dresden, 1942, pp. 251-263.
(2) M. J. Allen, *Anal. Chem.*, **22**, 804 (1950).
(3) All melting points reported were done on a Kofler hot-stage and are corrected.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.50; H, 6.87.

The compound was insoluble in dilute sodium carbonate which eliminated the possibility of it being a diether.

Acknowledgment.—The author wishes to express his appreciation to the Monsanto Chemical Company for supplying the carboxyacetophenone used in the experimental work.

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF HEALTH
BETHESDA, MD. RECEIVED FEBRUARY 17, 1951

Purification of 2,6-Lutidine

BY JOHN A. CATHCART AND DELBERT D. REYNOLDS

2,6-Lutidine is a very useful reagent in synthetic organic chemistry. It is a stronger base toward hydrogen chloride than is pyridine,[1] and it has less tendency to quaternize than does pyridine or the picolines.[2] The combination of these properties makes it especially useful in the chemistry of the sulfonates, in which quaternization is often an undesirable side reaction.

This note deals with the separation of 2,6-lutidine from the picolines. Commercial 2,6-lutidine contains β- and γ-picolines. Previous methods of separation have depended upon the fractional crystallization of derivatives such as hydrohalides, picrates, dimercurichlorides and oxalates, or upon azeotropic distillation.[3] The method described here is based upon the fact that 2,6-lutidine quaternizes with alkyl sulfonates much more slowly than do the picolines. Thus, when a mixture of 2,6-lutidine and the picolines reacts with an alkyl sulfonate, the picoline forms insoluble, undistillable quaternary salts which may be separated from the 2,6-lutidine by decantation or distillation. The effectiveness of this method is illustrated in the experimental section.

Experimental

The crude 2,6-lutidine was Eastman Kodak Co. Practical grade (m.p. −8.5°). The impurity is not water alone, since distillation over calcium hydride raised the melting point to only −7.6° instead of −5.9° which was the value found for pure 2,6-lutidine by repeated fractional crystallization.[3]

Any of the alkyl sulfonates may be used, but we prefer ethyl *p*-toluenesulfonate because of its availability and because of the rate with which it reacts with the picolines.

Removal of β- and γ-Picolines.—A. One kilogram of 2,6-lutidine (m.p. −8.5°) was mixed with 200 g. of ethyl *p*-toluenesulfonate and heated to reflux for one hour. The reaction mixture was cooled and the upper layer separated and distilled without fractionation. This product was refluxed over 100 g. of calcium hydride and distilled through a 20-inch column packed with glass helices; first fraction: b.p. < 144°, 25 g.; second fraction: b.p. 144°, 741 g., m.p. −6.15°.

B. This example omits the steps in which the quaternized product is separated and the distillation over calcium hydride.

One kilogram of 2,6-lutidine (m.p. −8.5°) was refluxed for one hour with 200 g. of ethyl *p*-toluenesulfonate. The 2,6-lutidine was distilled from the reaction mixture through a 20-inch packed column; first fraction: 24 g., b.p. 64–144°; second fraction: 780 g., b.p. 141°, m.p. −6.4°.

Removal of β-Picoline.—Four hundred and seventy-five grams of 2,6-lutidine (m.p. −6.3°) was mixed with 25 g. (5%) β-picoline. This mixture melted at −9.1°. One hundred grams of ethyl *p*-toluenesulfonate was added, the solution refluxed for one hour and then distilled as above; first fraction: 26 g., b.p. < 144°; second fraction: 350 g., b.p. 144°, m.p. −6.3°.

Redistillation of the second fraction over calcium hydride raised the melting point to −6.2°.

Removal of γ-Picoline.—Four hundred and seventy-five grams of 2,6-lutidine (m.p. −6.5°) was mixed with 25 g. of γ-picoline. The mixture (m.p. −9.1°) was refluxed for 1.5 hours with 100 g. of ethyl *p*-toluenesulfonate. The upper layer was separated and fractionally distilled; first fraction: b.p. < 144°, 18 g.; second fraction: 338 g. b.p. 144°, m.p. −6.3°.

Removal of α-Picoline.—Four hundred and seventy-five grams of 2,6-lutidine (m.p. −6.5°) was mixed with 25 g. of α-picoline. This mixture (m.p. −9.1°) was refluxed one hour with 100 g. of ethyl *p*-toluenesulfonate. The lutidine layer was separated and distilled; first fraction: b.p. < 144°, 42 g., second fraction: b.p. 144, 325 g., m.p. −6.4°.

RESEARCH LABORATORY
EASTMAN KODAK COMPANY
ROCHESTER, NEW YORK RECEIVED MARCH 22, 1951

Pyrido[3,2-d]thiazoles

BY SCOTT J. CHILDRESS[1] AND R. L. MCKEE

At the time of this work, previous reports of pyridothiazoles had been confined to the [2,3-d][2] and the [2,1-b][3] series. As a background for future research, the formation of the pyrido[3,2-d]thiazole system has been briefly investigated. During the course of this work, other examples of this system have appeared[4] and certain intermediates have been reported.[5]

The preparation of 5-methylpyrido[3,2-d]thiazole was accomplished by simultaneous reduction and cyclization of 5-methyl-3-nitro-2-pyridinethiol by means of iron filings and formic acid. The 2,5-dimethyl analog, similarly prepared, was not obtained in a pure condition.

Experimental

5-Methyl-2-nitraminopyridine was prepared from 1.0 g. of 2-amino-5-methylpyridine, 4.6 ml. of concentrated sulfuric acid and 0.7 ml. of concentrated nitric acid maintained below 10°. One gram of light yellow needles melting with decomposition at 181° was obtained.

Anal. Calcd. for $C_6H_7N_3O_2$: N, 27.4. Found: N, 27.3, 27.5.

2-Amino-5-methyl-3-nitropyridine was prepared as recently described.[5] The present authors were unable to obtain a yield greater than 36% of a dark yellow powder melting at 192–194°.

Anal. Calcd. for $C_6H_7N_3O_2$: N, 27.4. Found: N, 27.5.

5-Methyl-3-nitro-2-pyridol.—A. Following the procedure of Lapin and Slezak,[5] a crude yield of 55% was obtained. The purified product melted at 251–253.5°. B. The procedure of Hawkins and Roe[6] when applied to 2-amino-5-methylpyridine produced a crude yield of 40% of the desired compound melting at 250–252°.

Anal. Calcd. for $C_6H_6N_2O_3$: N, 18.2. Found: N, 18.2.

2-Chloro-5-methyl-3-nitropyridine.—The action of 50 ml. of phosphorus oxychloride under reflux for six hours upon 9.5 g. of 5-methyl-3-nitro-2-pyridol followed by treatment with crushed ice resulted in a crude yield of 94% of the desired compound melting at 49–51°. For analysis, a portion

(1) H. C. Brown, H. I. Schlesinger and S. Z. Cardon, THIS JOURNAL, **64**, 325 (1942).

(2) D. D. Reynolds and W. O. Kenyon, *ibid.*, **72**, 1596 (1950).

(3) E. A. Coulson and J. I. Jones, *J. Soc. Chem. Ind.*, **65**, 169 (1946).

(1) Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) J. Bernstein, B. Stearns, E. Shaw and W. A. Lott, THIS JOURNAL, **69**, 1151 (1947).

(3) L. Panizzi, *Gazz. chim. ital.*, **78**, 207 (1948).

(4) T. Takahashi and Y. Yamamoto, *J. Pharm. Soc. Japan*, **70**, 185 (1950).

(5) G. R. Lappin and F. B. Slezak, THIS JOURNAL, **72**, 2806 (1950).

(6) G. F. Hawkins and A. Roe, *J. Org. Chem.*, **14**, 328 (1949).

was recrystallized from methanol and sublimed *in vacuo* to give a white crystalline product, m.p. 50–51°.

Anal. Calcd. for $C_6H_5ClN_2O_2$: N, 16.2. Found: N, 16.2.

5-Methyl-3-nitro-2-pyridinethiol.—To a solution of 10 g. of potassium hydroxide in 100 ml. of methanol and saturated with hydrogen sulfide, 10 g of 2-chloro-5-methyl-3-nitropyridine was added in portions. After the vigorous reaction had subsided, the mixture was allowed to stand for five minutes, cooled, treated with 100 ml. of water, acidified with acetic acid, and thoroughly chilled. The product which separated at this point was contaminated with sulfur and hence was dissolved in hot, dilute ammonium hydroxide, filtered, and reprecipitated with acetic acid to give 2.5 g. of a yellow powder. The filtrate slowly deposited 0.1 g. of an orange substance melting at 240°, presumably the disulfide (see below). Recrystallized from 95% ethanol, the thiol appeared as fine yellow needles which decomposed slowly above 170°. On rapid heating, it was completely melted at about 200°.

Anal. Calcd. for $C_6H_6N_2O_2S$: N, 16.5; S, 18.8. Found: N, 16.5; S, 19.0

Five tenths of a gram of this disulfide was dissolved in 10 ml. of 5% sodium hydroxide and treated with a solution of 0.4 g. of iodine in alcohol to form 0.2 g. of **bis-(5-methyl-3-nitro-2-pyridyl) disulfide** an orange compound melting at 246° with decomposition after crystallization from benzene.

Anal. Calcd. for $C_{12}H_{10}N_4O_4S_2$: N, 16.6; S, 18.7. Found: N, 16.6; S, 18.9.

5-Methylpyrido[3,2-d]thiazole.—A suspension of 400 mg. of 5-methyl-3-nitro-2-pyridinethiol in 12 g. of 85% formic acid containing 3 g. of iron filings was boiled vigorously for 1.5 hours, cooled, made basic, and extracted with ether. The ether was evaporated and the residue sublimed *in vacuo* to yield 90 mg. of pale yellow crystals melting at 85–87°. A solution of the compound in methanol after treating with Norite, evaporating, and resubliming gave rise to white crystals melting at 85.5–87.5°. The compound had an odor resembling that of quinoline and turned yellow after standing for a few days.

Anal. Calcd. for $C_7H_6N_2S$: N, 18.7; S, 21.3. Found: N, 18.6; S, 21.4.

2,5-Dimethylpyrido[3,2-*d*]thiazole.—The reduction of 5-methyl-3-nitro-2-pyridinethiol with iron or zinc or of bis-(5-methyl-3-nitro-2-pyridyl) disulfide with iron followed by treatment with acetic anhydride apparently gave rise to the desired compound, but repeated crystallization and sublimation failed to give a product of satisfactory melting point or analysis. Thus, 1.0 g. of 5-methyl-3-nitro-2-pyridinethiol, 25 g. of acetic acid, 1.0 ml. of concentrated hydrochloric acid and 3 g. of iron filings were refluxed for 1.5 hours. After adding 11 g. of acetic anhydride, the mixture was boiled for an additional 15 minutes. The product was obtained by making the solution basic, distillation with steam, and extraction of the distillate with ether. Sublimation afforded 0.1 g. of white crystals which softened at 55° and melted from 63 to 66°. The most pure product obtained after resublimation softened at 63° and melted at 67.5–69.5° and retained an odor resembling that of quinoline.

Anal. Calcd. for $C_8H_8N_2S$: N, 17.1; S, 19.5. Found: N, 16.9; S, 18.9.

THE VENABLE CHEMICAL LABORATORY
THE UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C. RECEIVED MARCH 9, 1951

The Nature of the Vapor State of Hydrazine Monohydrate and Ethylenediamine Monohydrate

BY LOWELL V. COULTER

Experimental investigations of the vapor state of hydrazine monohydrate have led to contradictory conclusions regarding the extent of association in the vapor phase. Scott[1] has reported vapor densities at 99°, 367 mm. pressure and 138°, 744 mm. pressure that correspond to molecular weights of 31.8 and 25.0, respectively. These observations have been explained by Yost and Russell[2] by the dissociation equilibrium

$$N_2H_4{\cdot}H_2O(g) \rightleftharpoons N_2H_4(g) + H_2O(g)$$

Infrared absorption spectrum measurements[3] indicate, however, that no monohydrate species is present since the spectrum consists of the superposition of the spectra of hydrazine and water.

In view of the opportunity this system might afford for a study of the energy of a gaseous N····H-O hydrogen bond system, an exploratory study of vapor densities was conducted. Within the limits of error of these measurements it appears that the earlier observation, indicating association of water and hydrazine in the gas phase, was in error because of adsorption of vapors on the walls of the apparatus or the lack of complete volatilization of the sample in the Victor Meyer procedure. The results of this research indicate no appreciable association between hydrazine and water or ethylenediamine and water in the gas phase. The latter system was also selected for investigation because of the similarity of the two systems.

Experimental

Hydrazine monohydrate was prepared from the commercial product (National Biochemical Co.) by high vacuum distillation at room temperature and the addition of water to give an equimolecular solution of hydrazine and water. Analysis by acid titration and the iodate method[4] indicated 64.54 and 64.25% hydrazine, respectively (64.01% theoretical). The freezing point of the hydrazine monohydrate was −51.1°, which we compare with −51.7° reported by Mohr and Audrieth[5] for the freezing point. The ethylenediamine monohydrate was prepared from a purified commercial product by the quantitative addition of water. Anhydrous ethylenediamine was obtained by drying over calcium oxide both before and after fractional distillation. The anhydrous product froze at 11.1°, to be compared with 11.0° reported by Wilson.[6] By acid titration the monohydrate analyzed 0.5013 mole fraction diamine.

The experiments involved the determination of pressure-temperature relationships at constant vapor densities. The apparatus consisted of a calibrated glass bulb with an attached Bodenstein gage,[7] sensitivity 0.2 mm., that was employed as a null instrument for pressure measurements with a mercury manometer and cathetometer. The glass bulb and attached gage were completely thermostated in an oil-bath with temperature control usually better than 0.01°.

Samples of the hydrates were transferred to the apparatus with the aid of high vacuum techniques and inert protective gases thereby avoiding exposure of the preparations to atmospheric oxygen, water and carbon dioxide. In each isochore determination the vapor pressure of the liquid was determined prior to complete vaporization in order to ascertain the sharpness of the discontinuity at the point of complete vaporization. The P–T curves are presented in Fig. 1 for hydrazine monohydrate at two different pressure ranges and for ethylenediamine monohydrate at one pressure range. In drawing the vapor pressure curves of the liquid the steepness of the slope near the saturation pressure has been exaggerated in order to reveal the maximum deviation possible of observed pressures from the extrapolated curves (dotted portions).

On the basis of the pressure temperature curves it appears unlikely that any association between hydrazine or

(1) A. Scott, *J. Chem. Soc.*, **85**, 919 (1904).

(2) D. M. Yost and H. R. Russell, "Systematic Inorganic Chemistry," Prentice Hall, Inc., New York, N. Y., 1944, p. 115.

(3) P. A Giguère, *Trans. Roy. Soc. Can.*, **35**, 1 (1941), citing E. Eyster, Thesis, Calif. Inst. Tech., Pasadena, 1938.

(4) L. F. Audrieth and R. A. Penneman, *Anal. Chem.*, **20**, 1058 (1948).

(5) P. H. Mohr and L. F. Audrieth, *J. Phys. Chem.*, **53**, 901 (1949).

(6) A. L. Wilson, *Ind. Eng. Chem.*, **27**, 867 (1935).

(7) W. E. Vaughan, *Rev. Sci. Inst.*, **18**, 192 (1947).

ethylenediamine and water occurs in the vapor phase. Over the major portion of the temperature range the pressure shows a linear dependence on the temperature in both pressure ranges studied. The only deviations to be noted are those occurring within five degrees of the saturation pressure where surface adsorption effects are likely to be important. This was demonstrated experimentally by determining the influence of an increase in the surface–volume ratio on the pressure–temperature relationship. This is illustrated by a comparison of curves III and IV of Fig. 1, in which a more pronounced deviation of the pressure is apparent near the saturation region of curve IV. The data represented by curve IV were obtained with the same sample employed in obtaining the data represented by curve III but with a 2.5-fold increase in the surface–volume ratio. The deviation of the observed pressures in the liquid range from the extrapolated vapor pressure curve appears to be a vapor pressure lowering effect resulting from the accumulation of solute in the basic solutions. Silica residues were observed in the bottom of the vapor bulb following the removal of each sample by vacuum distillation.

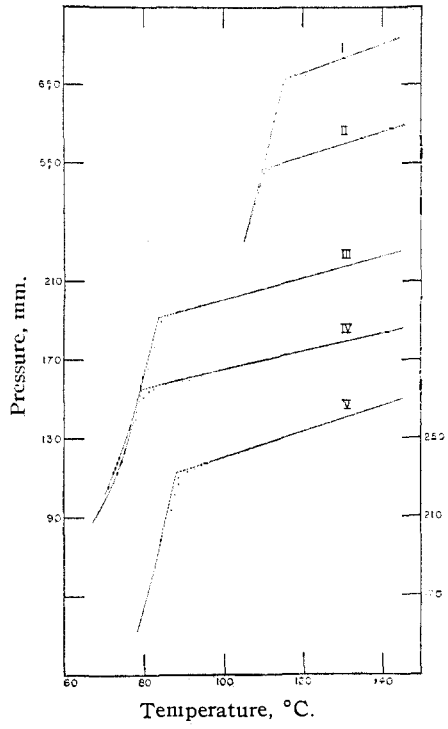

Fig. 1.—Pressure–temperature curves for hydrazine and ethylenediamine monohydrates: Curves I, II, III and IV hydrazine monohydrate; (ordinate on left); curve V ethylenediamine monohydrate (ordinate on right).

Molecular weights calculated from the observed vapor densities by means of the ideal gas law are presented in column 5 of Table I. We have included in column 6 the calculated molecular weights to be expected for the samples used in this research assuming no association of water and hydrazine in the vapor phase.

TABLE I

MOLECULAR WEIGHTS

Curve	Temperature range, °C.	Sample wt., g.	Volume, cc.	Molecular weight Obsd.	Calcd.
		Hydrazine Monohydrate			
III	92–140	0.0740	335.1	25.6 ± 0.3	25.1
IV	86–140	.7040	399.7	26.1 ± .3	25.1
I	118–140	.2376	335.2	26.1 ± .3	25.1
II	116–140	.2376	399.8	26.1 ± .3	25.1
		Ethylenediamine Monohydrate			
V	94–140	0.1343	335.1	38.7 ± .3	39.0

To what extent the 4% deviation of the molecular weight of the hydrate may be accounted for by usual non-ideal behavior is uncertain. Its constancy, however, appears to exclude the possibility of appreciable polymerization in the gas phase of the usual type.

A comparison of Scott's data with the vapor pressure curve of Fig. 1 indicates that his vapor density measurements suggesting association were probably made without complete volatilization of the sample or were accompanied by a significant surface adsorption effect.

Acknowledgment.—The author is indebted to the American Philosophical Society for financial assistance in support of this research. The technical assistance of Mr. Richard Blair is also acknowledged.

DEPARTMENT OF CHEMISTRY
BOSTON UNIVERSITY
BOSTON, MASS. RECEIVED FEBRUARY 5, 1951

The Effect of Aluminum Chloride on *n*-Propyl Chloride

BY THOMAS I. CROWELL AND GEORGE L. JONES, JR.

Anhydrous aluminum chloride is known to convert liquid *n*-propyl chloride to isopropyl chloride with evolution of hydrogen chloride and polymerization.[1] We have found that when small portions of aluminum chloride are added to *n*-propyl chloride, the degree of isomerization is less than 100% and depends on the proportions of the reactants. The equilibrium mixture was shown to contain 100% *i*-propyl chloride (within 0.8%), in agreement with the vapor phase data.[2] The incomplete reaction is, therefore, due to inactivation of the catalyst by the reaction products. Since amylene markedly inhibits the isomerization while hydrogen chloride has no effect, we assume that propylene forms with aluminum chloride a complex which does not promote isomerization.

A clear nitrobenzene solution of aluminum chloride also reacted with *n*-propyl chloride. This shows that solid aluminum chloride, believed necessary for chlorine exchange in carbon tetrachloride,[3] is unnecessary here.

Experimental

Anhydrous aluminum chloride was added to *n*-propyl chloride in a dry-box. Hydrogen chloride was copiously evolved and isomerization ceased within five minutes, though polymerization slowly continued. The mixture was shaken with concd. H_2SO_4 followed by water, and dried over K_2CO_3. The chlorine content of this product was 98.8% of the theoretical for propyl chloride. The samples were

TABLE I

Mole per cent. $AlCl_3$ added	Product composition *n*-PrCl, %	*i*-PrCl, %
0.10	98.0	2.0
.20	94.4	5.6
.35	91.5	8.5
.54	74.2	25.8
.90	54.6	45.4
.33[a]	0	100
.65[b]	96.9	3.1

[a] Started with 95% *i*-PrCl, 5% *n*-PrCl. [b] Added 10% amylene.

(1) E. Wertyporoch and T. Firla, *Ann.*, **500**, 295 (1933).

(2) (a) W. Nagai, *J. Chem. Soc. Japan*, **61**, 864 (1940); (b) L. M. Nash, T. I. Taylor and W. v. E. Doering, THIS JOURNAL, **71**, 1516 (1949).

(3) See C. H. Wallace and J. E. Willard, *ibid.*, **72**, 5278 (1950).

analyzed by immersing a thermometer in the refluxing liquid, observing the b.p. and comparing with the previously determined b.p.-composition curve for mixtures of the two isomers.[4] Superheating was negligible compared with the difference in b.p. of the isomers (11.9°). The barometric correction was 0.04 deg./mm. for both compounds.

Typical results are shown in Table I.

(4) George L. Jones, Jr., Thesis, University of Virginia, 1950.

COBB CHEMICAL LABORATORY
UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VA. RECEIVED FEBRUARY 9, 1951

The Preparation of Certain *s*-Trithianes[1,2]

BY IRWIN B. DOUGLASS AND WILLIAM R. HYDRO

In the course of recent work in this Laboratory[3] it was desired to find a method for the preparation of 2,4,6-tribenzyl-*s*-trithiane. The ordinary methods yielded chiefly a gummy, ill-smelling product but the procedure outlined below proved to be highly satisfactory. Fractional crystallization of the crude product from acetone yielded the α- and β-forms which structural theory would lead one to expect.

When the same procedure was applied to the preparation of 2,4,6-triphenyl-2,4,6-trimethyl-*s*-trithiane, a good yield was obtained in a much shorter time than by the best previous method.[4]

Experimental

2,4,6-Tribenzyl-s-trithiane (Trithiophenylacetaldehyde), $(C_6H_5CH_2CHS)_3$.—Dry hydrogen chloride was passed into 400 ml. of absolute alcohol contained in a three-neck flask fitted with mechanical stirrer and maintained at 0° or lower until 262 g. had been adsorbed. The solution was then cooled to −10 to −12° and hydrogen sulfide was passed in for 30 minutes following which the flow of hydrogen sulfide was continued while 132 g. of a 50% solution of phenylacetaldehyde in alcohol was added dropwise over a two- to three-hour period. The temperature was kept below −10° during the entire operation. The increase in weight due to hydrogen sulfide was 19 g.

After the last of the phenylacetaldehyde had been added the slurry of crystals was stirred for 15 min. longer and was then filtered. The filtrate was placed in the ice-chest overnight and then separated from the crystals which had formed. Concentration of the mother liquor and cooling further increased the yield. The combined crystals, after washing with cold alcohol, yielded 70 g. (73%) of practically odorless product melting 105–140°.

Separation of α- and β-Forms.—Ten grams of the dry reaction product was dissolved in 50 ml. of acetone and filtered while hot. The solution was covered and set aside to crystallize slowly. After several hours about 20 ml. of fresh acetone was added to the felted mass of crystals and the mixture was stirred and warmed. When the fine needles had dissolved the acetone solution was decanted from a residue of less soluble prismatic crystals. Cooling of the acetone solution and repeated recrystallization of the fine needles which separated gave the pure α-form with m.p. 122–123° (cor.).

Anal. Calcd. for $C_{24}H_{24}S_3$: C, 70.5; H, 5.92; S, 23.5; mol. wt., 408.6. Found: C, 70.1; H, 6.10; S, 22.5; mol. wt., 386.

Repeated recrystallization of the prismatic crystals from acetone gave the pure β-form with m.p. 168–169° (cor.).

Anal. Calcd. for $C_{24}H_{24}S_3$: C, 70.5; H, 5.92; S, 23.5; mol. wt., 408.6. Found: C, 70.4; H, 5.96; S, 23.6; mol. wt., 438.

(1) This note describes a portion of the work done on project NR 055 165 under contract N8onr77000 with the Office of Naval Research, United States Navy.

(2) Taken from a master's thesis presented by William R. Hydro.

(3) Douglass and Martin, *J. Org. Chem.*, **15**, 795 (1950).

(4) Reid, "A Study in the Chemistry of Thiones," Doctoral Thesis, Indiana University, Bloomington, Indiana, 1946.

Several separations, as above, indicated that the crude reaction mixture contained 14–22% of the higher melting β-form.

2,4,6-Triphenyl-2,4,6-trimethyl-*s*-trithiane, $(C_6H_5CSCH_3)_3$, (Trithioacetophenone).—One hundred fifty ml. of absolute alcohol was saturated with 99 g. of hydrogen chloride at 0 to 5° as previously described. Hydrogen sulfide was passed into the mixture for 30 min., the temperature was lowered to −10 to −12° and a solution of 25 g. of acetophenone dissolved in an equal weight of alcohol was added dropwise over a 2–3-hour period as described above.

The solution first turned a deep purple color and later began to precipitate white crystals. The mixture was stirred 15 min. after adding the last acetophenone and then filtered. After standing overnight additional crystals formed and on concentration of the liquors the yield was further increased. After washing the crude product in alcohol and drying 22.8 g. (80%) of white material was obtained which melted at 118–121°. Recrystallization of a portion gave a pure product melting at 121–122° and at the same temperature when mixed with an authentic sample of trithioacetophenone.

DEPARTMENT OF CHEMISTRY
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ORONO, MAINE RECEIVED FEBRUARY 26, 1951

Reactions of Ethylene Thiourea

BY NELSON R. EASTON, ALEX HLYNSKY AND HAROLD FOSTER

Very few S-substituted-2-imidazolidinethiones have been reported in the literature. The preparation of S-carboxymethyl-2-imidazolidinethione hydrochloride has been accomplished by the reaction of ethylene thiourea with chloroacetic acid[1] and S-carboethoxymethy-2-imidazolidinethione has been prepared by the action of ethyl chloroacetate on ethylene thiourea in the presence of sodium ethoxide.[2] The synthesis of S-dodecyl-2-imidazolidinethione has also been reported.[3]

We have prepared the S-benzyl, S-*p*-nitrobenzyl, S-*p*-chlorobenzyl and S-*o*-chlorobenzyl derivatives by condensing the appropriate halide with ethylene thiourea[4] and the treatment of the resulting salt with ammonium hydroxide. Due to its instability, however, the benzyl derivative could not be obtained in an analytically pure state. Table I gives the melting points and analyses.

TABLE I

S-2-IMIDAZOLIDINETHIONES

	M.p., °C.	Nitrogen, % Calcd.	Found	
Benzyl-	68–70	14.57	14.0, 14.1	
p-Nitrobenzyl-	158	17.70	17.70	
o-Chlorobenzyl-	63–64	12.36	12.35, 12.25	
p-Chlorobenzyl-	100–103	12.36	12.50	
Hydrochlorides				
				Yield, %
Benzyl-	173.4	12.25	12.32	82
p-Nitrobenzyl-	191	15.35	15.40	86
o-Chlorobenzyl-	214–215	10.63	10.54	97 crude
p-Chlorobenzyl-	172.5–175	10.63	10.67, 10.68	73

Experimental

Preparation of the S-Substituted-2-imidazolidinethione Hydrochlorides.—A mixture of 0.25 mole of ethylene thiourea and 0.25 mole of the halide in 90 ml. of ethanol was

(1) Johnson and Edens, THIS JOURNAL, **64**, 2706 (1942).

(2) Wilson, Baird, Burr, Munra and Stephen, *J. Roy. Tech. Coll. (Glasgow)*, **2**, no. 1, 56 (1929).

(3) Puetzen, U. S. Patent 2,156,193.

(4) Received through the kindness of Rohm and Haas Co., Philadelphia, Penna.

heated under reflux for one hour. At the end of this time the hot reaction mixture was filtered rapidly through a hot Buchner funnel. The filtrate on cooling deposited crystals of the desired hydrochloride. Completion of the precipitation was accomplished by adding ether. The product was recrystallized from ethanol.

Preparation of the S-Substituted-2-imidazolidinethiones.—A solution of 0.1 mole of the hydrochloride in 50 ml. of water was cooled in an ice-bath and treated with 35 ml. of a 25% solution of ammonium hydroxide. The precipitate which appeared immediately was collected on a Buchner funnel and was recrystallized from ethanol or better from a mixture of benzene and methylcyclohexane.

DEPARTMENT OF CHEMISTRY
LEHIGH UNIVERSITY
BETHLEHEM, PENNA. RECEIVED FEBRUARY 26, 1951

Optical Rotation of Peptides. I. Glycine and Alanine Dipeptides[1]

BY BERNARD F. ERLANGER AND ERWIN BRAND

The optical rotation of peptides may be considered an additive function of the contributions of the asymmetric carbon atoms of the constituent amino acid residues. It can be interpreted on the assumption that the contributions to the total rotation by an L- and by a corresponding D-amino acid residue are numerically the same, but opposite in sign.[2] As a first approach to this problem, a number of isomeric glycine and alanine dipeptides were synthesized and their optical rotation determined in the state NH_3^+, COO^- (in H_2O) and also in the state NH_3^+, COOH (in HCl). These dipeptides were first synthesized in the early years of this century by Emil Fischer[3] from α-halogen acid halides and about thirty years later by Bergmann[3] and collaborators from carbobenzoxy amino acid chlorides. We have used as starting materials the carbobenzoxy hydrazides of glycine and of alanine. These stable hydrazides are converted by the Bergmann technique[3] into their azides, which are coupled with amino acid ethyl or benzyl esters to yield carbobenzoxy dipeptide esters. The ethyl esters are either converted into carbobenzoxy dipeptide hydrazides or saponified to carbobenzoxy dipeptides, which are hydrogenated to the free dipeptides. The carbobenzoxy dipeptide benzyl esters are directly hydrogenated to dipeptides.

The specific rotation of six dipeptides, in H_2O and in 0.5 *N* HCl, is shown in Table II; the values in H_2O agree with those found by Emil Fischer[3] and Max Bergmann.[3] More detailed data on the specific rotation of these peptides and on the *residue rotations*[2] of alanine residues will be reported subsequently.

Experimental

Starting Materials. Carbobenzoxyamino Acid Hydrazides.—The preparation and properties of the glycine and alanine derivatives are reported, since these compounds have not been previously described.[4] The procedures used follow in a general way those given by Bergmann[5] for the corresponding lysine derivative. The carbobenzoxy hydrazides of glycine and of alanine are stable compounds.

1. **Carbobenzoxyglycine Hydrazide.**—Into a 500-cc. 3-neck flask equipped with a stirrer and immersed in an ice–salt-bath are placed 13.0 g. (0.1 mole) glycine ethyl ester hydrochloride, 75 cc. of water and 180 cc. of $CHCl_3$. With vigorous stirring, 5.2 g. (0.13 mole) of MgO is added in three portions over a period of 30 minutes, while 22.2 g. (0.13 mole) of carbobenzoxy chloride is dropped in. Stirring is continued for another 30 minutes, when 5 cc. of pyridine is added, followed in five minutes by acidification (congo) with 5 *N* HCl. The $CHCl_3$ layer is separated, washed first with 0.5 *N* HCl, then successively with water, 5% $NaHCO_3$, and water, dried over Na_2SO_4 and taken down *in vacuo*. The resulting oil is repeatedly (three times) treated with 50 cc. of anhydrous ethanol, which each time is distilled off *in vacuo*. The oil (carbobenzoxyglycine ethyl ester) is then dissolved in 100 cc. of anhydrous ethanol, 7 g. of hydrazine hydrate added, and the mixture allowed to stand overnight at room temperature. Most of the hydrazide crystallizes; it is filtered off, washed with cold anhydrous ethanol and dried; yield 15.2 g., m.p. 115°. Another 3.5 g. is recovered from the mother liquor; total yield 84%, based on glycine ethyl ester hydrochloride. For analysis the product is recrystallized from ethyl acetate; m.p. 115.5° (all m.p. cor.).

Anal. Calcd. for $C_{10}H_{13}O_3N_3$ (223.2): N, 18.8. Found: N, 18.9.

2. **Carbobenzoxy-L-alanine Hydrazide.**—The specific rotation $[\alpha]^{25}D$ of the alanine used in these and other syntheses varied from +14.5 to +14.7° for the L-isomer and from −14.4 to −14.7° for the D-isomer (2% in 6 *N* HCl). Most of the L- and D-alanine was prepared from acetyl-DL-alanine by Greenstein's enzymic resolution method[6] which made possible the preparation of relatively large batches.[7]

The carbobenzoxy hydrazide of L-alanine is prepared by the procedure described above for the corresponding glycine derivative and recrystallized from ethyl acetate. Total yield from 15.4 g. (0.1 mole) of L-alanine ethyl ester hydrochloride equals 18.7 g. (79%); m.p. 138.5°; $[\alpha]^{25}D$ −28.6° (2% in 0.5 *N* HCl).

Anal. Calcd. for $C_{11}H_{15}O_3N_3$ (237.3): N, 17.7. Found: N, 17.8.

3. **Carbobenzoxy-D-alanine Hydrazide.**—This compound is obtained from D-alanine ethyl ester hydrochloride by the same procedure and in the same yield as the corresponding L-derivative; m.p. 138.5°; $[\alpha]^{25}D$ +28.7° (2% in 0.5 *N* HCl).

Anal. Found: N, 17.7.

Amino Acid Benzyl Esters.—The use of amino acid benzyl esters[8] simplifies the "Carbobenzoxy" method for peptide synthesis, which involves the coupling of carbobenzoxy chlorides or azides with free amino acid esters. As is well known, the benzyl esters save one step in this synthesis, because the benzyl group is removed simultaneously with the N-carbobenzoxy groups by catalytic hydrogenation to yield free peptides, whereas other ester groups have to be saponified before hydrogenation. Moreover, the saponification of methyl and ethyl esters of carbobenzoxy peptides becomes increasingly difficult as the peptide chain is lengthened and the number of N-carbobenzoxy groups increased.[9]

The benzyl ester hydrochlorides of hydroxyproline,[10] of glycine and of cysteine (hydro-iodide[11]) have been well characterized. The γ-benzyl esters of both L- and D-glutamic acid were recently synthesized by Hanby, *et al.*,[12] by esterification of the amino acid with benzyl alcohol in the presence of constant-boiling hydriodic acid. Hydroxyproline[10] can be esterified with benzyl alcohol and dry HCl, but

(1) This report is part of a dissertation submitted by Bernard F. Erlanger in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A.C.S., Chicago, Ill., September, 1950.

(2) Brand and Erlanger, THIS JOURNAL, **72**, 3314 (1950).

(3) For references *cf.* Fruton, *Adv. Prot. Chem.*, **5**, 1 (1949).

(4) Since this paper went to press, Simmons, Harris and Fruton (*J. Biol. Chem.*, **188**, 251 (1951)) have reported the synthesis of carbobenzoxyglycinhydrazide (m.p. 116–117°) by a somewhat different procedure.

(5) Bergmann, Zervas and Greenstein, *Ber.*, **65**, 1692 (1932).

(6) Fodor, Price and Greenstein, *J. Biol. Chem.*, **178**, 503 (1949).

(7) For some enzyme preparations we are indebted to Armour and Company. We gratefully acknowledge the coöperation of Dr. Greenstein, who gave us part of the alanine and helped B.F.E. prepare the rest in the National Cancer Institute laboratories.

(8) Bergmann, Zervas and Ross, *J. Biol. Chem.*, **111**, 245 (1935), footnote 1.

(9) Brand and Erlanger, unpublished experiments.

(10) Smith and Bergmann, *J. Biol. Chem.*, **153**, 627 (1947); they did not obtain proline benzyl ester in analytically pure form.

(11) Harington and Mead, *Biochem. J.*, **30**, 1598 (1936).

(12) Hanby, Waley and Watson, *J. Chem. Soc.*, 3239 (1950).

TABLE I

GLYCINE AND ALANINE DIPEPTIDE DERIVATIVES

No.	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. cor.	N, % Calcd.	N, % Found	Neut. equiv.[b] Found
		Carbobenzoxy dipeptide esters					
7	Z.Gly-Ala.OEt (L)[c]	$C_{15}H_{20}O_5N_2$	308.3	65	9.1	9.0	
8	Z.Gly-Ala.OEt (D)	$C_{15}H_{20}O_5N_2$	308.3	66	9.1	9.0	
9	Z.Ala-Gly.OEt (L)[d]	$C_{15}H_{20}O_5N_2$	308.3	100			
10	Z.Ala-Gly.OBz (L)	$C_{20}H_{22}O_5N_2$	370.4	111	7.6	7.6	
11	Z.Ala-Gly.OBz (D)	$C_{20}H_{22}O_5N_2$	370.4	112	7.6	7.6	
12	Z.Ala-Ala.OEt (L-L)[e]	$C_{16}H_{22}O_5N_2$	322.4	116			
13	Z.Ala-Ala.OBz (L-L)	$C_{21}H_{22}O_5N_2$	384.4	138	7.3	7.3	
14	Z.Ala-Ala.OEt (D-D)	$C_{16}H_{22}O_5N_2$	322.4	116	8.7	8.7	
15	Z.Ala-Ala.OEt (L-D)	$C_{16}H_{22}O_5N_2$	322.4	92	8.7	8.7	
16	Z.Ala-Ala.OEt (D-L)	$C_{16}H_{22}O_5N_2$	322.4	92	8.7	8.7	
		Carbobenzoxy dipeptide hydrazides					
17	Z.Ala-Ala.$NHNH_2$ (L-L)	$C_{14}H_{20}O_4N_4$	308.4	209	18.3	18.2	
18	Z.Ala-Ala.$NHNH_2$ (D-D)	$C_{14}H_{20}O_4N_4$	308.4	208	18.3	18.2	
19	Z.Ala-Ala.$NHNH_2$ (L-D)	$C_{14}H_{20}O_4N_4$	308.4	193	18.3	18.3	
20	Z.Ala-Ala.$NHNH_2$ (D-L)	$C_{14}H_{20}O_4N_4$	308.4	193	18.3	18.3	
		Carbobenzoxy dipeptides					
21	Z.Gly-Ala.OH (L)[f]	$C_{13}H_{16}O_5N_2$	280.2	119.5	10.0	10.0	279
22	Z.Gly-Ala.OH (D)[g]	$C_{13}H_{16}O_5N_2$	280.2	119	10.0	10.0	280
23	Z.Ala-Ala.OH (D-D)	$C_{14}H_{18}O_5N_2$	294.3	153	9.5	9.6	297
24	Z.Ala-Ala.OH (L-D)	$C_{14}H_{18}O_5N_2$	294.3	116.5	9.5	9.6	294

[a] The following abbreviations are used (*cf.* Brand, *Ann. N. Y. Acad. Sci.*, **47**, 187 (1946); Brand and Edsall, *Ann. Rev. Biochem.*, **16**, 224 (1947); *Biochem. J.*, Suggestions to Authors, p. 3 (1949): Z: carbobenzoxy, $C_6H_5{\cdot}CH_2OCO$ Gly: $NH(CH_2)CO$; Ala: $NH(CHCH_3)CO$; peptide linkage indicated by hyphen: -; Et: C_2H_5; Bz: $C_6H_5CH_2$; configuration follows compound in parentheses: ( ). *E.g.*, carbobenzoxy-D-alanyl-L-alanine ethyl ester: Z.Ala-Ala.OEt (D-L); L-Alanyl-D-alanine: H.Ala-Ala.OH (L-D). [b] Neut. equiv.: neutralization equivalent by titration in alcohol.[20] [c] Previously prepared (*cf.* Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936)) from carbobenzoxyglycyl chloride with m.p. 59°. [d] Previously prepared (*cf.* Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935)) from carbobenzoxyalanyl chloride with the same m.p. [e] Previously prepared (*cf.* Stein, Moore and Bergmann, *J. Biol. Chem.*, **154**, 191 (1944)) from carbobenzoxyalanyl chloride with the same m.p. [f] $[\alpha]^{24}D$ −10.2° (2.8% in alcohol); previously prepared by Abderhalden and Neumann (*Fermentforschung*, **14**, 133 (1934)) with m.p. 155–156° and $[\alpha]^{20}D$ −6.4° (3% in alcohol) and by Bergmann and Fruton (*J. Biol. Chem.*, **117**, 189 (1937)) with m.p. 135° and $[\alpha]^{23}D$ −9.5° (5% in alcohol). [g] $[\alpha]^{23}D$ +10.1° (2.9% in alcohol), previously prepared (*cf.* Bergmann and Fruton, *J. Biol. Chem.*, **117**, 189 (1937)) with m.p. 135° and $[\alpha]^{23}D$ +9.3° (5% in alcohol).

TABLE II

GLYCINE AND ALANINE DIPEPTIDES ANALYTICAL DATA AND SPECIFIC ROTATION

No.	Compound[a]	Molecular formula	Mol. wt.	N, % Calcd.	N, % Found	Amino N, % Calcd.	Amino N, % Found	Neut. equiv.[b] Found	$[\alpha]D$, c = 2 H_2O 25° Literature	$[\alpha]D$, c = 2 H_2O 25° authors	0.5 *N* HCl 24° Authors
25	H.Gly-Ala.OH (L)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	[c]		144	−50[d]	−50.4	−59.3[k]
26	H.Ala-Gly.OH (L)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	9.6	9.6	145	+50.0[e] +50.3[f]	+50.6	+22.6
27	H.Ala-Gly.OH (D)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	9.6	9.5	144		−50.4[j]	−23.5
28	H.Ala-Ala.OH (L-L)[m]	$C_6H_{12}O_3N_2$	160.2	17.5	17.3	8.7	8.6	160	−21.7[g] −21.6[h]	−21.2	−37.3
29	H.Ala-Ala.OH (D-D)[m]	$C_6H_{12}O_3N_2$	160.2	17.5	17.4	8.7	8.7	160		+21.3	+37.9
30	H.Ala-Ala.OH (L-D)	$C_6H_{12}O_3N_2$	160.2	17.5	17.5	8.7	8.8	159	+68.94[i]	+71.2	+74.1[l]

[a,b] See Table I. [c] The value for amino nitrogen obtained in the manometric Van Slyke apparatus is too high, as is usual for peptides containing a terminal glycine amino group. [d] 8.7% at 20° (*cf.* Fischer and Schulze, *Ber.*, **40**, 943 (1907)). [e] 4% at 27° (see Table I, footnote *e*). [f] 10% at 18° (*cf.* Fischer, *Ber.*, **41**, 850 (1908)); [g] 5% at 24° (see Table I, footnote *e*). [h] 5% at 20° (*cf.* Fischer, *Ber.*, **39**, 453 (1906)). [i] 7.5% at 20° (*cf.* Fischer and Raske, *Ber.*, **39**, 3981 (1906)); [j] At 24°. [k] At 25°. [l] At 23°. [m] X-Ray studies on these crystals carried out by Dr. R. E. Pasternak in Dr. Pauling's Laboratory at the California Institute of Technology will be published by these authors.

this method gives an impure product in poor yield in the case of glycine.[13] Glycine benzyl ester hydrochloride[11,14] has been prepared in better yield from glycyl chloride hydrochloride.[15] Bergmann states[8] that amino acid carbamino anhydrides (Leuch's anhydrides) were frequently used in his laboratory for the preparation of amino acid benzyl esters, but he published no details.

For the Bergmann synthesis of amino acid benzyl esters, all reagents must be dry and moisture carefully excluded from all operations and filtrations (immersion filter) until the crystalline benzyl ester hydrochlorides are ready to be collected.

4. Glycine Benzyl Ester Hydrochloride.—To a mechanically stirred suspension of 12.6 g. (0.06 mole) of carbobenzoxy glycine[16] in 110 cc. of ether (300-cc. 3-neck flask, ice–salt-bath) is added 15 g. (0.07 mole) of PCl_5 over a pe-

(13) Abderhalden and Suzuki, *Z. physiol. Chem.*, **176**, 101 (1928).
(14) Ruggli, Ratti and Henzi, *Helv. Chim. Acta*, **12**, 361 (1929).
(15) Fischer, *Ber.*, **38**, 2914 (1905).
(16) Bergmann and Zervas, *ibid.*, **65**, 1192 (1932).

riod of 15 minutes; stirring is continued for an additional 20 minutes. From the undissolved excess PCl_5 the solution is filtered into a still and the ether removed *in vacuo* (bath temperature maintained throughout at 60°). In order to remove $POCl_3$, 75 cc. of ethyl acetate is added and then distilled off. The ethyl acetate treatment is repeated four times. The last portion of ethyl acetate is distilled off *in vacuo* until about 40 cc. of distillate has been collected. The residue is cooled in an ice-bath and treated with 25 cc. of petroleum ether. After one hour the supernatant is removed by suction and the residue (mostly dense crystals of glycine carbamino anhydride[17]) washed twice with 25 cc. of petroleum ether. The anhydride is then transferred with 30 cc. of benzyl alcohol to a 500-cc. flask containing 200 cc. of ether, previously saturated with HCl at 0°. On warming to 25° while stirring magnetically, CO_2 evolution begins and the benzyl ester hydrochloride starts to crystallize as long needles, while the anhydride dissolves. After continuing magnetic stirring overnight at 25°, the hydrochloride is filtered off without special precautions and washed with ether (9.5 g., m.p. 137–138°). Recrystallization from anhydrous methanol–ether yields 8.8 g. (70% based on carbobenzoxyglycine); m.p. 140°.

Anal. Calcd. for $C_9H_{11}O_2N\cdot HCl$ (201.7): N, 7.0; HCl, 18.1. Found: N, 7.0; HCl, 18.1.

5. **L-Alanine Benzyl Ester Hydrochloride.**—Alanine carbamino anhydride[17] is obtained more easily than the corresponding glycine derivative. Following the method of Hunt and du Vigneaud[18] with minor changes (stirring, etc.), 22 g. (0.1 mole) of carbobenzoxy-L-alanine[16] is treated with 25 g. (0.12 mole) of PCl_5. The carbobenzoxy-L-alanyl chloride is converted, at a bath temperature of 40–45°, into the well-crystallizing anhydride. After washing with petroleum ether, the anhydride is dissolved in 50 cc. of benzyl alcohol and added to 500 cc. of ether previously saturated with HCl at 0°. After standing at 25° overnight, 16 g. (m.p. 137–138°) of benzyl ester hydrochloride is obtained, which yields 15 g. on recrystallization from anhydrous methanol–ether (70% based on carbobenzoxyalanine); m.p. 140°; $[\alpha]^{25}D$ −10.9° (2% in 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}O_2N\cdot HCl$ (215.7): N, 6.5; NH_2-N, 6.5; HCl, 16.9. Found: N, 6.5; NH_2-N, 6.5; HCl, 17.0.

6. **D-Alanine Benzyl Ester Hydrochloride.**—This compound is obtained from carbobenzoxy-D-alanine with the same procedure and yield as the L-isomer; m.p. 139–140°; $[\alpha]^{25}D$ +10.5° (2% in 0.1 *N* HCl).

Anal. Found: N, 6.6; NH_2-N, 6.5; HCl, 16.9.

Carbobenzoxydipeptide Esters (Compounds 7–16).—In a mixture of 60 cc. of glacial acetic acid, 24 cc. of 5 *N* HCl and 250 cc. of water, 0.05 mole of a carbobenzoxy amino acid hydrazide is dissolved and cooled to −5°. On adding in one portion a cold, concentrated, aqueous solution of sodium nitrite (0.053 mole), the azide precipitates as a sirup[19] and is taken up in 300 cc. of cold ether. The ether layer is kept cold while washing successively with water, 3% $NaHCO_3$, and again with water. After brief drying over sodium sulfate, the azide solution is added in one portion to a dry, cold, ethereal solution of an amino acid ester (previously prepared from 0.07 mole of the amino acid ester hydrochloride). After standing for about 20 hours at room temperature, the reaction mixture is washed successively with 0.5 *N* HCl, water, 3% $NaHCO_3$ and water; after drying over sodium sulfate and removing the ether *in vacuo*, crystalline products are obtained, which are recrystallized from ethyl acetate–petroleum ether; yield of pure compounds is 65–70% based on the hydrazide used.

Carbobenzoxy-dipeptide Hydrazides (Compounds 17–20).—For the preparation of a hydrazide, 0.05 mole of carbobenzoxy dipeptide ethyl ester is dissolved in 80–100 cc. of hot, absolute alcohol, 0.10–0.13 mole of hydrazine hydrate added, and the solution refluxed for one hour. After standing for about 20 hours at room temperature, most of the hydrazide has crystallized; only small amounts can be obtained from the mother liquor after cooling and addition of ether. Recrystallization from ethyl alcohol–ether yields 80–90% of pure carbobenzoxy dipeptide hydrazide.

Carbobenzoxy Dipeptides (Compounds 21–24).—The carbobenzoxy dipeptide ethyl esters are saponified in acetone–*N* NaOH (about 15–20% excess of NaOH) for about ½ hour. After addition of a slight excess of *N* HCl, the mixture is concentrated *in vacuo*. Compounds 21, 22 and 24 are recrystallized from ethyl acetate–petroleum ether, 23 from hot water. The yield of pure compounds is somewhat variable, 65–85%. The neutralization equivalent (neut. equiv.) is obtained by titration in alcohol.[20]

Dipeptides (Compounds 25–30).—Hydrogenolysis of of 0.02 mole of a carbobenzoxy dipeptide is carried out in about 100 cc. of methanol containing a few drops of acetic acid with palladium black as catalyst in a rapid stream of hydrogen. About 6 cc. of palladium black suspension (0.5 g. Pd) in the appropriate solvent is used per 0.01 mole of the group to be reduced (carbobenzoxy or benzyl). Water is added, if necessary, to keep the peptide in solution during hydrogenation. After about two hours the hydrogenation of carbobenzoxy dipeptides is complete, as indicated by cessation of CO_2 evolution. Carbobenzoxy dipeptide benzyl esters are then hydrogenated for an additional two hours. Concentration *in vacuo* of the filtrate and washings results in crystallization of the peptides, which are recrystallized from water-alcohol. The yield of pure peptides varies from 70 to 85%; it is larger in the case of the benzyl esters, where the yield may be as high as 95%.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 122–260).

(17) The carbamino anhydrides (oxazolid-2,5-diones) of glycine and alanine were recently synthesized directly from the amino acids by treatment with carbonyl chloride by Farthing (*J. Chem. Soc.*, 3213 (1950)). This author, incidentally, states that preparation of benzyl chloroformate according to Bergmann,[16] using a toluene solution of carbonyl chloride, gave colored crude products. Such reports from the United Kingdom have come to our attention previously. However, investigators in this country have no trouble in obtaining colorless pure benzyl chloroformate by Bergmann's method. The reason for this discrepancy remains unexplained.

(18) Hunt and du Vigneaud, *J. Biol. Chem.*, **124**, 699 (1938).

(19) Carbobenzoxyglycine azide is crystalline.

(20) Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April 1950, Abstracts p. 56-C.

DEPARTMENT OF BIOCHEMISTRY
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Optical Rotation of Peptides. II. Glycine and Alanine Tripeptides[1]

BY ERWIN BRAND, BERNARD F. ERLANGER, HOWARD SACHS AND JEROME POLATNICK

The first paper in this series dealt with the synthesis and specific rotation of dipeptides of alanine.[2] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of nine glycine and alanine tripeptides are presented. More detailed data on their specific rotations and on the *residue rotations*[3] of alanine residues will be reported subsequently.

Experimental

The synthesis and properties of most of the starting materials have been previously described[2]: L- and D-alanine, benzyl esters of glycine and of L- and D-alanine (ref. 2, Compounds 4–6), four isomeric carbobenzoxy-alanyl-alanine hydrazides (ref. 2, Compounds 17–20). Carbobenzoxy-glycyl-L-alanine hydrazide and its D-isomer were prepared according to Bergmann.[4]

Carbobenzoxy Tripeptide Esters (Compounds 1–13).—The coupling of the azides of carbobenzoxy dipeptide hydrazides (0.025 mole) with amino acid esters (0.0375 mole) is carried out as described in detail for the synthesis of dipeptide esters[2] with the following changes: only 0.025 mole of a carbobenzoxy dipeptide hydrazide is dissolved in the

(1) Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A. C. S., Chicago, Ill., September, 1950.

(2) Erlanger and Brand, THIS JOURNAL, **73**, 3508 (1951).

(3) Brand and Erlanger, *ibid.*, **72**, 3314 (1950).

(4) Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936).

TABLE I

GLYCINE AND ALANINE TRIPEPTIDE DERIVATIVES

Number	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
	Carbobenzoxy tripeptide esters					
1	Z.Gly-Ala-Gly.OEt (L)	$C_{17}H_{23}O_6N_3$	365.4	145	11.5	11.3
2	Z.Gly-Ala-Gly.OBz (L)	$C_{22}H_{25}O_6N_3$	427.4	144	9.8	9.9
3	Z.Gly-Ala-Gly.OBz (D)	$C_{22}H_{25}O_6N_3$	427.4	144	9.8	9.9
4	Z.Gly-Ala-Ala.OEt (L-L)	$C_{18}H_{25}O_6N_3$	379.5	128	11.1	11.0
5	Z.Gly-Ala-Ala.OEt (L-D)	$C_{18}H_{25}O_6N_3$	379.5	126	11.1	11.2
6	Z.Ala-Ala-Ala.-OEt (3L)	$C_{19}H_{27}O_6N_3$	393.4	192	10.7	10.7
7	Z.Ala-Ala-Ala.OEt (L-D-L)	$C_{19}H_{27}O_6N_3$	393.4	142	10.7	10.6
8	Z.Ala-Ala-Ala.OEt (L-L-D)	$C_{19}H_{27}O_6N_3$	393.4	176	10.7	10.7
9	Z.Ala-Ala-Ala.OBz (3L)	$C_{24}H_{29}O_6N_3$	455.5	201.5	9.2	9.4
10	Z.Ala-Ala-Ala.OBz (3D)	$C_{24}H_{29}O_6N_3$	455.5	201.5	9.2	9.3
11	Z.Ala-Ala-Ala.OBz (L-D-L)	$C_{24}H_{29}O_6N_3$	455.5	148–9	9.2	9.2
12	Z.Ala-Ala-Ala.OBz (L-L-D)	$C_{24}H_{29}O_6N_3$	455.5	180.5	9.2	9.4
13	Z.Ala-Ala-Ala.OBz (D-L-L)	$C_{24}H_{29}O_6N_3$	455.5	173	9.2	9.3
	Carbobenzoxy tripeptide hydrazides					
14	Z.Ala-Ala-Ala.$NHNH_2$ (3L)	$C_{17}H_{25}O_5N_5$	379.4	235	18.5	18.3
15	Z.Ala-Ala-Ala.$NHNH_2$ (L-D-L)	$C_{17}H_{25}O_5N_5$	379.4	194	18.5	18.6
16	Z.Ala-Ala-Ala.$NHNH_2$ (L-L-D)	$C_{17}H_{25}O_5N_5$	379.4	205	18.5	18.5
	Carbobenzoxy tripeptides					
17	Z.Gly-Ala-Ala.OH (L-L)[b]	$C_{16}H_{21}O_6N_3$	351.5	172	12.0	12.0
18	Z.Gly-Ala-Ala.OH (L-D)[c]	$C_{16}H_{21}O_6N_3$	351.5	146	12.0	12.0

[a] The following abbreviations are used (*cf.* ref. 2, Table I, Footnote *a*): Z: carbobenzoxy, $C_6H_5\cdot CH_2OCO$; Gly: NH-$(CH_2)CO$; Ala: $NH(CHCH_3)CO$; peptide linkage indicated by hyphen: -; Et: C_2H_5; Bz: $C_6H_5CH_2$; configuration follows compound in parentheses; *e.g.*, carbobenzoxy-L-alanyl-D-alanpl-L-alanine benzyl ester: Z.Ala-Ala-Ala.OBz (L-D-L); carbobenzoxy-L-alanyl-L-alanyl-L-alanine hydrazide: Z.Ala-Ala-Ala.$NHNH_2$ (3L); D-alanyl-L-alanyl-L-alanine: H.Ala-Ala.OH (D-L-L). [b] N.E. = 353 (N.E.: neutralization equivalent obtained by titration in alcohol (*cf.* Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April, 1950, Abstracts p. 56-C)). [c] N.E. = 351.

TABLE II

GLYCINE AND ALANINE TRIPEPTIDES

Analytical data and specific rotation in 0.5 *N* HCl

Number	Compound[a]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Found	Amino N,[c] % Calcd.	Found	Neut. equiv.[b] Found	$[\alpha]^{23}D$ (c = 2)
19	H.Gly-Ala-Gly.OH (L)[d]	$C_7H_{13}O_4N_3$	203.2	20.7	20.5			Insol.	− 65.3[e]
20	H.Gly-Ala-Gly.OH (D)	$C_7H_{13}O_4N_3$	203.2	20.7	20.6			Insol.	+ 65.5[e]
21	H.Gly-Ala-Ala.OH (L-L)	$C_8H_{15}O_4N_3$	217.2	19.3	19.5			219	−103.0
22	H.Gly-Ala-Ala.OH (L-D)	$C_8H_{15}O_4N_3$	217.2	19.3	19.2			219	− 21.7
23	H.Ala-Ala-Ala.OH (3L)[f,g]	$C_9H_{17}O_4N_3$	231.3	18.2	18.2	6.1	5.9	230	− 85.4
24	H.Ala-Ala-Ala.OH (3D)[g]	$C_9H_{17}O_4N_3$	231.3	18.2	18.1	6.1	6.0	231	+ 85.9[e]
25	H.Ala-Ala-Ala.OH (L-D-L)	$C_9H_{17}O_4N_3$	231.3	18.2	18.0	6.1	5.9	232	+ 37.0
26	H.Ala-Ala-Ala.OH (L-L-D)	$C_9H_{17}O_4N_3$	231.3	18.2	18.2	6.1	6.0	231	− 4.6
27	H.Ala-Ala-Ala.OH (D-L-L)	$C_9H_{17}O_4N_3$	231.3	18.2	18.0	6.1	6.0	231	−115.2

[a,b] See Table I. [c] Incorrect values for terminal glycine amino groups omitted.[2] [d] Previously prepared (Fischer, *Ber.*, **41**, 850 (1908)) with $[\alpha]^{20}D$ −64.3° (4.3% in H_2O); we find $[\alpha]^{24}D$ −63.7° (2% in H_2O). [e] At 24°. [f] Previously prepared (Abderhalden and Gohdes, *Fermentforschung*, **13**, 56 (1933)) with analytical data to fit 1/2 mole of water which could not be removed in high vacuum at 130°, $[\alpha]^{18}D$ −70.2° (3.5% in 2 *N* HCl). Our tripeptide analyzed correctly without water and showed $[\alpha]^{25}D$ −79.2° (2% in 2 *N* HCl). [g] X-Ray studies on these crystals carried out by Dr. R. E. Pasternak in Dr. Pauling's Laboratory at the California Institute of Technology will be published by these authors.

mixture of 50 cc. of glacial acetic acid, 25 cc. of 5 *N* HCl and 200 cc. of water, treated with $NaNO_2$ (0.0275 mole) and extracted with 200 cc. of 1:1 (v/v) ether–ethyl acetate. The cold, dry solution of the azide is added in one portion to the previously prepared, cold, dry ethereal solution of amino acid ester; crystals of the coupling product begin to appear within a few minutes. After standing at 25° for about 20 hours, the mixture is cooled to −5°, the crystals are collected, washed with ether and recrystallized from ethanol. The yield of pure compounds is 70–75%, based on the hydrazide used.

Carbobenzoxy-Tripeptide Hydrazides (Compounds 14–16).—The hydrazides were prepared with hydrazine hydrate from carbobenzoxy tripeptide ethyl esters as described for carbobenzoxy dipeptide hydrazides.[2] Recrystallization from ethanol–ether results in pure compounds with 80–90% yield.

Carbobenzoxy Tripeptides (Compounds 17–18).—The carbobenzoxy tripeptide ethyl esters are saponified in methanol–2 *N* NaOH (about 10% excess of NaOH) for one hour at 37°. After acidification, the methanol is completely removed *in vacuo* with repeated additions of water. The oily residue is extracted with hot ethyl acetate and the warm (40°) solution dried with sodium sulfate. The dry ethyl acetate solution is cooled to −5° and crystallization induced by the addition of petroleum ether. Recrystallization from ethyl acetate–petroleum ether yields 80–85% of the pure compounds.

Tripeptides (Compounds 19–27).—Hydrogenolysis with palladium black as catalyst is carried out as previously described.[2] Methanol is the solvent used for carbobenzoxy tripeptides, while carbobenzoxy tripeptide benzyl esters are hydrogenated in 80% acetic acid (150 cc. per 0.015 mole).

The yield of pure, recrystallized (water-ethanol) peptides is 85–90%.

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Dipole Moments of Central-Atom Molecules

BY A. D. FRANKLIN

The general equation for the mean square dipole moment of a molecule with a rigid skeleton given by Eyring[1] may be solved in detail for the case of a central atom to which several different rotating polar groups are attached. An example is ethyl orthocarbonate. The observed moment should correspond to the square root of this mean square moment.

Eyring's equation in this case reduces to

$$\overline{\vec{\mu}^2} = m^2 + \sum_i s_i^2 + 2\sum_i \overline{(\vec{m}\cdot\vec{s}_i)} + 2\sum_{i>j} \overline{(\vec{s}_i\cdot\vec{s}_j)}$$

where the subscript i refers to the i^{th} group, $\vec{m} = \sum_i(\vec{m}_i + \vec{r}_i)$, $\vec{m}_i$ is the moment associated with the bond joining the group to the central atom, and $\vec{r}_i$ and $\vec{s}_i$ are the components of the group moment along and perpendicular to this bond, respectively. The averages, which drop out for the case of free rotation, are to be taken over the various orientations of the polar groups.

In Table I are gathered the observed moments and those calculated assuming free rotation for several examples of this type of molecule.

TABLE I

Et represents the ethyl group; Me the methyl; and Ph the phenyl group.

Compound	Debye units Calcd.	Obsd.
$(EtO)_3SiH$	2.8	1.78[2]
$(EtO)_4Ti$	2.1	1.41[3]
$(EtO)_4Si$	2.1	1.70[4]
$(EtO)_4C$	2.1	1.1[5]
$(MeO)_4C$	2.1	0.8[5]
$(EtO)_3TiCl$	1.8	2.87[3]
$(PhO)TiCl_3$	1.3	2.97[3]
$(CH_2Cl)_4C$	2.8	0[6]
$(CH_2Br)_4C$	2.6	0[6]
$(CH_2I)_4C$	2.3	0[6]
$(EtO)_2SO$	3.0	2.96[4]
$(EtO)_3PO$	2.9	3.07[4]

All bond angles about the C, Si, Ti, P and O atoms were assumed to be tetrahedral. The configuration of $(EtO)_2SO$ was taken as identical to $SOCl_2$.[6] Bond moments were either taken from Smyth and co-workers[7,8,9] or else calculated from Pauling's[10] electronegativity values, and the equations given by Hannay and Smyth.[11]

There is no agreement evident in the table, the observed values lying below the calculated in most cases. It has been suggested that this trend is due to an increase in the bond angle at the polar group.[3,12] Although this may occur with the Ti and Si compounds, it is not likely to be the cause of the zero moment observed with the neopentyl compounds. Since it can readily be shown that dipole–dipole interaction alone is of the same order as kT, and combined with steric hindrance would tend to exclude configurations with large moments, sufficient reason for the low moments can be found in lack of free rotation. Yamasaki, *et al.*,[13] came to the same conclusion regarding $(MeO)_4Si$ on the basis of electron diffraction studies.

Until more is known about the interactions between rotating groups upon the same molecule, it can only be concluded that calculations based upon free rotation in these molecules are unsatisfactory, and although the dipole results do not rule out the possibility of a wider oxygen bond angle in the Ti and Si molecules, neither do they give any real information on this point.

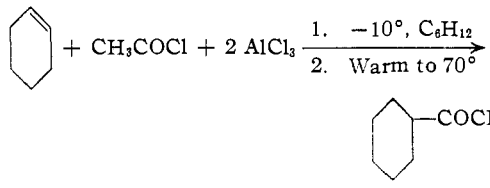
(1) H. Eyring, *Phys. Rev.*, **39**, 746 (1932).
(2) H. Spauschus, A. Mills, J. Scott and C. MacKenzie, THIS JOURNAL, **72**, 1377 (1950).
(3) R. Crowe and C. Caughlan, *ibid.*, **72**, 1694 (1950).
(4) W. Svirbely and J. Lander, *ibid.*, **70**, 4121 (1948).
(5) L. Ebert, R. Eisenschitz and H. V. Hartel, *Naturwissenschaften*, **15**, 668 (1927).
(6) K. Palmer, THIS JOURNAL, **60**, 2360 (1938).
(7) C. P. Smyth and K. McAlpine, *J. Chem. Phys.*, **2**, 499 (1934).
(8) C. P. Smyth, G. Lewis, A. Grossmann and F. Jennings, THIS JOURNAL, **62**, 1219 (1940).
(9) C. P. Smyth, *ibid.*, **60**, 183 (1938).
(10) L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1939, p. 64.
(11) N. Hannay and C. P. Smyth, THIS JOURNAL, **68**, 171 (1946).
(12) R. Sauer and D. Mead, *ibid.*, **68**, 1794 (1946).
(13) K. Yamasaki, A. Kotera, M. Yokoi and Y. Ueda, *J. Chem. Phys.*, **18**, 1414 (1950).

PHILADELPHIA, PENNA. RECEIVED FEBRUARY 23, 1951

A Rearrangement in the Nenitzescu Reaction of Cycloheptene with Acetyl Chloride and Aluminum Chloride

BY S. L. FRIESS AND REX PINSON, JR.

In the course of preparation of a series of acetylcyclanes an attempt was made to synthesize methyl cycloheptyl ketone (I) using the acylation procedure of Nenitzescu and Cioranescu.[1] In the general procedure for the reaction, two moles of aluminum chloride are added in portions to a mixture of the olefin and acid chloride in cyclohexane solvent at about −10°, and upon warming slowly to 70°, HCl is evolved and the saturated ketone is obtained. For example

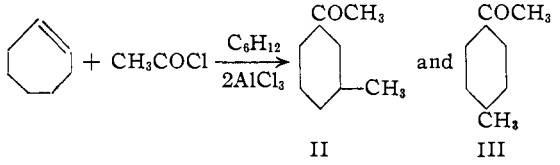


Nenitzescu found that the reaction progresses quite satisfactorily for 5- and 6-membered cyclic olefins, with the solvent acting as the ultimate hydrogen donor for the production of the saturated

(1) C. D. Nenitzescu and E. Cioranescu, *Ber.*, **69B**, 1820 (1936).

ketone. He pointed out[1] the utility of the reaction with cyclic olefins for producing saturated ketones in which the ring size remains unchanged, in contrast to the reaction of the saturated compound cyclohexane[2,3] with acetyl chloride and aluminum chloride in which ring contraction to a methylcyclopentane derivative occurs.

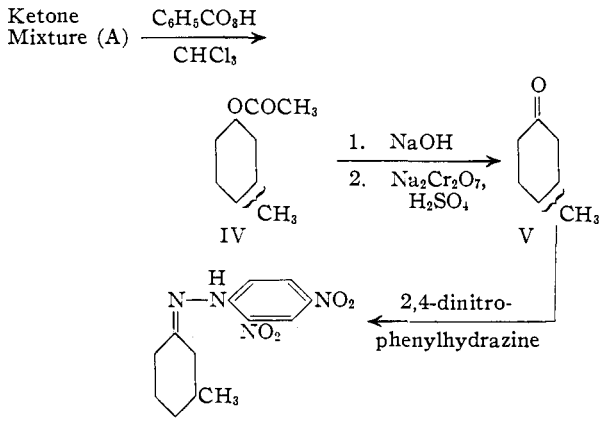
In the present work, it has been observed that the reaction of the olefin cycloheptene does not furnish the normal product (I), but leads to a 40% yield of a mixture (A), which apparently contains methyl 3-methylcyclohexyl ketone (II) and methyl 4-methylcyclohexyl ketone (III).



II III

In preliminary experiments a semicarbazone and a 2,4-dinitrophenylhydrazone prepared from the ketone mixture (A) were found to be different from the corresponding derivatives prepared from an authentic sample of (I).[4] Further, on oxidation of the mixture (A) with sodium hypobromite there was obtained a saturated acid which could be transformed to a solid amide differing from that reported for the amide of cycloheptanecarboxylic acid.

Evidence for the presence of II as a component of the original ketone mixture (A) was obtained by application of the degradation scheme



VI (isolated)

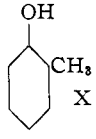
The methyl ketones of the mixture were first converted to the acetates (IV) with perbenzoic acid,[5] followed by saponification and oxidation of the resulting alcohols to the cyclohexanone mixture (V). This sequence of reactions, carried out without purification of intermediates, eliminates the complicating possibilities of stereoisomerism present in (A) and facilitates solution of the simpler problem of the relative positions of the methyl and acetyl groups in the isomeric components of the mixture.

Mixture (V) was converted to its mixture of 2,4-dinitrophenylhydrazones which, after preliminary purification by passage over a column of alumina and repeated fractional crystallization from ethanol gave a small yield of pure (VI). Attempted chromatographic separation[6] of the mixture failed to yield any other pure component.

Evidence for the presence of the 4-methyl isomer in the original mixture (A) was obtained by dehydrogenation with sulfur at the reflux temperature. The ketone product of this reaction was converted to the 2,4-dinitrophenylhydrazone which, upon repeated crystallization from benzene, furnished a small yield of pure *p*-methylacetophenone 2,4-dinitrophenylhydrazone (VII), as shown by mixed melting point behavior with a known sample.

Additional evidence as to the complex nature of (A) was furnished by a study of the apparent C-methyl content of this mixture and of various reference compounds. The method of Barthel and LaForge[7] was employed, with the results shown in Table I.

TABLE I

Compound				
Ketone mixture (A)	 VIII	IX 	X 	
0.94	0.83	0.13	0.73	

Apparent C-methyl content (moles HOAc/mole of compound)

The data of Table I would appear to indicate that, in addition to the *ca.* 0.8 mole of acetic acid to be obtained from the acetyl group (as in VIII), the presence of an adjacent ring methyl group (X) would lead to an increment of 0.7 mole of acetic acid, whereas a non-adjacent ring methyl group (as in IX) would give in contrast approximately 0.1 mole of acetic acid. The fact that mixture (A) gives slightly more than 0.9 mole of acetic acid therefore points strongly to the absence of any significant amount of a constituent of the mixture possessing a ring methyl group adjacent to the acetyl function. Compounds (IX) and (X) were used as models to evaluate the relative quantities of acetic acid formed from methyl groups at various positions on the ring because of the probability that initial cleavage of the acetyl group in mixture (A) with chromic acid does leave an oxygen function directly on the ring.

It was observed in the course of these C-methyl determinations that methylcyclohexane gives only a trace of acetic acid (*ca.* 0.01 mole), and that to ensure detection of a ring methyl group in this series it is essential that the starting compound possess some polar function to promote solubility in the chromic acid mixture, and prevent escape from the reaction zone because of ready volatility.

(2) (a) C. D. Nenitzescu and C. N. Ionescu, *Ann.*, **491**, 189 (1931); (b) C. D. Nenitzescu and I. P. Cantuniari, *Ber.*, **65**, 1449 (1932).

(3) F. Unger, *ibid.*, **65**, 467 (1932).

(4) Prepared by the method of M. S. Newman and W. T. Booth, THIS JOURNAL, **67**, 154 (1945).

(5) S. L. Friess, *ibid.*, **71**, 14 (1949).

(6) The procedure employed was that of J. D. Roberts and C. Green, *Ind. Eng. Chem., Anal. Ed.*, **18**, 335 (1946).

(7) W. F. Barthel and F. B. LaForge, *ibid.*, **16**, 434 (1944).

Experimental[8]

Acylation of Cycloheptene.—Using 0.5 mole of cycloheptene,[9] 0.5 mole of acetyl chloride, 1.0 mole of granular aluminum chloride, and 100 ml. of cyclohexane as solvent, the acetylation was carried out essentially according to the procedure of Nenitzescu and Cioranescu.[1] In the final distillation of the product (A) there was obtained 28.3 g. (40%, based on olefin) of ketone, b.p. 65–66° at 7 mm., $n^{18}D$ 1.4518.

Product (A) readily formed a semicarbazone, white plates from diluted ethanol, m.p. 169–170°. *Anal.* Calcd. for $C_{10}H_{19}N_3O$: C, 60.89; H, 9.71. Found: C, 61.16; H, 9.53.

A crystalline 2,4-dinitrophenylhydrazone also was formed, m.p. 115–120°.

The oxidation of 5.5 g. of ketone (A) with a sodium hypobromite solution prepared from 24 g. of bromine and 15.2 g. of sodium hydroxide in 140 cc. of water gave a 92% yield of saturated acids, b.p. 121–123° (7 mm.). The acids readily formed an amide (or mixture of amides), white needles from water, m.p. 168–170° (lit. value[10] for the amide of cycloheptanecarboxylic acid, 194–195°).

Preparation of Methyl Cycloheptyl Ketone (I).—An authentic sample of this material was prepared from cycloheptyl bromide in 38% yield by the method of Newman and Booth,[4] and its structure proved by conversion to the acetate ester with perbenzoic acid and saponification to the known product, cycloheptanol.

The ketone was used to prepare a semicarbazone, white plates from 50% ethanol, m.p. 175–176°. *Anal.* Calcd. for $C_{10}H_{19}N_3O$: C, 60.89; H, 9.71. Found: C, 61.01; H, 9.65.

A 2,4-dinitrophenylhydrazone was also prepared, orange-yellow needles from ethanol, m.p. 117–118°. *Anal.* Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29. Found: C, 56.50; H, 6.26.

These derivatives caused depression of the melting points when mixed with the corresponding derivatives of (A).

Reaction of (A) with Perbenzoic Acid.—Using known[5] procedures, a mixture of 7.4 g. (0.053 mole) of (A) and 150 ml. of a chloroform solution containing 0.057 mole of perbenzoic acid was allowed to react at room temperature for three days, and the ester product isolated.

The crude ester was saponified with 25% aqueous sodium hydroxide, the alcohol fraction separated by ether extraction, and the ether solution dried and evaporated. The crude alcohol was oxidized directly.

Oxidation of the Alcohol.—The alcohol obtained above was added in small portions with vigorous shaking to a solution of 8.4 g. of sodium dichromate and 7.0 g. of concentrated sulfuric acid in 42 ml. of water. The temperature rose to about 60°. After all the alcohol had been added, the flask was stoppered and shaken mechanically for two hours. The organic material was removed by ether extraction, and the ether solution washed with 5% sodium hydroxide until the washings were nearly colorless. The ether was evaporated, and the ketones converted directly to a 2,4-dinitrophenylhydrazone mixture, m.p. 110–126°.

Preliminary purification of this derivative was effected by passage through a column of alumina in 1:1 (by volume) benzene–hexane solvent, with a recovery of 95% of crystalline material. Fractional crystallization from 95% ethanol gave a small yield of pure (VI), m.p. and mixed m.p. with an authentic sample, 153–155°. The fractionation process failed to yield any other pure compound. Chromatography on alumina and on silicic acid—Super-Cel[6] also failed to yield any other pure isomer.

Dehydrogenation of (A) with Sulfur.—A mixture of 2.80 g. (0.02 mole) of (A) and 1.92 g. (0.06 g. atom) of powdered sulfur was heated under reflux (190–200°) for 18 hours. Evolution of hydrogen sulfide was noted throughout the interval. The mixture was then steam distilled, and part of the resulting oil was used to prepare a 2,4-dinitrophenylhydrazone, which was recrystallized repeatedly from benzene to a constant melting point; red needles from benzene, m.p. and mixed m.p. with an authentic sample of VII, 253–255°.

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(8) Melting points are corrected; boiling points are uncorrected.

(9) Prepared from cycloheptanol according to the procedure of J. Böeseken and C. J. A. Hanegraaf, *Rec. trav. chim.*, **61**, 69 (1942).

(10) E. Buchner and A. Jacobi, *Ber.*, **31**, 2008 (1898).

Chromones. V. The Preparation of 2-Methyl-7-hydroxychromone and 2-Methyl-5,8-dimethoxy-7-hydroxychromone

BY T. A. GEISSMAN

The preparation of 2-methylchromones from polyhydroxyacetophenones by the reaction of *o*-hydroxyacetophenones with acetic anhydride and sodium acetate[1] is often unsatisfactory because of the formation of 4-methylcoumarin derivatives or of 3-acetyl-2-methyl-chromones which must be deacylated in a separate step. The C-acylation of *o*-hydroxyacetophenone with ethyl acetate and sodium[2] is a reaction which does not readily lend itself to extension to polyhydroxyacetophenones because of the formation of insoluble sodium salts; and the modification of this reaction in which a polyacetoxyacetophenone is used also leads in some cases to 3-acetyl-2-methylchromones.[3] Alternative methods of masking the hydroxyl groups during the condensation of the acetyl group with ethyl acetate include the benzylation and subsequent hydrogenolysis of the benzyloxy groups; but the multiplicity of steps and the over-all losses in yields accompanying such devices caused us to seek a superior method of performing syntheses of 2-methylchromones based upon the resorcinol and substituted resorcinol nucleus.

The successful preparation of 2,6-dihydroxybenzoic acid by a procedure involving the protection of the hydroxyl groups by tetrahydropyranyl ether formation[4] suggested the use of a similar procedure in the present work. The method proved to be an excellent one for the preparation of 2-methyl-7-hydroxychromone (from resacetophenone) and 2-methyl-5,8-dimethoxy-7-hydroxychromone (from 2,4-dihydroxy-3,6-dimethoxyacetophenone). In the case of the former synthesis, intermediates were isolated and characterized in the course of exploratory experiments; in the latter, the several steps were carried out without the isolation of intermediate compounds.

The extension of this reaction to the preparation of 2-methyl-5,7-dihydroxychromone from phloroacetophenone has so far proved to be unsatisfactory.

Experimental

Resacetophenone 4-Tetrahydropyranyl Ether.—To a mixture of 10.0 g. of purified resacetophenone and 25 ml. of redistilled dihydropyran was added 6 drops of concentrated hydrochloric acid. (In later runs *p*-toluenesulfonic acid was used.) The mixture was warmed gently to effect solution of the resacetophenone and allowed to stand overnight in a water-bath at room temperature. Ether and dilute aqueous potassium hydroxide were added and the aqueous layer separated. The ether layer was dried and evaporated and the oily residue converted to 2-methyl-7-hydroxychromone in the manner described below.

The aqueous layer was acidified and extracted with ether. The dried ether solution was allowed to evaporate slowly, and large colorless prisms separated (5.2 g.). Recrystallized from ether–petroleum ether, the compound formed glistening prisms, m.p. 76–78°. The compound gave a wine-red color with methanolic ferric chloride.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 66.10; H, 6.83. Found: C, 66.38; H, 7.23.

(1) S. v. Kostanecki and A. Rozycki, *Ber.*, **34**, 102 (1901).

(2) G. Wittig, *ibid.*, **57B**, 88 (1924).

(3) T. A. Geissman, unpublished observations; see also W. Baker, *J. Chem. Soc.*, 1381 (1933); 1953 (1934) for related work.

(4) W. E. Parham and E. L. Anderson, THIS JOURNAL, **70**, 4187 (1948).

2-Hydroxy-4-tetrahydropyranyloxybenzoylacetone.—A solution of 5.0 g. of resacetophenone 4-tetrahydropyranyl ether in 35 ml. of dry ethyl acetate was added to 3.0 g. of powdered sodium. The reaction was lively but controlled; it was allowed to proceed at room temperature for 12 hours. Ice was added and the aqueous layer was separated, washed with ether, then poured onto a mixture of crushed ice and dilute sulfuric acid. The pasty precipitate soon became crystalline and after trituration with cold methanol formed a colorless crystalline solid (4.4 g.). Recrystallization from dilute methanol afforded colorless prisms, m.p. 97–98°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.76; H, 6.51. Found: C, 64.91; H, 6.51.

Treatment of the diketone with methanolic hydrochloric acid resulted in ring closure and the simultaneous loss of the tetrahydropyranyl group with the formation in excellent yield of 2-methyl-7-hydroxychromone.

For preparative purposes, the three stages of the synthesis (tetrahydropyranylation, acylation and ring closure) are best carried out without isolation of the above-described intermediates.

2-Methyl-7-hydroxychromone.—A mixture of 15.2 g. (0.10 mole) of resacetophenone, 50 ml. of dihydropyran and 100 mg. of *p*-toluenesulfonic acid monohydrate was allowed to stand for 12 hours. Ether, 15 ml. of water and 2 ml. of 6 *N* sodium hydroxide were added, and the aqueous layer was separated and acidified. The monotetrahydropyranyl ether which separated was recrystallized from ether–petroleum ether (3.0 g.) and added to the alkali-washed ether solution containing the bulk of the material. The ether solution was dried over potassium carbonate and evaporated under reduced pressure to a semicrystalline residue. (Note: The weight of this residue, determined in another run, indicated that the main product was a bis-tetrahydropyranyl ether. This compound was not isolated.) The crude residue was dissolved in 75 ml. of dry ethyl acetate and 7.5 g. of powdered sodium was added. After two days, ice was added and the aqueous layer separated, washed with ether, and acidified. The gummy solid was stirred with cold methanol, leaving 17.0 g. of a nearly white, crystalline solid. This was dissolved in a mixture of 50 ml. of methanol and 5 ml. of concentrated hydrochloric acid, the solution was refluxed for several minutes, diluted with water, and cooled. The crystalline (pink-buff prisms) chromone weighed 10.0 g. Treatment of the methanol with which the gummy diketone had been triturated with hydrochloric acid afforded an additional 1.8 g. of chromone, m.p. 251–252°. The total yield was 11.8 g. (67% over-all) of chromone sufficiently pure for further use. This yield represents an average yield of 88% on each of the three chief steps in the over-all synthesis. When purified by recrystallization from methanol, the chromone forms colorless prisms, m.p. 253–254° (reported[1] 250°).

2-Methyl-5,8-dimethoxy-7-hydroxychromone.—A solution of 5.0 g. of 2,4-dihydroxy-3,6-dimethoxyacetophenone in 25 ml. of dihydropyran and a trace of *p*-toluenesulfonic acid was allowed to stand overnight. Ether and a few drops of dilute sodium hydroxide were added and the ether layer was separated, dried over anhydrous potassium carbonate and evaporated. The oily residue was dissolved in 50 ml. of dry ethyl acetate and added to 2 g. of powdered sodium. The next day crushed ice was added and the aqueous layer separated, washed with ether, acidified with iced dilute sulfuric acid and extracted with ether. The sirup remaining after removal of the ether was refluxed for an hour with 20 ml. of methanol and 5 ml. of concentrated hydrochloric acid. Water (75 ml.) was added and the solution cooled. The crystalline product which separated was washed with ether, the washings being used to extract the aqueous alcoholic mother liquors. The residual material from this ether extract was treated again with methanol–hydrochloric acid, yielding a second crop of crystalline chromone. The two crops (2.8 and 1.3 g.) were combined and recrystallized from methanol, yielding 2.8 g. (53%) of pure chromone, white needles, m.p. 247–248°.

The identity of the chromone was established by its independent synthesis in the following way:

2-Hydroxy-3,6-dimethoxy-4-benzyloxyacetophenone was prepared by (A) the monobenzylation of 2,4-dihydroxy-5,8-dimethoxyacetophenone (5.0 g.) in acetone (150 ml.) with benzyl chloride (3.5 g.) in the presence of potassium carbonate (15 g.). The product (5.1 g.) formed pale yellow needles, m.p. 109–110°; (B) the reaction of 2,5-dimethoxyresorcinol dibenzyl ether with acetyl chloride and aluminum chloride in benzene solution at 0°. The yield of the desired compound, m.p. 109.5–110°, was about 35%, a non-phenolic by-product being formed in about an equivalent amount.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.23; H, 5.95.

2-Methyl-7-benzyloxy-5,8-dimethoxychromone was prepared by the C-acylation of the above acetophenone in the usual way with ethyl acetate and sodium, followed by ring closure of the resulting diketone. The chromone formed rosettes of crisp needles, m.p. 164–165°, from benzene–ethyl acetate.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.91; H, 5.56. Found: C, 69.57; H, 5.55.

2-Methyl-5,8-dimethoxy-7-hydroxychromone.—A solution of 6.2 g. of 2-methyl-5,8-dimethoxy-7-benzyloxychromone in 150 ml. of warm ethanol was hydrogenated in the presence of 3 g. of 10% palladium–charcoal at an initial pressure of about 1.7 atm. of hydrogen. The absorption of the calculated amount (1 mole) of hydrogen was completed in about 5 min. The catalyst was removed by filtration and washed with dilute alcoholic sodium hydroxide (to remove chromone which had crystallized during the hydrogenolysis). The acidified and diluted filtrate yielded 4.1 g. (92%) of the hydroxychromone, m.p. 247–248°, identical with that obtained by way of the tetrahydropyranylation route.

The chromone was characterized by the preparation of the following ethers by treatment with the corresponding halides and potassium carbonate in acetone:

7-Carboethoxymethoxy Ether.—M.p. 124–125° (from ether–petroleum ether).

Anal. Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.31; H, 5.68.

7-*n*-Propyl Ether.—M.p. 103–105° (from dilute methanol).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.51; H, 6.50.

7-*n*-Butyl Ether.—M.p. 110–112° (from dilute methanol).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.80; H, 6.92. Found: C, 66.02; H, 6.76.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES, CALIF. RECEIVED FEBRUARY 2, 1951

The Reversibility of the Friedel-Crafts Condensation. Carbomethoxystilbenes

BY REYNOLD C. FUSON AND H. G. COOKE, JR.

The transformation of various types of substituted styryl compounds into the corresponding unsubstituted 1,1-diphenylethyl derivatives takes place in the presence of benzene, hydrogen chloride and aluminum chloride. For example, nuclear halostilbenes yield 1,1,2-triphenylethane.[1] The process involves the replacement of a halophenyl radical by a phenyl radical.

$$XC_6H_4CH{=}CHC_6H_4X \xrightarrow[AlCl_3]{C_6H_6} (C_6H_5)_2CHCH_2C_6H_5 + 2C_6H_5X$$

Experiments have been carried out to determine whether phenyl groups bearing substituents other than halogen could also be expelled from the molecule in this manner. Experiments with *p*-tolyl radicals[2] indicated that the phenomenon might be general for aryl groups that carry only ortho, para-directing substituents. As expected, benzalquinaldines and benzallepidines failed to yield quino-

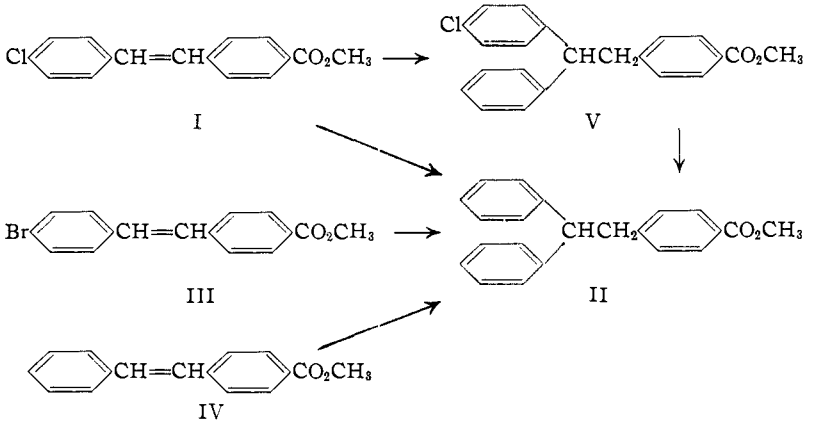
(1) L. L. Alexander and R. C. Fuson, THIS JOURNAL, **58**, 1745 (1936).

(2) J. T. Eaton, D. B. Black and R. C. Fuson, *ibid.*, **56**, 687 (1934).

line when treated with benzene and aluminum chloride.[3] That the addition of the benzene was selective and did not affect the attachment of the quinoline nucleus was attributed to the fact that the ethylenic linkage is part of a heteroconjugated system.

Similar results have now been obtained with a phenyl radical bearing a carbomethoxyl group. A study of the action of benzene and aluminum chloride on *p*-carbomethoxystilbenes, in which the central ethylenic linkage is conjugated (through a benzene ring) with the carbomethoxy group, has shown that benzene adds reversibly to the lateral double bond. The addition takes place in the manner characteristic of heteroconjugated systems and is selective; the entering phenyl radical is joined to the carbon atom remote from the benzoate nucleus.

4-Chloro-4′-carbomethoxystilbene (I) reacts with benzene to yield a chlorine-free product, 1,1-diphenyl-2-*p*-carbomethoxyphenylethane (II). The phenyl group must become attached to the carbon atom adjacent to the chlorophenyl radical in order to eliminate chlorobenzene from the molecule. It was assumed that in the second step benzene was added in the same sense. This assumption was confirmed by oxidative degradation, which produces benzophenone.



The same product (II) was obtained from 4-bromo-4′-carbomethoxystilbene (III) and from 4-carbomethoxystilbene (IV). An indication of the course of the reactions with the halogen compounds was obtained by interrupting the condensation process after a short time. In this way it was shown that the chloro ester (I) condenses with benzene to yield initially 1-phenyl-1-*p*-chlorophenyl-2-*p*-carbomethoxyphenylethane (V). Oxidation of this product produces *p*-chlorobenzophenone. Although chlorobenzene was not isolated as a product of the conversion of V to II, its formation seems certain in view of the results reported for analogous transformations.[4]

Experimental

4-Chloro-4′-carbomethoxystilbene[5] and Benzene.—A solution of 2.5 g. of the stilbene in 100 ml. of dry benzene was saturated with dry hydrogen chloride. Four grams of aluminum chloride was added and the mixture shaken for five hours in a stoppered flask. Decomposition with ice and hydrochloric acid yielded a benzene solution of 1,1-diphenyl-2-*p*-carbomethoxyphenylethane. The solvent was distilled and the ethane recrystallized from methanol; m.p. 113–114°; yield 76%.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.55; H, 6.38. Found: C, 83.75; H, 6.47.

The foregoing preparation was repeated with the reaction time diminished to one hour. The product was 1-phenyl-1-*p*-chlorophenyl-2-*p*-carbomethoxyphenylethane (V). It was recrystallized from methanol; m.p. 107–108°; yield 62%.

Anal. Calcd. for $C_{22}H_{19}O_2Cl$: C, 75.61; H, 5.50. Found: C, 75.53; H, 5.71.

Further treatment of the chloroethane (V) under the conditions outlined above converted it to the chlorine-free ethane (II); melting point and mixed melting point 113–114°; yield 55%.

The same ethane was obtained in a 63% yield by subjecting 4-carbomethoxystilbene to the action of benzene, hydrogen chloride and aluminum chloride. When 4-bromo-4′-carbomethoxystilbene was used and the reaction allowed to continue for five hours, the bromine-free ethane (II) was produced in a 75% yield.

Oxidation of 1-phenyl-1-*p*-chlorophenyl-2-*p*-carbomethoxyphenylethane (V) produced *p*-chlorobenzophenone, which was isolated as the 2,4-dinitrophenylhydrazone; m.p. 192–194°. Grieve and Hey[6] reported a melting point of 184–185°. The 2,4-dinitrophenylhydrazone of a known sample of *p*-chlorobenzophenone was found to melt at 195–196° and gave the following analytical values:

Anal. Calcd. for $C_{19}H_{13}O_4N_4Cl$: C, 57.50; H, 3.30; N, 14.12. Found: C, 57.69; H, 3.36; N, 14.19.

A mixture of this compound and that from the oxidation melted at 192–195°.

1,1-Diphenyl-2-*p*-carbomethoxyethane (II) was oxidized by a method similar to that used by Böeseken and Bastet[7] in the oxidation of 1,1,2-triphenylethane. A mixture of 1 g. of the ethane, 2 g. of chromic anhydride and 50 ml. of glacial acetic acid was heated on a steam-bath for 20 hours. It was poured into 200 ml. of water containing 2 g. of sirupy phosphoric acid, and an excess of ammonium hydroxide was added. Ether extraction of this mixture yielded an oil which reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of benzophenone; melting point and mixed melting point 237–239°.

(3) R. C. Fuson, L. L. Alexander, E. Ellingboe and A. Hoffman, *ibid.*, **58**, 1979 (1936).

(4) R. C. Fuson, A. P. Kozacik and J. T. Eaton, *ibid.*, **55**, 3799 (1933).

(5) For the preparation of the carbomethoxystilbenes see R. C. Fuson and H. G. Cooke, Jr., *ibid.*, **62**, 1180 (1940).

(6) W. S. M. Grieve and D. H. Hey, *J. Chem. Soc.*, 1797 (1934).

(7) J. Böeseken and M. C. Bastet, *Rec. trav. chim.*, **32**, 184 (1913).

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RECEIVED MARCH 3, 1951

Complex Formation between Nickel Ion and Hydrazine in Solution

BY E. C. GILBERT AND WM. H. EVANS[1]

When hydrazine is added to a solution of a nickel salt, a deep blue color is formed, followed shortly by the precipitation of a red-violet solid complex salt if the solution is at all concentrated. This is of course accompanied by the disappearance of the blue color. If nickel sulfate is used the precipitation occurs at a very low concentration. The limited solubility of these nickel hydrazine complexes has been used to prepare a considerable number of them, including the sulfate, acetate,

(1) Abstracted from Ph.D. thesis of Wm. H. Evans, 1947.

benzoate, chloride, bromide, pyrophosphate, oxalate and cyanide. By the use of nickel nitrate however a much more intense color may be secured in the solution before precipitation occurs. This is probably due both to the variation in the stability of any complexes formed with the change in ionic strength occasioned by the change in anion, and to greater solubility of the complex nitrate.

Franzen and Mayer[2] prepared a complex with nickel nitrate containing $Ni(N_2H_4)_3^{++}$. This was a red violet solid and appears to be the precipitate that forms when nickel nitrate and hydrazine solutions are allowed to stand. Sommer and Weise,[3] however, report the preparation of a deep blue hydrated nickel sulfate containing but one molecule of hydrazine, and Curtius and Schrader,[4] prepared a sulfate complex containing $Ni(N_2H_4)_2^{++}$.

This behavior indicates that there might occur stepwise addition of hydrazine to the nickel ion, with the monohydrazine nickel ion as an intermediate step in the formation of di- or trihydrazine complexes. It would be of interest to know what complexes are capable of existence in solution, their relative stability, and proportions if soluble enough to be detected.

Experimental

A spectrophotometric study of the system nickel nitrate–hydrazine hydrate was made with monochromatic light in bands of 100 Å. width over the spectral range of 4000–7200 Å. using a Cenco-Sheard Photelometer, with 1 cm. Corex absorption cells. Solutions (0.02 molal) were made from Baker C.P. nickel nitrate low in cobalt, and Edwal 100% hydrazine hydrate, in the ratio of $1Ni:1N_2H_4$, $1Ni:2N_2H_4$, $1Ni:3N_2H_4$. Higher ratios were not experimentally feasible as they caused precipitation of the insoluble trihydrazine nickel salt. The optical density log I_0/I (where I_0 is the intensity of light transmitted by a reference solution of sodium nitrate of the same ionic strength as that used in the nickel solutions) was plotted against wave length as shown in Fig. 1. It would appear from first inspection of these that only one complex was present (even in solutions concentrated enough for precipitation to take place). This could be due to absorption by different complexes in the same spectral region, or such low solubility that they did not affect the absorption.

Recourse was to Job's principle of continuous variation.[5]

The method has been extended by Vosburgh.[6] A series of solutions $0.02\ (1-x)\ M$ in nickel nitrate and $0.02x\ M$ in hydrazine was prepared with x varying from 0.0 to 0.75 and the absorption determined for the wave lengths 5890, 6000 and 6200 Å. These results are shown in Fig. 2 where it is apparent that there is good evidence for maxima at $x = 0.5$ and $x = ca.\ 0.66$ indicating the formation of two complexes $Ni(N_2H_4)^{++}$ and $Ni(N_2H_4)_2^{++}$. It is generally assumed that the divalent nickel ion is hexacovalent. It is probable therefore that in solution these complexes with hydrazine are also partially hydrated. There is no evidence for this from the present experiment, so simple formulas are used.

The stability constant of the monohydrazinate was next approximated by the use of a series of solutions $0.04(1-x)$ M in nickel nitrate and $0.08x\ M$ hydrazine where the absorption was again measured at 5800, 6000 and 6200 Å., results being shown in Fig. 3. The maximum value oc-

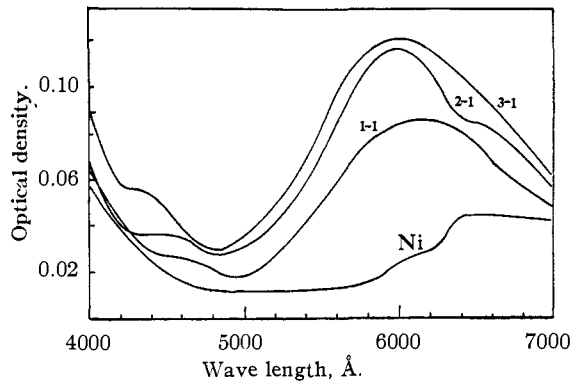


Fig.1.—Absorption spectra of 0.02 M nickel nitrate solutions with various ratios of added hydrazine.

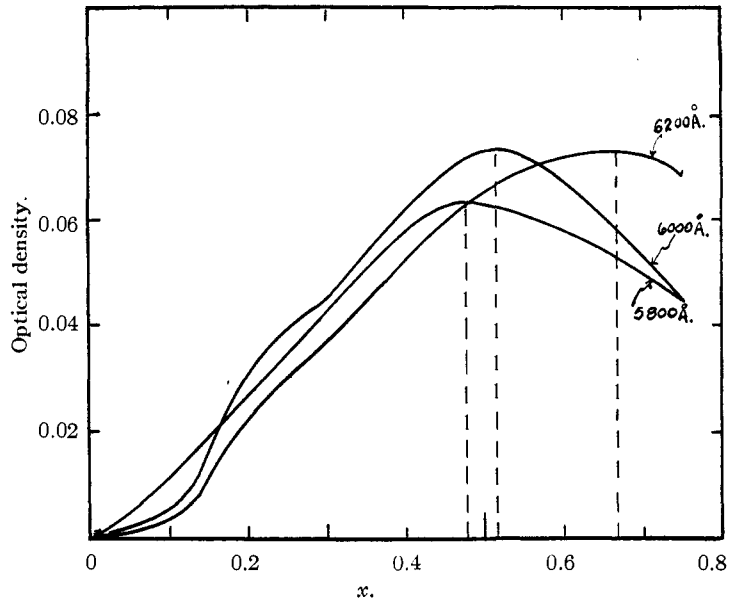


Fig. 2.—Absorption of $(1 - x)$ liters of 0.02 M nickel nitrate and x liters of 0.02 M hydrazine.

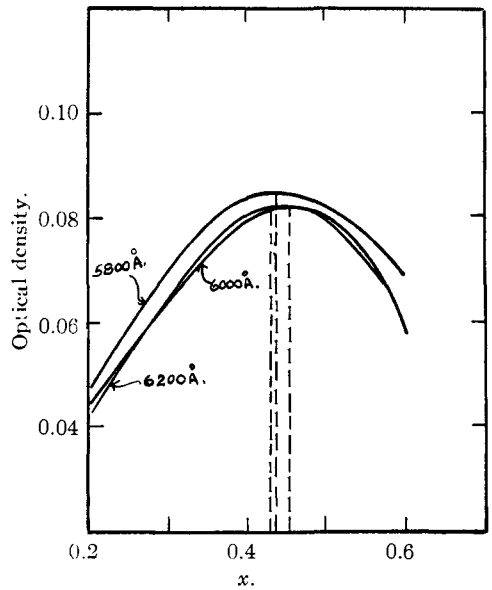


Fig. 3.—Absorption of $(1 - x)$ liters of 0.04 M nickel nitrate and x liters of 0.08 M hydrazine.

(2) H. Franzen and O. von Mayer, *Z. anorg. Chem.*, **60**, 247 (1908).
(3) F. Sommer and K. Weise, *ibid.*, **94**, 51 (1916).
(4) T. Curtius and F. Schrader, *J. prakt. Chem.*, [2] **50**, 341 (1894).
(5) (a) P. Job, *Compt. rend.*, **180**, 928 (1925); (b) *Ann. chim.*, [10] **9**, 113 (1928); (c) [11] **6**, 97 (1936).
(6) W. C. Vosburgh and G. R. Cooper, THIS JOURNAL, **63**, 437 (1941); W. C. Vosburgh and R. K. Gould, *ibid.*, **64**, 1630 (1942).

curred at $x = 0.443$. Substitution in the appropriate equation (ref. 5b, equation 7) gives 0.1 for $K = ([Ni^{++}][N_2H_4])/([Ni(N_2H_4)^{++}])$. The stability constant of the dihydrazinate could not be determined because of the interfering absorption of the first complex in the same region. In addition precipitation prevented sufficiently high concentrations. The evidence is therefore only quantitative for the existence of the monohydrazine nickel(II) ion in solution.

DEPARTMENT OF CHEMISTRY
OREGON STATE COLLEGE
CORVALLIS, OREGON RECEIVED DECEMBER 26, 1950

Perfluorinated Grignard Derivatives

BY ALBERT L. HENNE AND WILLIAM C. FRANCIS

Since the recent disclosure by Haszeldine[1] that we had obtained perfluorinated Grignard derivatives, we have received repeated requests for experimental directions. The following general procedure, while not yet optimum, will permit others to proceed with practical results.

We have made our Grignard derivatives from iodides, $C_nF_{2n+1}I$, and most of the work was done with C_3F_7I. Contrary to a general impression, the formation of C_3F_7MgI is exceedingly easy; its stability is, however, so poor that complete decomposition occurs promptly at room temperature.

A clue to this behavior was obtained when the Grignard was prepared in an atmosphere of dry carbon dioxide. Under these conditions $C_3F_7CO_2H$ resulted in 6 to 10% yield. When the reaction was carried out in a nitrogen atmosphere and later carbonated, little or no acid was obtained. At 0°, the Grignard is still unstable, but it is possible to form it in ether solution at this temperature, drop it promptly into water or a slurry of Dry Ice in ether[2] and isolate C_3F_7H or $C_3F_7CO_2H$, respectively, in 5 to 7% yields. These experiments show that perfluorinated Grignard reagents exist as such, and appear to react normally.

If Grignard formation is carried out at about −80° in an ether solution of C_3F_7I containing a suspension of magnesium and Dry Ice, a 45% yield of $C_3F_7CO_2H$ is easily obtained, presumably improvable by refining the mechanical handling.

Reaction in a carbon dioxide atmosphere using the "extreme dilution" procedure usually applied to allylic halides appears promising, but at the present time the recommended procedure is the low-temperature reaction just described.

Pilot tests have shown that these procedures can be extended to reaction with the carbonyl function, and acetone gives the expected carbinol. More detailed information will be presented later.[3]

(1) R. N. Haszeldine, *Nature*, **167**, 139 (1951).

(2) A. S. Hussey, THIS JOURNAL, **73**, 1364 (1951).

(3) In a preprinted abstract for the New York Meeting of the A.C.S., September, 1951, Haszeldine states that perfluorinated Grignard Reagents appear to condense normally with a series of conventional functions (private communication).

DEPARTMENT OF CHEMISTRY
OHIO STATE UNIVERSITY
COLUMBUS, OHIO RECEIVED MAY 9, 1951

The Synthesis of 4-Chloro-3-indoleacetic Acid

BY CORWIN HANSCH AND JOHN C. GODFREY

4-Chloro-3-indoleacetic acid has been synthesized by the procedure of Snyder and Pilgrim[1] for assessment as a plant growth-regulator. This substance has been tested by the avena test as part of a program[2] to correlate plant growth activity with chemical structure. The compound was found by Dr. Robert Muir of the State University of Iowa to be active in promoting plant growth; his complete results will be published elsewhere. The starting point for the synthesis of the 4-substituted acid was 4-chloroindole[3] a generous sample of which was supplied by Dr. F. C. Uhle of Harvard University.

(1) H. R. Snyder and F. J. Pilgrim, THIS JOURNAL, **70**, 3770 (1948).

Experimental

4-Chlorogramine.—To 1.42 ml. of 25% aqueous dimethylamine cooled in an ice-bath was added 1 g. of cold acetic acid and 0.58 g. of cold 40% formalin. This solution was then poured onto 1.12 g. of 4-chloroindole, the beaker being rinsed with 1/3 ml. of water. The mixture was allowed to come to room temperature and after some shaking all of the chloroindole dissolved. This solution was allowed to stand overnight and then heated to 30–40° for 2 hours after which 1.35 g. of KOH in 10 ml. of water was added. The oil which separated crystallized quickly and after standing in an ice-bath 2 hours, the crystals were separated and dried. Dilution of the filtrate with the wash water caused more crystals to separate. Yield of crude chlorogramine was 1.4 g., m.p. 135–143°. After crystallization from acetone the m.p. was 147.6–148.4°.

Anal.[4] Calcd. for $C_{11}H_{13}N_2Cl$: C, 63.31; H, 6.24. Found: C, 63.40; H, 6.50.

The picrate was prepared in ethanol solution and recrystallized from the same solvent; m.p. 157.4–158.6°.

Anal. Calcd. for $C_{17}H_{16}N_5O_7Cl$: C, 46.63; H, 3.66. Found: C, 46.60; H, 4.10.

4-Chloro-3-indoleacetic Acid.—To 0.91 g. of potassium cyanide dissolved in 1.7 ml. of water and 5.4 ml. of 95% ethanol was added 0.57 g. of 4-chlorogramine. This mixture was heated under reflux for 98 hours and then diluted with 12 ml. of water. The resulting precipitate (presumably amide of 4-chloroindoleacetic acid) was removed by filtration (no free 4-chloroindoleacetic acid was obtained from this filtrate on acidification) and hydrolyzed by boiling with 2 *N* KOH for 4 hours. Acidification of the KOH solution caused a considerable precipitate of silicic acid and chloroindoleacetic acid. This precipitate and solution was evaporated to dryness and the residue extracted with ether. After evaporation of the ether the residue was crystallized from alcohol and ethylene chloride; yield 0.1 g., m.p. 179–180°.

Anal. Calcd. for $C_{10}H_8O_2NCl$: C, 57.28; H, 3.82. Found: C, 56.90; H, 4.30.

(2) C. Hansch and R. M. Muir, *Plant Physiol.*, **25**, 389 (1950).

(3) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

(4) All analyses were made by C. F. Geiger of Chaffey College, Ontario, California.

DEPARTMENT OF CHEMISTRY
POMONA COLLEGE
CLAREMONT, CALIF. RECEIVED FEBRUARY 26, 1951

Preparation of N,N,N′,N′-Tetrasubstituted Diamines

BY THOMAS M. LAAKSO AND DELBERT D. REYNOLDS

Recent investigations in our laboratory required the use of certain N,N,N′,N′-tetrasubstituted diamines. A general method for their preparation is not described in the literature.

The method described here involves the reaction of glycol disulfonates with secondary amines as indicated by

$$RSO_2O-(CH_2)_x-OSO_2R + 4R'R''NH \longrightarrow \begin{matrix} R' \\ R'' \end{matrix}\!\!>\!N-(CH_2)_x-N\!<\!\!\begin{matrix} R' \\ R'' \end{matrix} + 2RSO_2OH\cdot HNR'R''$$

R may be alkyl, aryl, and so forth; R′ and R″ may

TABLE I

N,N,N′,N′-TETRASUBSTITUTED DIAMINES

Amine	Sulfonate derivative	Tertiary amine	M.p. or b.p., °C. (mm.)	Analyses, % Calcd.	Found	Yield
Dicyclohexyl	1,2-Di-(benzenesulfonoxy)-ethane	N,N,N′,N′-Tetracyclohexyl-ethylenediamine	M. 102–104	C, 80.4	80.5	
				H, 12.3	12.2	85.9
				N, 7.2	7.0	
Diethyl	1,2-Di-(benzenesulfonoxy)-ethane	N,N,N′,N′-Tetraethylethylene-diamine	B. 89 (31.5)	C, 70.0	70.3	
				H, 13.7	14.1	55
				N, 16.3	16.7	
Diisopropyl	1,3-Di-(*p*-toluenesulfonoxy)-propane	N,N,N′,N′-Tetraisopropyltri-methylenediamine	B. 83 (10.25)	C, 74.5	74.8	
				H, 14.0	13.8	85.7
				N, 11.5	11.5	
Diphenyl	1,3-Di-(*p*-toluenesulfonoxy)-propane	N,N,N′,N′-Tetraphenyltri-methylenediamine	B. 118–121 (0.3)	C, 85.7	85.3	
				H, 6.9	7.0	64.8
				N, 7.4	7.0	
Di-*n*-butyl	1,4-Di-(*p*-toluenesulfonoxy)-butane	N,N,N′,N′-Tetra-*n*-butyltetra-methylenediamine	B. 107–108 (1)	C, 77.0	77.1	
				H, 14.1	14.0	77.5
				N, 9.0	9.2	
Methylphenyl	1,4-Di-(*p*-toluenesulfonoxy)-butane	N,N′-Dimethyl,N,N′-diphenyl-tetramethylenediamine	M. 82–83	C, 80.6	80.2	
				H, 8.9	8.8	24.3
				N, 10.5	10.8	
Piperidine	1,5-Di-(methanesulfonoxy)-pentane	N,N′-Dipiperidylpenta-methylenediamine	B. 110 (0.5)	C, 75.6	75.4	
				H, 12.6	12.7	25
				N, 11.7	11.9	
Dibenzyl	1,5-Di-(methanesulfonoxy)-pentane	N,N,N′,N′-Tetrabenzylpenta-methylenediamine	B. 218–222 (0.6)	C, 85.7	86.0	
				H, 8.2	7.8	10
				N, 6.1	6.0	
Morpholine	2,5-Di-(benzenesulfonoxy)-hexane	2,5-(Dimorpholino)-hexane	B. 130–132 (0.3)	C, 65.1	64.7	
				H, 10.9	10.6	66.5
				N, 10.8	11.0	
Diethyl	β,β′-Di-(benzenesulfonoxy)-diethyl ether	β,β′-(Diethylamino)-diethyl ether	B. 69–70 (1)	C, 66.6	66.6	
				H, 12.9	12.8	13
				N, 12.9	13.1	
Diisopropyl	β,β′-Di-(benzenesulfonoxy)-diethyl ether	β,β′-(Diisopropylamino)-diethyl ether	B. 96.5 (0.5)	C, 70.5	70.9	
				N, 13.2	13.2	49.2
				N, 10.4	10.3	
Diisopropyl	1,3-Di-(*p*-toluenesulfonoxy)-butane	1 3-(Diisopropylamino)-butane	B. 85–87 (1)	C, 75.0	74.5	
				H, 14.0	14.1	65
				N, 11.0	10.7	

TABLE II

GLYCOL DISULFONATES

Glycol	Sulfonate derivative	M.p., °C.	Analyses, % Calcd.	Found	Yield, %
Ethylene glycol	1,2-Di-(benzenesulfonoxy)-ethane	48–50	C, 49.2	49.4	64.7
			H, 4.1	4.2	
			S, 18.6	18.3	
Propane-1,3-diol	1,3-Di-(*p*-toluenesulfonoxy)-propane	92–93	C, 53.2	52.9	
			H, 5.2	5.2	69.4
			S, 16.8	16.5	
Butane-1,4-diol	1,4-Di-(*p*-toluenesulfonoxy)-butane	81–82	C, 54.3	54.3	
			H, 5.5	5.5	67
			S, 16.1	15.9	
Pentane-1,5-diol	1,5-Di-(Methanesulfonoxy)-pentane	35–36	C, 32.4	32.3	
			H, 6.1	6.1	82.7
			S, 24.6	24.2	
Hexane-2,5-diol	2,5-Di-(benzenesulfonoxy)-hexane	104–105	C, 54.3	54.2	
			H, 5.5	5.3	73.7
			S, 16.1	16.3	
Diethylene glycol	β,β′-Di-(benzenesulfonoxy)-diethyl ether	38–39	C, 49.7	49.6	
			H, 4.6	4.7	66.1
			S, 16.6	16.7	
Butane-1,3-diol	1,3-Di-(*p*-toluenesulfonoxy)-butane	58–59	C, 54.3	54.6	
			H, 5.5	5.5	77.0
			S, 16.1	16.4	

be the same or different, alkyl, aryl, cyclic, and so forth. This process has a broad application, since, for a given disulfonate, a large number of secondary amines may be chosen. Moreover, the availability of the glycol disulfonates is being greatly increased by the ever-increasing number of glycols which are appearing on the market.

Table I lists the amines synthesized by this method and Table II contains the glycol disulfonates which were prepared as intermediates.

Experimental

General Procedure for the Preparation of Glycol Disulfonates.—The anhydrous glycol (1 mole) is dissolved in 3 to 5 volumes of anhydrous pyridine and the appropriate sulfonyl chloride (2 moles) is added to this well-stirred solution. The temperature is maintained between 5 and 15°. After the reaction is completed, the reaction mixture is stirred into three times its volume of finely crushed ice. The crystalline product which separates is washed with ice-water and then dried. It is purified by recrystallization from ethanol.

General Procedure for the Preparation of N,N,N',N'-Tetrasubstituted Diamines.—A glycol disulfonate is refluxed with 20 equivalents of anhydrous secondary amine under anhydrous conditions, with stirring, for approximately 20 hours. The secondary amine is fractionally distilled, after which an excess of 40% sodium hydroxide solution is added. The oil layer is separated and the water layer extracted with ether. The oil and ether extracts are combined and dried over anhydrous potassium carbonate. After distillation of the ether, the residual oil is fractionated under reduced pressure through a glass-packed column using a variable take-off stillhead.

RESEARCH LABORATORY
EASTMAN KODAK COMPANY
ROCHESTER, NEW YORK RECEIVED MARCH 22, 1951

On the Preparation of Xanthurenic Acid

BY ALEXANDER D. MEBANE AND WILLIAM OROSHNIK

Xanthurenic acid was first synthesized by Musajo and Minchilli,[1] who reported a melting point of 283–285° (dec.) "with fast heating." Subsequent preparations[2,3,4] have resulted in melting points varying from 250°[3] (in spite of correct elementary analyses) to as high as 289°.[4] When the synthesis was carried out in this Laboratory, a product of m.p. 255° was obtained, although all intermediates had been carefully purified. The explanation was found to lie in incomplete ether-fission under the conditions specified by Musajo and Minchilli; more exhaustive treatment with hydriodic acid raised the melting point to 294°. A subsequent examination of two of the above-mentioned preparations showed the 250° specimen[3] to contain 8.3% of methoxyl, corresponding to 58 mole per cent. of the 8-methyl ether; the 289° specimen,[4] on the other hand, proved to contain only 3.3 mole per cent. of the methyl ether.

Reprecipitation of methoxyl-free material was ineffective in freeing it of inorganic contaminants. None of the common organic solvents permitted recrystallization, but dilute hydrochloric acid proved to be quite satisfactory, giving a chloride-free crystalline product decomposing at 297°.

(1) L. Musajo and M. Minchilli, *Ber.*, **74B**, 1842 (1941).

(2) E. C. Miller and C. A. Baumann, *J. Biol. Chem.*, **157**, 554 (1945); **159**, 174 (1945).

(3) C. C. Porter, I. Clark and R. H. Silber, *ibid.*, **167**, 575 (1947). A sample of this material was kindly made available to us by Dr. Silber.

(4) F. Rosen, J. W. Huff and W. A. Perlzweig, *J. Nutrition*, **33**, 561 (1947). The melting point was not reported in the original publication.

A simplified version of the Musajo–Minchilli synthesis which embodies these improvements is described below.[5]

Experimental

Commercial sodium salt of oxalacetic ester (49 g.) was shaken with 300 ml. of ether and 400 ml. of ice-cold 5% sulfuric acid until all had dissolved, and the aqueous layer was reextracted with ether. The combined extracts, after drying over anhydrous $MgSO_4$, were concentrated at 20 mm. The residue (38 g., 0.2 *M*) was heated in a boiling water-bath with 25 g. (0.2 *M*) of *o*-anisidine for 90 minutes, after which the water that had separated was evaporated at 20 mm.

The resulting orange sirup was stirred with 1 liter of mineral oil while heating to 240° in an electric mantle. After five minutes at 240–250°, the flask was cooled with an air blast. When the temperature had fallen to 60°, the solution was decanted from precipitated tar, diluted with 2 liters of petroleum ether, and stored for several days in the refrigerator. Tan-colored crystals of crude ethyl xanthurenate 8-methyl ether (23 g.) were obtained. Recrystallization of this material (from toluene, with ligroin) was undesirable for practical purposes, since the best crops were the later and smaller ones (colorless needles, m.p. 100–101°).

The crude ether-ester was dissolved in 350 ml. of 57% hydriodic acid (freshly distilled from hypophosphorous acid; b.p. 126–128°), and the liquid was distilled slowly at atmospheric pressure under an 8″ Vigreux column until the stillhead temperature had reached 110° (3 hours). The HI was then distilled off to near-dryness at 20 mm. and the residue taken up in water, made alkaline with bicarbonate, filtered, and acidified to *p*H 3 with dilute HCl in the presence of a little bisulfite. After chilling, the xanthurenic acid was filtered off with water washes and sucked as dry as possible: sulfur-yellow, non-crystalline.

The damp filter cake was dissolved, by boiling, in a mixture of 400 ml. of concd. HCl and 500 ml. of distilled water, and filtered hot with a little Norit and SuperCel, washing with 70 ml. of the hot solvent. To the filtrate was added 2400 ml. of boiling-hot distilled water, and the solution was allowed to stand overnight. Filtration, with water and then acetone washes, furnished 14.5 g. (35% based on *o*-anisidine) of crystalline xanthurenic acid; small, imperfectly-rhombic ochre-yellow flakes.

Anal. Calcd. for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.59, 58.34; H, 3.52, 3.67; N, 6.61, 6.66; methoxyl, none; ash, none; Cl^-, none; Fe, none.

The melting point is quite sensitive to the rate of heating. If the temperature was brought rapidly to 270° and thereafter raised 5° per minute, decomposition occurred at 297°.

At *p*H 6.95, the ultraviolet absorption spectrum of xanthurenic acid in water shows two smooth peaks: $\lambda_{max.}$ 243 mμ, ε 30,000; $\lambda_{max.}$ 342 mμ, ε 6,500.

Acknowledgments.—We are indebted to Mr. Robert A. Mallory for checking this procedure, and to Mr. Joseph Grodsky for the microanalyses.

(5) A paper by A. Furst and C. J. Olsen (*J. Org. Chem.*, **16**, 412 (1951)), which appeared after this note had been submitted, describes more extensive improvements in this preparation. The melting point of 284° for crystalline material reported by Furst and Olsen is presumably due to a difference in heating rate.

ORTHO RESEARCH FOUNDATION
RARITAN, NEW JERSEY RECEIVED MARCH 19, 1951

The Activity Coefficients of the Alkaline Earth and Magnesium Perchlorates from Freezing Point Data

BY DAN E. NICHOLSON[1] AND W. A. FELSING

In a previous article,[2] experimental data were presented in which the freezing points for aqueous solutions of barium, strontium, calcium and magnesium perchlorates had been used to calculate the

(1) Materials Chemistry Division, Oak Ridge National Laboratory.

(2) D. E. Nicholson with W. A. Felsing, THIS JOURNAL, **72**, 4469 (1950).

activity coefficients of these salts over a wide range of solute concentrations hear 0°. Dr. R. A. Robinson[3] has pointed out that in our calculations an error in *sign* was made for the term

$$\int_0^M \Delta j \, d \log M$$

in the Scatchard[4] modification of the Lewis–Randall[5] equation relating the freezing point depression to the activity coefficient, at a given concentration of electrolyte. The recalculated values are given in Table I.

TABLE I

VALUES OF THE ACTIVITY COEFFICIENT, γ', FOR THE ALKALINE EARTH AND MAGNESIUM PERCHLORATES

Molality	Lim. Law	$Ba(ClO_4)_2$	$Sr(ClO_4)_2$	$Ca(ClO_4)_2$	$Mg(ClO_4)_2$
0.001	0.910	0.897	0.900	0.900	0.901
.002	.841	.864	.871	.869	.869
.005	.760	.805	.815	.814	.814
.01	.678	.751	.763	.763	.764
.02	.577	.689	.706	.706	.707
.05	.420	.602	.630	.633	.633
.1	.293	.541	.580	.587	.587
.2	.176	.489	.543	.554	.567
.3	.119	.463	.526	.551	.575
.4	.086	.449	.534	.561	.598
.5	.064	.441	.542	.579	.630
.6		.438	.555	.603	.668
.7		.437	.572	.633	.713
.8		.438	.594	.668	.767
.9		.442	.619	.710	.828
1.0		.449	.648	.763	.898

(3) Private communication from University of Malaya, Singapore.

(4) Scatchard, Jones and Prentiss, THIS JOURNAL, **54**, 2676 (1932).

(5) Lewis and Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, p. 286.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN, TEXAS

RECEIVED MARCH 19, 1951

Ferric-Catalyzed Hydrogen Peroxide Decomposition: Effect of Nitrate Ion

BY SIGFRED PETERSON[1]

The ferric-catalyzed hydrogen peroxide decomposition in nitrate solution shows deviations from first order kinetics which have been explained by Andersen[2] in terms of a non-chain mechanism involving atomic oxygen. It appears necessary, however, to use a chain mechanism as first proposed by Haber and Weiss[3] to explain the rapid evolution of oxygen when the iron is first added as ferrous,[3] the effect of ferric ion on the ferrous reaction,[4,5] the promotion of both ferrous and ferric reactions by cupric ion,[5] the oxidation of organic compounds,[6] the hydroxylation of aromatic compounds[7] and the initiation of polymerization[8] by ferrous–peroxide solutions and the inhibition by acetanilide[9] of the decomposition.

The mechanism evolved by several investigators[3,4,5] consists of the chain initiating step

$$Fe^{+++} + HO_2^- \longrightarrow Fe^{++} + HO_2 \qquad (1)$$

and three chain carrying steps

$$Fe^{++} + H_2O_2 \longrightarrow Fe^{+++} + OH^- + OH \qquad (2)$$

$$OH + H_2O_2 \longrightarrow H_2O + HO_2 \qquad (3)$$

$$Fe^{+++} + O_2 \longrightarrow Fe^{++} + O_2 \qquad (4)$$

with the chain ended by the reverse of (1)

$$Fe^{++} + HO_2 \longrightarrow Fe^{+++} + HO_2^- \qquad (5)$$

The species O_2^- and HO_2^- are presumed to be in rapid equilibrium with their conjugate acids. Application of steady state considerations to these equations gives the first order rate equation of Bertalan[10]

$$-d(H_2O_2)/dt = k(Fe^{+++})(H_2O_2)/(H^+)$$

Barb, Baxendale, George and Hargrave[5] suggest that the additional chain termination becomes important with diminishing peroxide/iron ratio and increases the order of reaction with respect to peroxide as found by Andersen.

$$Fe^{++} + OH \longrightarrow Fe^{+++} + OH^- \qquad (6)$$

During the investigation of the inhibition of this reaction by acetanilide,[9] deviations from first order decomposition were observed in some of the experiments without inhibitor. These experiments have been analyzed in terms of Andersen's equation

$$\log \frac{a}{x} + A\left(\frac{1}{x} - \frac{1}{a}\right) = Bt$$

in which a and x represent the concentration of hydrogen peroxide at the start of the experiment and time t, respectively. Table I gives pertinent data and the values of A and B obtained from graphs of $\left(\log \frac{a}{x}\right)\Big/\left(\frac{1}{x} - \frac{1}{a}\right)$ *versus* $t\Big/\left(\frac{1}{x} - \frac{1}{a}\right)$. The materials used are described in the previous paper[9]; the experimental technique did not differ significantly from that of Andersen.

TABLE I

a[a]	(Fe^{+++})[a]	(H^+)[a]	(ClO_4^-)[a]	(NO_3^-)[a]	A[a]	B (min.$^{-1}$)
0.077	0.019	0.040	1.78[b]	0.000	0.0004	0.0182
.085	.061	.133	0.317	.000	.0008	.0214
.442	.066[c]	.28	.47	.000	−.001	.0079
.425	.102	.22	.53	.000	.0005	.0208
.212	.31	.66	1.58	.000	.0002	.0266
.059	.12	.18	0.18	.37	.022	.034
.059	.12	.18	.18	.37	.025	.038
.059	.11	.36	.36	.34	.025	.018
.059	.11	.36	.36	.34	.037	.022

[a] Moles/l. [b] $NaClO_4$ added. [c] 24°. Other experiments at 25°.

The uncertainties in A in Table I are of the order of magnitude of the value for the first five experi-

(1) The experiments reported in this paper were performed at the University of California under the direction of the late Prof. William C. Bray.

(2) V. S. Andersen, *Acta Chem. Scand.*, **2**, 1 (1948); **4**, 914 (1950).

(3) F. Haber and J. Weiss, *Proc. Roy. Soc.* (*London*), **A147**, 332 (1934).

(4) C. W. Humphrey and J. Weiss, *Nature*, **163**, 691 (1919).

(5) W. G. Barb, J. H. Baxendale, P. George and K. R. Hargrave, *ibid.*, **163**, 692 (1949).

(6) J. H. Merz and W. A. Waters, *J. Chem. Soc.*, S15 (1949); I. M. Kolthoff and A. I. Medalia, THIS JOURNAL, **71**, 3777, 3784 (1949).

(7) H. Loebl, G. Stein and J. Weiss, *J. Chem. Soc.*, 2074 (1949); J. H. Merz and W. A. Waters, *ibid.*, 2427 (1949).

(8) J. H. Baxendale, M. G. Evans and G. S. Park, *Trans. Faraday Soc.*, **42**, 155 (1946); A. I. Medalia and I. M. Kolthoff, *J. Polymer Sci.*, **4**, 377 (1949).

(9) W. C. Bray and S. Peterson, THIS JOURNAL, **72**, 1401 (1950).

(10) J. van Bertalan, *Z. physik. Chem.*, **95**, 328 (1920).

ments and about one-tenth the value in the other experiments.

Table I shows that the deviation from first order (as measured by A) over a wide variety of conditions is negligible if the only anion is perchlorate. However, when the ferric is added as nitrate, the deviations become quite significant. The variety of conditions in the experiments with nitrate present is not great enough to lead to conclusions as to the nitrate dependence of A, but combination with Andersen's results shows that the nitrate dependence is not simple. The peroxide/iron ratio is even less in these experiments than in Andersen's.

The reactions

$$OH + NO_3^- \longrightarrow OH^- + NO_3 \quad (7)$$
$$NO_3 + H_2O_2 \longrightarrow NO_3^- + H^+ + HO_2 \quad (8)$$

suggested by Taube and Bray[11] to account for the effect of nitrate on the reaction between ozone and hydrogen peroxide will not by themselves account for a decrease in the hydrogen peroxide decomposition rate since they neither start nor stop reaction chains. However, the chain termination processes

$$NO_3 + Fe^{++} \longrightarrow NO_3^- + Fe^{+++} \quad (9)$$
$$NO_3 + O_2^- \longrightarrow NO_3^- + O_2 \quad (10)$$

appeal to be plausible substitutes for reaction (6). A reaction of NO_3 with hydroxyl radicals is improbable since the products would include the highly endothermic atomic oxygen or its conjugate acid. Since in Andersen's work both the acid and iron were used as nitrates and A is proportional to the ferric concentration, reaction (10) which is diminished by acid is probably a factor in the nitrate effect.

Application of steady state considerations to the scheme including reactions (7), (8) and (9) or (10) but not (6) leads to a complex rate equation which for zero nitrate concentration reduces to the simple Bertalan equation. It might be remarked that the combination of reactions (7) and (9) amounts to a nitrate catalysis of the chain ending process (6).

(11) H. Taube and W. C. Bray, THIS JOURNAL, **62**, 3357 (1940).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE 8, KENTUCKY

RECEIVED MARCH 5, 1951

Ethylenimine by Flash Distillation[1]

BY WILSON A. REEVES, GEORGE L. DRAKE, JR., AND CARROLL L. HOFFPAUIR

Since Gabriel in 1888[2] first successfully prepared ethylenimine by treating 2-bromoethylamine hydrobromide with silver oxide in water, several other methods for its production have been proposed. Such methods include reaction of 2-haloethylamine hydrohalides with sodium or potassium hydroxide in water[3] and treating 2-aminoethyl hydrogen sulfate with sodium hydroxide.[4] The latter method is usually used since 2-aminoethyl hydrogen sulfate can be conveniently made from ethanolamine and sulfuric acid by the method of Wenker[4] or by a modification of this method by Leighton and others.[5]

The usual method of converting 2-aminoethyl hydrogen sulfate to ethylenimine is to mix it with an excess of aqueous sodium hydroxide solution and distill.[4,6] Yields of 37% ethylenimine which have been reported[6] appear to be the highest heretofore attained.

The present investigation of this reaction indicated that the rate at which the neutralized 2-aminoethyl hydrogen sulfate is heated in contact with excess base critically controls not only the yield but also the purity of the product. Where the rate of heating was such that the neutralized sulfate in contact with the base was virtually instantaneously raised from room temperature to a temperature above the boiling point of the imine, the product was volatilized as rapidly as it was formed and could be isolated in yields as high as 83% from the water which distilled with it.

Experimental

A 5-liter, 3-neck flask containing 100 ml. of 14% sodium hydroxide solution and fitted with a dropping funnel, a stirrer and a condenser arranged for distillation was heated in a 115-volt a.c., 1200-watt, 5-liter size metal safety heater until distillation was proceeding at a rapid rate. Then 420 g. of 2-aminoethyl hydrogen sulfate dissolved in a cool alkali solution made from 250 g. of sodium hydroxide and 1800 ml. of water was added to the distillation flask through the dropping funnel at a rate such that the amount of liquid in the flask remained about constant. The superheated distillate which came over at about 110° was collected in a second 5-liter, 3-neck flask which was partially immersed in an ice–salt-bath and which was fitted with an upright ice-water condenser.

After the distillation was complete, the receiving flask was fitted with two upright ice-water condensers to provide adequate cooling and a mechanical stirrer. The imine was salted out by adding 1200 g. of solid sodium hydroxide to the distillate through one of the condensers. While salting out, the temperature of the distillate was not allowed to rise much above room temperature. The ethylenimine, which was separated with a separatory funnel weighed 107 g. and boiled at 56°. Redistilled ethylenimine also boils at 56°. The yield obtained by this flash distillation procedure was 83% based on the 2-aminoethyl hydrogen sulfate.

(1) Contribution from one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Gabriel, *Ber.*, **21**, 1049 (1888).

(3) Gabriel, *ibid.*, **21**, 2665 (1888); Gabriel and Stelzner, *ibid.*, **28**, 2929 (1895); Knorr and Meyer, *ibid.*, **38**, 3130 (1905); U. S. Patent 2,212,145 (1940).

(4) Wenker, THIS JOURNAL, **57**, 2328 (1935).

(5) Leighton and Perkins, THIS JOURNAL, **69**, 1540 (1947).

(6) "Organic Syntheses," Vol. 30, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 38–40.

SOUTHERN REGIONAL RESEARCH LABORATORY
NEW ORLEANS, LA.

RECEIVED MARCH 12, 1951

Mannich Bases Derived from a Hantzsch Pyridine Synthesis Product

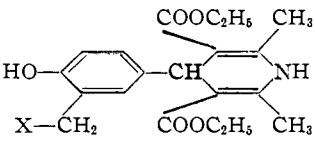
BY ARTHUR P. PHILLIPS

In an earlier paper[1] a series of products was reported which had been made for testing for possible physiological activity. The compounds were prepared through the Hantzsch pyridine synthesis and resulted in substances bearing a basic amino or quaternary ammonium salt group on the 4-phenyl substituent. Other routes were sought to introduce basic salt-forming groups into the same general ring system involved. Use of the Mannich reaction on a phenolic Hantzsch synthesis product

(1) A. P. Phillips, THIS JOURNAL, **71**, 4003 (1949).

TABLE I

MANNICH BASES FROM A HANTZSCH PYRIDINE SYNTHESIS PRODUCT

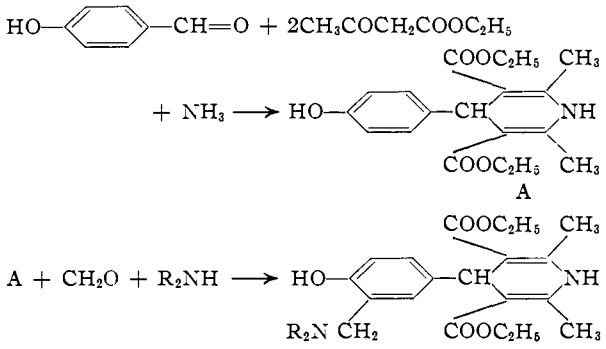


Compd.	X	Yield, %	M.p., °C.[a]	Crystn. solvent[b]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	$(CH_3)_2N$	97	200–205 Sinters 160–200	Æ.H	65.6	65.7	7.5	7.2
II	$(CH_3)_3NI$	40	214–215	M.E.	50.7	51.0	6.1	6.3
III	$(C_2H_5)_2N$	40	157–158	Æ.H	66.9	67.0	8.0	7.6
IV	$(CH_2)_5N$[c]	85	192–193	M	67.8	67.9	7.7	7.6
V	$O(C_2H_4)_2N$[d]	99	182–183	A	64.8	64.8	7.3	7.0

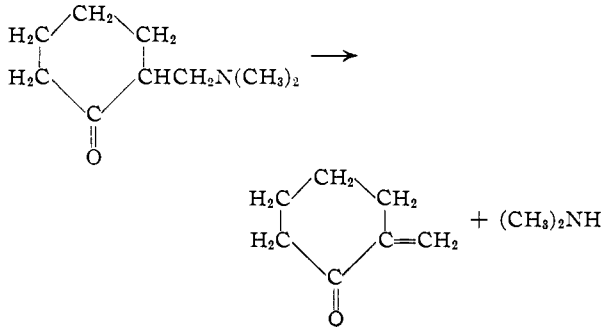
[a] All melting points are uncorrected. [b] A = ethanol; Æ = ethyl acetate; E = ethyl ether; H = hexane; M = methanol. [c] $(CH_2)_5N$ = piperidino. [d] $O(C_2H_4)_2N$ = morpholino.

afforded an alternative type of compound containing a basic side chain.

The 2,6 - dimethyl - 3,5 - dicarbethoxy - 4 - (4′-hydroxyphenyl)-1,4-dihydropyridine (A, see below) was prepared[2] by condensation of *p*-hydroxybenzaldehyde, acetoacetic ester and ammonia. This phenolic dihydropyridine then readily reacted with formaldehyde and secondary amines to give the series of Mannich bases listed in Table I.



One of the compounds in Table I (II) is a quaternary methiodide made from I. The poor yield as well as the unfavorable results obtained in attempts to make the corresponding methiodides from one or two of the other Mannich bases suggests that these salts are rather unstable. Although it is well-known that many Mannich bases are relatively unstable, usually these are cases in which by elimination of the elements of the secondary amine an unsaturated compound can result, such as



In the examples described in the present paper some other basis for instability must be considered.

(2) L. E. Hinkel and W. R. Madel, *J. Chem. Soc.*, 750 (1929).

Experimental

Preparation of the Mannich Bases.—A mixture of the 4-(4′-hydroxyphenyl)-dihydropyridine, A (0.02 *M*), formaldehyde (0.022 *M*, as formalin), the secondary amine (0.022 *M*) and 70 cc. of ethanol was heated for four hours on a steam-bath allowing the alcohol to evaporate slowly. After cooling and scratching the oily product gradually crystallized. After purification by recrystallization from the appropriate solvents the results recorded in Table I were obtained.

Acknowledgment.—The author wishes to express appreciation to Mr. Samuel W. Blackman who obtained the microanalytical results included.

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, N. Y. RECEIVED DECEMBER 29, 1950

Pyrolysis of Perfluoro-*n*-pentane[1]

BY GAIL C. ROGERS AND GEORGE H. CADY

In spite of the fact that the high degree of stability of fluorocarbons is now well known, little specific information regarding either the temperatures required to bring about pyrolysis or the nature of the products formed has been published. This note reports the results of a brief and only partially complete study of the pyrolysis of a single saturated fluorocarbon, perfluoro-*n*-pentane, *n*-C_5F_{12}.

Before the work could be started it was necessary to find a material suitable for the construction of the reaction vessel. Glass and silica offer problems, because at high temperatures they react with fluorocarbons.[2] It was found that both stainless steel and tungsten react rapidly with carbon tetrafluoride at 1000° but that platinum is attacked only very slowly, even at 1500°. With this information at hand a reaction vessel was constructed from a one-liter Pyrex glass flask having at its center a coil wound from a 23 cm. length of 0.0255 cm. diameter platinum wire. During a run, the glass remained cool enough to avoid reaction with the fluorocarbon, while the wire was heated electrically to a desired temperature in the neighborhood of 1000°. Several runs were made to learn the effect of the temperature of the wire upon the reaction. The reaction was followed by the change in pressure of the gas and by measuring the density of the gas. An optical pyrometer was used to

(1) From the M.S. degree thesis of Gail C. Rogers, 1948.
(2) L. White, Jr., and O. K. Rice, THIS JOURNAL, **69**, 267 (1947).

TABLE I

PYROLYSIS OF n-C_5F_{12}

Temp. Pt filament, °C.	Approx. half time of reaction, min.	Initial pressure C_5F_{12} vapor	Volatile products Moles per mole of C_5F_{12} used CF_4	C_2F_6	C_3F_6	C_3F_8 + C_3F_8	C_4F_8 + higher FC's	Solid polymer, g./mole of C_5F_{12} used
840	∞	150						
900	300	155	0.0	0.0	..	0.4	0.8[a]	12
940	60	262	.0	.2	0.33	.8	.4	5.5
960	12	153	.0	> .14	..	.7	.2	10
1150	3	155	.02	.9	0.38	.6	.2	9
1325	<2	219	.005	1.1	..	.14	.0	37

[a] Most of this material was unreacted C_5F_{12}.

measure the temperature of the filament and it is probable that the temperatures so observed were correct to within about 20°. After the reaction appeared to be complete, the products were identified by making an analytical fractional distillation using a very small fractionating column. Vapor densities and boiling ranges of the different cuts were measured, and in two runs the C_3 cut was chlorinated to permit determination of perfluoropropene. Under these conditions pyrolysis of the fluorocarbon was not detected at 840° and it was slow when the filament was held at 900°. As the temperature was increased above this value the rate became much greater.

The clearly identified reaction products were CF_4, C_2F_6, C_3F_8 and C_3F_6 (perfluoropropene). Evidence was also obtained for the presence of one or more forms of C_4F_8. A high polymer having properties of polytetrafluoroethylene collected on the walls of the flask. A trace of a black material, thought to be free carbon, because it disappeared when heated in air, formed on the hot filament.

Results of the different runs are summarized in Table I. Data regarding rates are too few in number to justify their consideration as a means of determining the order of the reaction. The proportions of the different products as given are not to be regarded as very accurate; however, they do indicate in general the influence of temperature upon the composition of the product.

While the observations do not permit one to draw definite conclusions about the mechanism of the reaction, they do furnish some basis for speculation. The data are in accord with a mechanism in which a molecule of C_5F_{12} may dissociate in either of two ways

$$C_5F_{12} = C_2F_4 + C_3F_8 \quad (1)$$

$$C_5F_{12} = C_2F_6 + C_3F_6 \quad (2)$$

If C_2F_4 is formed, it disappears due to rapid polymerization to yield one or more forms of C_4F_8, and $(CF_2)_n$. A part of the perfluoropropene, C_3F_6, may also polymerize. Carbon tetrafluoride may be formed at the higher temperatures due to the decomposition of fluorocarbons resulting from the first steps of the pyrolysis of C_5F_{12}. If reactions 1 and 2 are the primary reactions, it follows that reaction 1 predominates at about 900° and that reaction 2 is the more prevalent at the higher temperatures.

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DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASH. RECEIVED JANUARY 24, 1951

The Reaction of Benzyl Chloride with n-Heptylmagnesium Bromide[1]

BY ROBERT W. SCHIESSLER, RHOADS M. SPECK[2] AND JOSEPH A. DIXON

The effect of a number of aliphatic Grignard reagents on benzyl chloride and substituted benzyl chlorides at 100° has been studied by Späth.[3] Fair yields of the normal reaction products were obtained. From the reaction of methyl or ethyl Grignard reagents with benzyl chloride, a product later shown[7] to be 1-benzyl-4-(phenylethyl)-benzene was isolated. Miller and Bachman[4] examined the action of phenyl-, n-butyl, n-amyl- and cyclohexylmagnesium bromide and ethylmagnesium iodide on 9-chlorofluorene (a "benzyl" type halide). They found that in ether solution only ethylmagnesium iodide gave an appreciable yield of alkylfluorene. The other Grignard reagents produced 70 to 95% yields of bifluorenyl, in either benzene or ether solution.

Earlier in this Laboratory[5] it was found that the action of n-heptylmagnesium bromide on benzyl chloride produced a high yield of bibenzyl instead of the coupling product, phenyloctane. The present investigation was undertaken to determine other products of the reaction and to gain some understanding of this result, since with allyl bromide and a normal alkyl Grignard reagent the yield of coupling product is usually about 90%.

Benzyl chloride was added to a filtered[6] ether solution of n-heptylmagnesium halide. Aliquots were removed at regular intervals to follow the disappearance rates of the Grignard reagent and halide. Concentrations of the two reactants were determined by an hydrolysis procedure, plots of log concentration of Grignard reagent and benzyl chloride *vs.* time appear in Fig. 1.

(1) American Petroleum Institute Project 42. Presented before the Organic Division American Chemical Society, Atlantic City, N. J., 1949.

(2) American Petroleum Institute Research Fellow. Abstracted from an M.S. thesis by Rhoads M. Speck, 1949.

(3) Späth, *Monatsh.*, **34**, 1965 (1913).

(4) Miller and Bachman, THIS JOURNAL, **57**, 766 (1935).

(5) F. B. Fiseld and R. W. Schiessler, unpublished data.

(6) See Experimental.

For the first 40% of the reaction (after all the benzyl chloride had been added) straight line relationships were obtained and the slopes of the curves are roughly equivalent. Approximately 25% of the Grignard reagent and benzyl chloride disappeared during the addition of the benzyl chloride, which required one hour. After 5.25 hours, when about 75% of the *n*-heptylmagnesium bromide and benzyl chloride had been consumed, the temperature control was lost.

The reaction products were separated by fractional distillation and identified by the physical properties of the fractions. The products and yields are shown in Table I.

TABLE I

Products	Yields Moles[a]	Mole %[b]	Wt. %[c]
n-Heptane	1.68	46.5	24.5
1-Heptene	1.11	30.8	15.9
Benzyl chloride	0.34	9.4	6.2
Bibenzyl	1.14	63.2	30.3
1-Phenyloctane	Trace	..	..
n-Tetradecane	Trace	..	..
1-Benzyl-4-phenylethylbenzene[7]	0.04	2.2	1.5
Unidentified	..	..	21.6

[a] Although 4.38 moles of Grignard reagent and the same amount of benzyl chloride were charged, 17.6% of the original volume was lost by the removal of aliquots and spurting of the reaction mixture when aliquots were taken. Thus 3.61 moles of each reactant would yield 687 g. of products. [b] The mole % is based on 3.61 moles of each reagent and assuming the reaction: $2C_6H_5CH_2Cl + 2C_7MgBr = C_6H_5CH_2CH_2C_6H_5 + C_{7(+H)} + C_{7(-H)} + 2Mg(Br)Cl$. [c] The weight % is based on the 687 g. of products as noted in (*a*).

There appears to be a relation between the amounts of *n*-heptane, 1-heptene and bibenzyl that are formed. If the heptane formed from decomposition of the unreacted Grignard reagent (0.37 mole) is deducted, the amounts of *n*-heptane and 1-heptene found are 1.31 and 1.11 moles, respectively. Therefore, it appears from the bibenzyl equivalents isolated (1.18 moles) that for every mole of bibenzyl approximately one mole each of *n*-heptane and 1-heptene is formed. The proportion probably is even more exact since some bibenzyl undoubtedly was lost during purification.

Although the amount of metallic impurities present was extremely small (maximum 3×10^{-2} mole %), their concentration may be sufficient to initiate a free radical reaction of the type suggested by Kharasch, *et al.*[8,9] This postulation assumes the formation of an intermediate organo-metallic compound, $C_7H_{15}MBr$, which may dissociate into two free radicals, $C_7H_{15}\cdot$ and $\cdot MBr$. Disproportionation of the heptyl radical would account for the formation of equivalent amounts of *n*-heptane and 1-heptene. The benzyl halide is presumed necessary to regenerate MBrX so that the chain can be continued. In the case of ethyl, *n*-propyl and *n*-butyl halides, Kharasch[10] found that the corresponding radicals do not dimerize to any appreciable extent, if at all, but disproportionate to alkanes and alkenes. This was found to be the case with *n*-heptyl bromide in the present study, for a negligible amount of tetradecane was found. Furthermore, the mechanism accounts for the formation of nearly equivalent amounts of bibenzyl, *n*-heptane and 1-heptene. If any benzylmagnesium bromide was formed during the reaction, it probably reacted with benzyl chloride to give bibenzyl since no toluene was isolated. In the reaction only a small amount of phenyloctane was formed, and thus the "allylic" coupling reaction seems to be much slower than some of the others.

If "free and uncombined" alkyl radicals were formed during the reaction, it is probable that they would attack the solvent, producing a preponderance of heptane over heptene. The data, however, do not agree with this idea. Perhaps the radicals are not "free," but combined in some sort of complex from which they can disproportionate.[11]

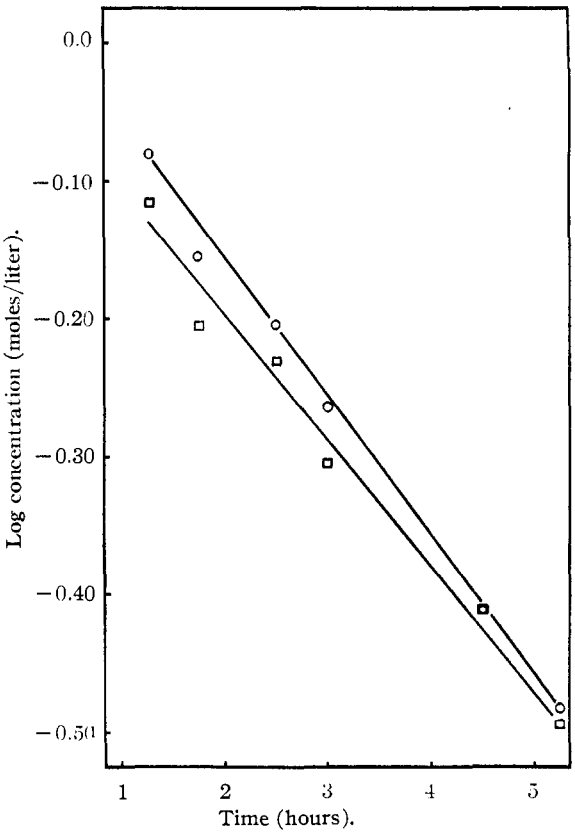

Fig. 1.—Log concentration *vs.* time: O, benzyl chloride; □, *n*-C_7MgBr.

Experimental

Magnesium.—The Dow Chemical Co. furnished the following analysis: aluminum, 0.003%; copper, 0.003; iron, 0.03; manganese, 0.08; nickel, 0.001; silicon, 0.005; magnesium (by difference), 99.878.

***n*-Heptyl Bromide.**—*n*-Heptanol (Columbia Organic Chemical Co.) was purified by fractional distillation,[12a] b.p. 177° (738 mm.), $n^{20}D$ 1.4238. The alcohol was saturated with

(7) Fuson, THIS JOURNAL, **48**, 2937 (1926), has shown that this product is probably formed from bibenzyl and benzyl chloride during distillation of the reaction mixture rather than during the actual process of the Grignard reaction.

(8) Kharasch and Fuchs, *J. Org. Chem.*, **10**, 292 (1945).

(9) Kharasch, Lambert and Urry, *ibid.*, **10**, 298 (1945).

(10) Kharasch, Lewis and Reynolds, THIS JOURNAL, **65**, 493 (1943).

(11) Kharasch and Urry, *J. Org. Chem.*, **13**, 10 (1948).

(12) (a) The columns are of the total condensation-partial takeoff type, packed with carefully sorted 3/32" single turn glass helices. The columns had packed sections of 2.5 × 90 cm. and 35–40 theoretical plates. (b) Same as (12a) except that packed section was 1.5 × 46 cm.

anhydrous hydrogen bromide (Dow Chemical Co.) at 110–115° to constant weight. After separation of the aqueous layer the organic material was chilled to 2°, washed with two ice-cold portions of concentrated sulfuric acid, 3% ammonia water, twice with water, and dried over anhydrous calcium chloride followed by anhydrous potassium carbonate. Fractional distillation[12a] gave the purified bromide, b.p. 111° (96 mm.), $n^{20}D$ 1.4500, in 85% yield.

Benzyl Chloride.—Fractional distillation[12a] of Eastman Kodak Co. White Label benzyl chloride yielded pure material: b.p. 124° (150 mm.), $n^{20}D$ 1.5386.

The Grignard reagent prepared in 2500 ml. of anhydrous ether from 121.5 g. (5 g. atoms) of magnesium and 860 g. (4.8 moles) of *n*-heptyl bromide was filtered from the excess magnesium. After standing 84 hours the Grignard reagent was pumped away from the sludge. It was heated to reflux (42°), and 554 g. (4.38 moles) of benzyl chloride added over a period of one hour. The reaction was continued for 44 hours, removing aliquots intermittently for analysis. The analytical data are shown in Table II. The product was

TABLE II

Sample	Time, hr.	Temp., °C.	Moles of Grignard	Moles of $C_6H_5CH_2Cl$
1	0	20	4.38	0.0
2	1.25	42	3.42	3.13
3	1.75	41	2.86	2.54
4	2.5	41	2.43	2.29
5	3	42	2.11	1.95
6	4.5	41.5	1.39	1.39
7	5.25	41.5	1.18	1.15
8	7.5	38	0.76	0.70
9	9	36	.69	..
10	13.75	33	.55	.53
11	20	32	.45	.45
12	44	28	.37	.33

hydrolyzed on ice and the organic material separated by ether extraction. After removal of the ether, fractionation[12b] of the organic material led to the isolation of an unidentified low boiling material: 35.7 g., b.p. 51–52.5°, $n^{20}D$ 1.3604–1.3929; 280.3 g. of heptane and heptene; 42.6 g. of unreacted benzyl chloride; 41.4 g. of a complex high boiling material and a 286.5 g. of residue. Refractionation[13] of the heptane–heptene mixture yielded 109 g. (1.11 moles) of 1-heptene, b.p. 92.0–92.7°, $n^{20}D$ 1.3989–1.3998 and 168 g. (1.68 moles) of *n*-heptane, b.p. 97.0–97.3°, $n^{20}D$ 1.3877–3882. The hydrocarbons were identified by comparing their properties with those of the pure materials. The benzyl chloride fractions (50.9 g.) contained 42.6 g. (0.34 mole) of the halide as determined by the hydrolysis procedure.[14] An anilide prepared from the benzyl chloride had a m.p. 115–116°, mixed m.p. 114–115°. The residue was chilled to −5° to give 186 g. (1.02 moles) of bibenzyl, which after recrystallization from ether melted at 51–52°, mixed m.p. 51–52°. The liquid residue plus the high boiling fractions above were distilled through a high vacuum column,[15] at 1 mm. The following products were identified: an additional 21.8 g. (0.12 mole) bibenzyl; 2.0 g. of tetradecane, m.p. 5.5–6.5°, mixed m.p. 6.0–6.5°; 10 g. (0.04 mole) benzylphenylethylbenzene, mol. wt. calcd. 273, found 265, mol. ref. calcd. 88.5, found 86.7, $n^{20}D$ 1.5929,[7] found 1.5941. A few fractions (5.2 g.), which were suspected to contain 1-phenyloctane, were selectively adsorbed on silica gel. Two-tenths gram of material was obtained which is believed to be 1-phenyloctane; $n^{20}D$ 1.4847,[16] found 1.4846–1.4850, m.p.[16] −37.0°, found −43 to −36°. The bulk of the fractions could not be identified but from their properties appeared to be mixtures of polyaromatics.

(13) The column was of the total condensation, partial take-off type packed with 3/64" stainless steel helices. The column, with a packed section 1.1 × 75 cm., had 80 theoretical plates.

(14) The fractions had amounts of benzyl chloride varying from 33–100%. Qualitative tests showed no halogen present but chlorine; however analysis for total halogen indicated that some additional chlorine-containing compound was present in these fractions. This could not be identified and amounted to approximately 4 g.

(15) Nine to ten theoretical plates. To be described in a separate publication to be submitted to *Analytical Chemistry*.

(16) Schiessler, *et al.*, *Proc. A.P.I.*, **26** (III), 254–302 (1946).

Analysis of the $C_6H_5CH_2Cl$–RMgX Mixtures.—*n*-Heptylmagnesium bromide was determined using a procedure similar to Gilman's[17] except that the heating operation was avoided. After the addition of the sample to 50 ml. of cold distilled water, a measured excess of standard acid was added. The mixture was allowed to stand for one-half hour at 25° and then the acid neutralized with standard base. This titration yielded the amount of RMgX present. The method of estimating benzyl chloride in the presence of *n*-heptylmagnesium bromide depends on the difference in the rate of hydrolysis of the two compounds.

After the Grignard titration, the benzyl chloride was determined by adding 50 ml. of 0.2 *N* NaOH and making the solution up to a volume of about 150 ml. To the alkaline solution was added 60 ml. of 95% ethanol; thus the solution was approximately 0.045 *N* NaOH in 27% ethanol. Hydrolyses were carried out at the reflux temperature of the mixture for one-half hour. After cooling, excess alkali was titrated with standard acid. A blank determination was run. Analyses of synthetic mixtures indicated an accuracy of ±2% and infrared analyses of two mixtures for benzyl chloride agreed within ±2% of the titration values.

Acknowledgment.—The authors express their appreciation to the American Petroleum Institute for the grant which made this research possible.

(17) Gilman and Meyers, THIS JOURNAL, **45**, 159 (1923).

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STATE COLLEGE, PENNA. RECEIVED NOVEMBER 11, 1950

Dehalogenation of 2-Amino-4-methyl-6-chloropyrimidine

BY D. SHAPIRO

Hydrogen is evolved vigorously from an alcoholic or aqueous solution of ammonium chloride, when heated with zinc in presence of Raney nickel. It appears that Raney nickel catalyzes the otherwise sluggish[1,2] reaction

$$2NH_4Cl + Zn \longrightarrow ZnCl_2 + 2NH_3 + H_2$$

Part of the ammonia, liberated according to this equation, accompanies the hydrogen; part is bound by the zinc salt.

The above system was found to dehalogenate smoothly 2-amino-4-methyl-6-chloropyrimidine to the 2-amino-4-methyl compound which is an intermediate in the synthesis of sulfamerazine.[3]

A solution of 20 g. of 2-amino-4-methyl-6-chloropyrimidine[4] in a mixture of 16 cc. of concentrated hydrochloric acid and 250 cc. of water (40–50°) was neutralized with a solution of 7 g. of sodium hydroxide in 100 cc. of water, with vigorous stirring; the temperature was raised to 70–75°, and 20 g. of ammonium chloride and 1.5 g. of Raney nickel added. Over a period of 90 minutes, 40 g. of zinc dust was introduced, causing a lively effervescence of the mass. (Occasionally, it was found advisable to add another 2 g. of Raney nickel to the mixture.) Stirring and heating were continued for one more hour and, after addition of a solution of 26 g. of sodium hydroxide in 80 cc. of water, for 30 more minutes and at 90–95°. The solid was removed by filtration, washed with hot water, and the filtrate evaporated *in vacuo* to a volume of about 200 cc. At boiling temperature, 100 cc. of 30% sodium hydroxide solution was added. After 12 hours, the crystals of 2-amino-4-methyl-pyrimidine were filtered and dissolved in boiling acetone. The filtered solution, upon concentration, gave 12 g. (80%) of product of correct m.p. 159–161°. The method is quicker

(1) Ritthausen, *J. prakt. Chem.*, **60**, 473 (1893).
(2) Drucker, *Z. Elektrochem.*, **29**, 412 (1923).
(3) Roblin, *et al.*, THIS JOURNAL, **62**, 2002 (1940).
(4) Gabriel and Coleman, *Ber.*, **32**, 2921 (1899).

and more reliable than the reduction with zinc dust and water, described by Gabriel and Coleman.[4]

An attempt was also made to reduce 4-methyl-2,6-dichloropurine[5] by the same method. According to E. Fischer,[6] however, the expected 7-methyl-2-chloropurine is not stable in contact with dilute alkali, but is converted into 7-methyl-2-hydroxypurine (m.p. 323°) and an unidentified substance of the composition $C_5H_7ClN_4$ (m.p. 251°). Indeed, two substances of these melting points, respectively, were isolated, when the reaction product was worked up.

(5) E. Fischer, *ibid.*, **30**, 2400 (1897).
(6) E. Fischer, *ibid.*, **31**, 2550 (1898).

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REHOVOTH, ISRAEL RECEIVED MARCH 1, 1951

Integral Diffusion Coefficients of Potassium Chloride Solutions for Calibration of Diaphragm Cells

BY R. H. STOKES

Gosting[1] has recently obtained absolute measurements of the differential diffusion coefficients of potassium chloride in water at 25° from 0.1 N to 3.9 N by the Goüy interference technique. Harned and Nuttall,[2] using a conductimetric method, have also obtained absolute values in the range 0.00125 N to 0.5 N, which are in extraordinarily good agreement with those of Gosting in the overlapping part of the range. Thus the combined data may be used with complete confidence for testing and calibrating other types of diffusion apparatus. For diaphragm-cell measurements, however, it is convenient to start the diffusion with solution on one side of the diaphragm and pure water on the other,[3] in which case the diffusion coefficient obtained is a rather complicated average value, $\bar{D}$, called the "diaphragm-cell integral coefficient."

Under these conditions, denoting the mean of the initial and final concentrations on the solution side by $c_{m'}$, and the mean concentration on the other side by $c_{m''}$ (which is half the final concentration on the side which was initially pure water), it has been shown[3] that

$$\bar{D}^0_{(c_{m'})} = \bar{D} - \frac{c_{m''}}{c_{m'}}[\bar{D} - \bar{D}^0_{(c_{m''})}] \qquad (1a)$$

or

$$\bar{D} = \left[\bar{D}^0_{(c_{m'})} - \frac{c_{m''}}{c_{m'}}\bar{D}^0_{(c_{m''})}\right] \Big/ \left(1 - \frac{c_{m''}}{c_{m'}}\right) \qquad (1b)$$

Here the quantity $\bar{D}^0_{(c)}$ is the "integral diffusion coefficient for a run of vanishingly short duration" between the concentration c and pure water, given by

$$\bar{D}^0_{(c)} = \frac{1}{c}\int_0^c D\,dc \qquad (2)$$

D being the true differential diffusion coefficient as measured for example by the optical or conductimetric methods. It is consequently very useful in diaphragm-cell work to have a table of values of the quantity $D^0_{(c)}$ for all values of c for the calibration solution, as it is then unnecessary to select a particular length of run or initial concentration of the calibration solution, and the cell may readily be checked for constancy of "cell constant" over a range of concentration. Table I provides these data, obtained by tabular and graphical integration of the results of Gosting and of Harned and Nuttall according to equation (2).

(1) L. J. Gosting, THIS JOURNAL, **72**, 4418 (1950).
(2) H. S. Harned and R. L. Nuttall, *ibid.*, **69**, 736 (1947); **71**, 1460 (1949).
(3) R. H. Stokes, *ibid.*, **72**, 763, 2243 (1950).

TABLE I

INTEGRAL DIFFUSION COEFFICIENTS OF POTASSIUM CHLORIDE SOLUTIONS AT 25°

$\bar{D}^0 = \frac{1}{c}\int_0^c D\,dc$. ($c$ in moles/liter, $\bar{D}^0$ in cm.^{2} sec.$^{-1}$ × 10^{-5})

c	$\bar{D}^0$	c	$\bar{D}^0$	c	$\bar{D}^0$
0.000	1.996	0.05	1.893	1.4	1.874
.001	1.974	.07	1.883	1.6	1.882
.002	1.966	.1	1.873	1.8	1.892
.003	1.960	.2	1.857	2.0	1.901
.005	1.951	.3	1.850	2.5	1.927
.007	1.945	.5	1.848	3.0	1.953
.01	1.938	.7	1.851	3.5	1.979
.02	1.920	1.0	1.859	3.9	2.000
.03	1.908	1.2	1.866		

TABLE II

FURTHER DIAPHRAGM CELL MEASUREMENTS ON POTASSIUM CHLORIDE SOLUTIONS AT 25°

$c_{m'}$ in moles/liter, $\bar{D}^0_{c_{m'}}$ in cm.^{2} sec.$^{-1}$ × 10^{-5}

$c_{m'}$	$\bar{D}^0_{c_{m'}}$	$c_{m'}$	$\bar{D}^0_{c_{m'}}$
0.3877	1.853	0.8721	1.854
.3911	1.849	.8344	1.854
.6310	1.842	.8820	1.851
.6188	1.851	.8972	1.852
.6462	1.851		

In the figure, the data of Table I are compared graphically with the diaphragm-cell results previously reported by the writer.[3] (The open circles on this graph represent the means of each pair of approximately duplicate runs reported in Table III of reference (3).) It is clear that, though the average deviation of the points from the standard curve is less than 0.3%, most of this deviation is due to the points near the minimum. As the measurements represented by these points hap-

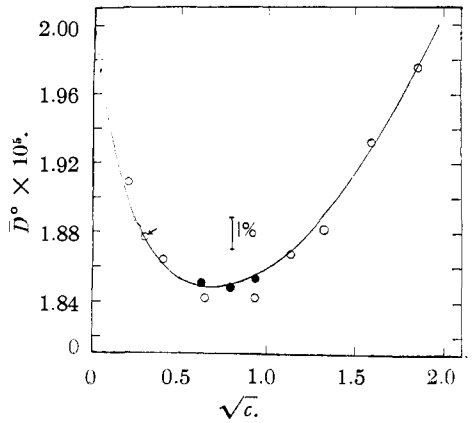

Fig. 1.—Integral diffusion coefficients of potassium chloride at 25°: full curve, calculated from differential values of Gosting, Harned and Nuttall (Table I); open circles, original diaphragm-cell measurements (reference 3); filled circles, new measurements (Table II); arrow, calibration point for diaphragm-cells.

pened to be among the earliest made in the development of the magnetically-stirred diaphragm-cell, and were possibly not of the standard of precision obtained later, it seemed worthwhile to make some further measurements in this region. The technique used was closely similar to that described in reference (3), and gave the results in Table II, where the $\bar{D}$ values have been converted to D^0 values by the use of equation (1a). The means of the four new measurements using initially 1 N potassium chloride solution, the three using initially 0.7 N solution and the two using initially 0.45 N solution are shown as filled circles in the figure. It is evident that the original measurements near the minimum were in error by two or three times the estimated experimental error of 0.2%. In consequence of this, the smooth curve drawn through the open circles was appreciably different in shape near the minimum from what it should have been. Hence the differential diffusion coefficients obtained from it and reported in reference (3) differ in some cases by nearly 1% from those reported by Gosting.[1] It would appear that in using the diaphragm-cell method especially great care should be taken in regions of rapid change of slope of the integral diffusion coefficient. With this reservation it is clear that the diaphragm-cell measurements agree very well with the new absolute data obtained by Gosting.

In conclusion it would perhaps be as well to mention that in calibrating diaphragm-cells with the use of Table I, it is unwise to use any solution below 0.1 N in concentration at the start of the experiment, as at lower concentrations the anomalous surface-transport effect[3] becomes prominent.

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NEDLANDS, W. A. RECEIVED FEBRUARY 23, 1951

Allyl Butyl Ethers[1]

BY E. A. TALLEY, ANN S. HUNTER AND E. YANOVSKY

It has been suggested that in our work on allyl starch,[2] one of the butyl alcohols might serve as a reaction solvent. The obvious objection to the use of alcohols in this reaction is the formation of ethers at the expense of allyl halide used for the main reaction. When an attempt was made to separate the allyl butyl ethers by fractionation of the organic layer of the reaction, azeotropes of the ether and alcohol were obtained.[3] Since attempts to separate the two by extracting the butyl alcohols with water were unsuccessful, at least in the case of normal and isobutyl alcohols, it was deemed advisable to learn more about the properties of pure allyl butyl ethers. In the literature, only the allyl isobutyl ether has been reported.[4] It was prepared by catalytic dehydration of a mixture of the two corresponding alcohols. The boiling point (108–110°) was the only property given. We have, therefore, prepared the four allyl butyl ethers and determined some of their properties.

Experimental

Preparation and Properties of Allyl Butyl Ethers.—All ethers were prepared in the same manner. One to one and a half moles of butyl alcohol in 200 to 300 cc. of xylene was placed in a 1-liter three-necked flask furnished with a condenser, a stirrer and a separatory funnel. An equimolar quantity of sodium was gradually added to the solution. After the entire amount of sodium had been added, the reaction slowed down somewhat owing to coating of alkoxide on the metal. At this point, the bath temperature was raised to about 115° and the stirrer was started. The sodium melted, and the reaction proceeded. After all the sodium had disappeared, the flask was cooled to room temperature, and an equimolar amount of allyl bromide was gradually added through the separatory funnel. When the entire amount of allyl bromide had been added, the bath temperature was raised to 110–115° and kept at this temperature for about five hours. If any blue color remained at this time, methanol was added until the blue color disappeared. The mixture was then washed with water, dried and distilled. The theoretical amounts of allyl bromide were used for convenience of procedure at the expense of better yields. Under the conditions of the experiments, the yields were about 25% for the allyl *t*-butyl ether, 40% for the ether of isobutyl alcohol and 60% for the ethers of normal and secondary butyl alcohols.

Table I gives the properties of the four ethers.

TABLE I

PROPERTIES OF ALLYL BUTYL ETHERS

Butyl group	Allyl (by Wijs), % (theory, 36.0%)	B.p., °C.	Mm.	d^{20}_4	$n^{20}D$	Mole refraction Calcd.[a]	Found
Normal	36.0	117.8–118.0	763	0.7829	1.4057	35.87	35.80
Secondary	36.0	107.1–107.4	762	.7792	1.4023	35.70	35.70
Iso	36.0	106.6–107.0	749	.7735	1.4008	35.90	35.85
Tertiary	36.1	99.2–100.0	760	.7770	1.4011	35.83	35.71

[a] A. I. Vogel, *J. Chem. Soc.*, 1842 (1948).

(1) Contribution from one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) P. L. Nichols, Jr., R. M. Hamilton, Lee T. Smith and E. Yanovsky, *Ind. Eng. Chem.*, **37**, 201 (1945); R. A. Talley, R. M. Hamilton, J. H. Schwartz, C. A. Brown and E. Yanovsky, U. S. Dept. Agr., Bur. Agr. and Ind. Chem., AIC-140, (Eastern Regional Research Laboratory) Feb. 1947 (Processed).

(3) *Cf.* D. N. Kursanov and O. M. Shemyakina, *Doklady Akad. Nauk S. S. S. R.*, **62**, 341–343 (1948); C. A., **43**, 2159*b* (1949).

(4) A. Mailhe and F. de Godon, *Bull. soc. chim.*, [4] **27**, 328 (1920).

EASTERN REGIONAL RESEARCH LABORATORY
PHILADELPHIA 18, PENNA. RECEIVED MARCH 1, 1951

Unsaturated Lactones. II. The Relationship Between Chemical Constitution and Absorption Spectra in a Group of Crotonolactones[1]

BY F. W. SCHUELER AND CALVIN HANNA

In a previous report[2] we had occasion to discuss the relationship between chemical constitution and the ultraviolet absorption spectra in a group of unsaturated azlactone derivatives. In the present communication we have extended this discussion to include a series of crotonolactones which derive part of their interest from the close chemical and physical similarities that they hold with respect to the unsaturated azlactones.

Out of a group of twenty crotonolactones[3] synthesized during this investigation four were re-

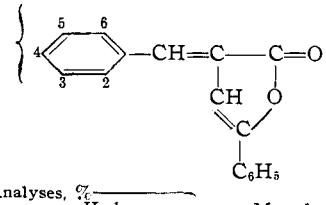
(1) This work was aided by a grant from the U. S. Public Health Service.

(2) F. W. Schueler and S. C. Wang, THIS JOURNAL, **72**, 2220 (1950).

(3) These together with the azlactones and a group of related materials have been studied for cardiac activity and reported elsewhere. F. W. Schueler and C. Hanna, *Arch. Intern. Pharmacodyn. et Therapie*, in press, 1951.

TABLE I

α-BENZAL-γ-PHENYLCROTONLACTONE DERIVATIVES R'



No.	R'	M.p., °C	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Max. 1 mμ	Max. 1 ε × 10⁴	Max 2 mμ	Max 2 ε × 10⁴
1	2-NO_2–	202	$C_{17}H_{11}O_4N$	69.64	69.22	3.78	3.55	246	2.51	380	1.99
2	3-NO_2–[4]	208						254	1.67	385	1.67
3	2,6-di-Cl–	170	$C_{17}H_{10}O_2Cl_2$	64.37	64.05	3.18	3.08	250	2.12	360	2.44
4	2-Cl–	164	$C_{17}H_{11}O_2Cl$	72.22	71.99	3.92	3.73	252	2.12	388	2.52
5	3-CH_3C–OO–	134	$C_{19}H_{13}O_4$	74.74	74.17	4.29	4.11	250	1.44	388	1.98
6	No subs.[5]	155						250	1.87	384	2.97
7	2,3-di-CH_3O– (o.)[a]	141	$C_{19}H_{16}O_4$	74.01	74.36	5.23	5.75	252	2.53	389	3.43
8	4-CH_3COO–	193	$C_{19}H_{13}O_4$	74.74	74.52	4.29	4.20	252	2.10	395	3.07
9	4-CH_3–	150	$C_{18}H_{17}O_2$	82.42	82.81	6.54	6.72	250	1.82	393	3.49
10	4-iso-C_3H_7–	88	$C_{20}H_{18}O_2$	82.73	82.58	6.25	6.46	250	1.74	400	2.86
11	4-CH_3COO-3-CH_3O- (o.)[a]	158	$C_{20}H_{16}O_5$	71.42	71.15	4.80	4.86	253	2.72	394	3.87
12	3-Cl-4,5-di-CH_3O–	160	$C_{19}H_{15}O_4Cl$	66.43	66.51	4.41	4.17	255	2.78	400	4.57
13	4-CH_3O–[5]	171						253	1.85	402	3.51
14	α-Furfural (br.)[a,b]	116	$C_{16}H_{10}O_3$	75.62	75.25	4.23	4.02	259	1.78	405	3.81
15	4-NO_2–	295	$C_{17}H_{11}O_4N$	69.64	69.37	3.78	3.39	256	0.76	415	0.72
16	3,4-OCH_2O–	177	$C_{18}H_{12}O_4$	73.96	73.58	4.14	4.02	256	2.52	408	4.52
17	β-Phenylvinyl[5] (o.)[a,b]	154						260	1.43	411	3.52
18	3,4-di-CH_3CH_2O–	128	$C_{21}H_{20}O_4$	74.99	74.55	5.99	5.63	258	1.37	412	2.62
19	β-Furylvinyl (br.)[a,b]	143–144.5	$C_{17}H_{12}O_3$	77.26	77.43	4.58	4.69	259	0.50	424	1.77
20	4-$(CH_3)_2N$– (r.)[a]	175	$C_{19}H_{17}O_2N$	77.70	77.05	5.88	5.52	249	1.84	462	5.36

[a] All compounds had a yellow color except as otherwise noted, thus o. orange, r. red, br. brown. [b] These replace the benzal group.

corded in the literature and no spectroscopic data appear to have been reported on any of these materials. This is in direct contrast to the literature bearing upon the corresponding azlactones which have been widely investigated because of their importance as intermediates in the synthesis of amino acids, aryl acetic acids and many natural products. The crotonolactones synthesized in this study are detailed in Table I together with their absorption maxima, melting points and analysis.

A comparison of the colors and melting points of the crotonolactones with the azlactones of the previous study[2] reveals the fact that the parallel crotonolactones are uniformly more deeply tinted whereas the melting points hold no constant relationship. The color relationship is borne out by a study of the absorption spectra. Thus a comparison of the absorption maxima of the present series of crotonolactones with the parallel series of azlactones previously discussed[2] reveals that the crotonolactones are in general more bathochromic but otherwise exhibit a parallel behavior with regard to substitution. Curves illustrating the relationship between spectra in these series are given in Fig. 1.

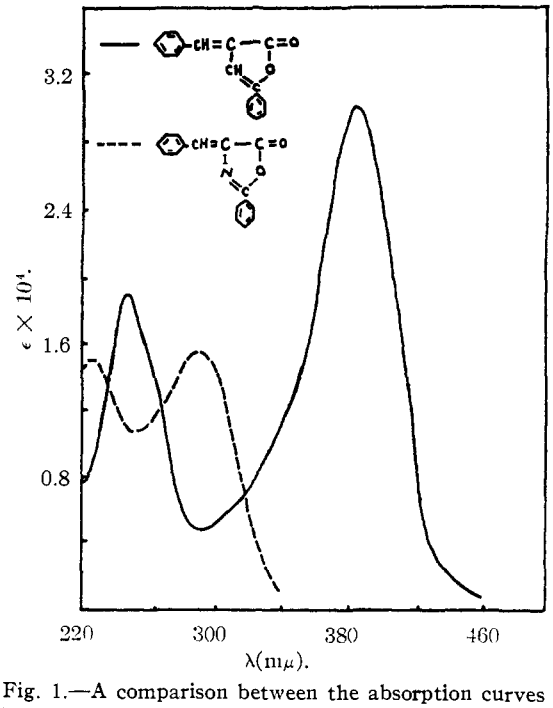


Fig. 1.—A comparison between the absorption curves of α-benzal-γ-phenylcrotonolactone (No. 6 of Table I) and the analogous azlactone, 2-phenyl-4-benzal-5-oxazolone.

Experimental

Absorption Spectra.—All spectra were determined with a Beckman quartz spectrophotometer, model DU, using ethanol as a solvent as outlined previously.[2]

Preparation of Materials.—The crotonolactones were prepared by the following general procedure: A mixture of 0.05 mole of the aldehyde, 0.05 mole of dry, powdered β-benzoylpropionic acid, 0.05 mole of freshly fused sodium acetate and 16 ml. of acetic anhydride was heated in a beaker on a hot-plate until a complete solution was obtained. The beaker was then transferred to a steam-bath and heating was continued until crystals separated. The reaction was next poured into water, the solid product filtered with suction, washed with water and finally recrystallized repeatedly

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

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

from 95% ethanol until a constant melting point was obtained. The yield, in general, ranged from 40–75%.

DEPARTMENT OF PHARMACOLOGY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA RECEIVED APRIL 3, 1951

Preparation of Methyl 2,3,4-Triacetyl-α-D-xyloside[1]

BY ROY L. WHISTLER, K. ANN KIMMELL AND DONALD F. DURSO

During the course of work in this Laboratory it became necessary to prepare methyl 2,3,4-triacetyl-α-D-xylopyranoside in fairly large quantities. Direct preparation of this compound from D-xylose involves the preparation of pure methyl α-D-xyloside and subsequent acetylation.[2] The procedure adopted in this work was to acetylate commercially available methyl β-D-xyloside to yield the corresponding triacetate,[3] from which the desired compound was easily prepared by isomerization with boron trifluoride using the procedure of Lindberg.[4] The yield of crystalline product was 85%.

Experimental

Methyl 2,3,4-Triacetyl-β-D-xyloside.—Commercially available crystalline methyl β-D-xyloside (15.00 g.) was acetylated at 110° with sodium acetate and acetic anhydride. The acetate was isolated in the usual manner and recrystallized from 95% ethanol. The yield was 23.85 g. of material whose m.p. 114.5–115.5° and $[\alpha]^{25}D$ −61.2 (*c*, 2.42 in chloroform) agreed with the constants previously reported.[3]

Anal. Calcd. for $C_6H_9O_5(CH_3CO)_3$: acetyl, 44.49. Found: acetyl, 44.3.

Methyl 2,3,4-Triacetyl-α-D-xyloside.—The β-compound (5.00 g.) was dissolved in 150 ml. of dry chloroform and the solution saturated with BF_3. Saturation was indicated by the formation of a white gelatinous precipitate in 10 min. The flow of gas was interrupted and the reaction flask stoppered. After 24 hours, the solution was treated with two 100-ml. portions of saturated sodium bicarbonate solution followed by three 150-ml. washes with water. The chloroform solution was dried over anhydrous sodium sulfate. Upon removal of the chloroform the product crystallized spontaneously. The yield was 4.29 g. After recrystallization from 95% ethanol, m.p. was 86–87° and $[\alpha]^{25}D$ +120.1 (*c*, 1.59 in chloroform). These values agreed with those previously reported for the desired product.[2]

Anal. Calcd. for $C_6H_9O_5(CH_3CO)_3$: acetyl, 44.49. Found: acetyl, 44.4.

(1) Paper No. 528 of the Purdue Agricultural Experiment Station.
(2) C. S. Hudson and J. K. Dale, THIS JOURNAL, **40**, 997 (1918).
(3) J. K Dale, *ibid.*, **37**, 2745 (1915).
(4) B. Lindberg, *Acta Chem. Scand.*, **2**, 426 (1948).

DEPARTMENT OF AGRICULTURAL CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA RECEIVED MARCH 12, 1951

β-Amyrin from *Chimaphila umbellata*[1a]

BY F. P. VEITCH, JR., AND PEARL ADAIR WELTON[1b]

During our investigation of the plant *Chimaphila umbellata* as a possible source of steroids having an oxygen function in the 11 or 12 position, a white crystalline material was isolated in 0.25% yield. From the physical constants of this compound and its derivatives (Table I) we have concluded that it is β-amyrin, a substance not previously reported as being present in this plant.

(1) (a) Obtained from S. B. Penick, New York. (b) Taken from a thesis submitted to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Master of Science.

Experimental

Four kilograms of air dry *Chimaphila umbellata* was obtained in a finely divided state by the use of a Williams crusher, rollers, and a Wiley mill. The finely ground material was treated by essentially the same process as that described by Marker[2] for the isolation of sapogenins from plant sources. Upon concentration of the final ethereal extract and addition of acetone, about 20 g. of crude crystalline material precipitated. Purification of this material was effected by recrystallization from acetone followed by formation of the acetate which could be crystallized from ethyl acetate. Saponification of the acetate followed by crystallization of the regenerated compound from ethyl alcohol gave 8.5 g. of material (0.21% yield based on the weight of air-dry plant) having the following characteristics: m.p. 200°; $[\alpha]^{20}D$ +87.7° (in $CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.43; H, 11.82. Found: C, 84.47, 84.58; H, 12.00, 12.00.

The acetate, benzoate and *p*-nitrobenzoate of this compound were prepared according to standard procedures. The physical constants of these derivatives and their analyses are summarized in Table I.

TABLE I[a]

Compound	M.p.,[b] °C.	$[\alpha]^{20}D$[d]	Analyses, %: Found[c] Carbon	Found[c] Hydrogen	Calculated Carbon	Calculated Hydrogen
β-Amyrin	200	+87.7	84.47	12.00	84.43	11.82
Acetate	243	+80.66	82.02	11.22	82.00	11.18
Benzoate	232	.....	83.68	10.57	83.71	10.26
p-Nitrobenzoate	257	.....	...	...	...	...

[a] The values reported here are in agreement with the values reported by other workers: *cf.* L. C. King, *et al.*, THIS JOURNAL **65**, 1168 (1943); A. Vesterburg, *Ber.*, **23**, 3186 (1890); N. H. Cohen, *Rec. trav. chim.*, **28**, 391; G. L. Powers, and W. E. Powers, *Pharm. Assoc.*, **29**, 175 (1940). [b] All melting points were determined on a Fisher-Johns melting point block. [c] We are indebted to Mrs. Mary Aldridge for the micro analyses reported here. [d] All rotations are in chloroform.

Values of 411 and 443 g. were obtained by the Rast method of molecular weight determination on the isolated compound, and 423 g. by the saponification method of the acetate. β-Amyrin has a molecular weight of 426 g.

(2) R. Marker, *et al.*, THIS JOURNAL, **69**, 2167 (1947).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MARYLAND
COLLEGE PARK, MARYLAND RECEIVED MARCH 7, 1951

The Melting Point and the Heat of Sublimation of Plutonium Trifluoride[1]

BY EDGAR F. WESTRUM, JR., AND JAMES C. WALLMANN

Careful measurements by an effusion technique of the equilibrium vapor pressures over plutonium trifluoride (PuF_3) have been reported.[2a,b] The slight deviation from linearity of the log *p versus* $1/T$ plot was represented by these authors without a stated reason as two straight lines intersecting at 1169 ± 9°, which temperature was interpreted as the melting point of plutonium trifluoride.

(1) Based on work reported in MB-IP 327, September 17, 1948, issued as Report UCRL-697 (May 19, 1950).

(2) (a) T. E. Phipps, G. W. Sears, R. L. Seifert and O. C. Simpson, *J. Chem. Phys.*, **18**, 713 (1950); (b) T. E. Phipps, G. W. Sears, R. L. Seifert, and O. C. Simpson, National Nuclear Energy Series, Plutonium Project Record, Vol. 14B, "The Transuranium Elements: Research Papers," Paper No. 6.1a (McGraw-Hill Book Co., Inc., New York, N. Y., 1949).

The heat of fusion was reported as 7.9 ± 0.5 kcal. mole^{-1} with a heat of sublimation of 96.6 ± 0.5 kcal. mole.$^{-1}$ Inasmuch as the deviation from linearity may alternatively be accounted for by assuming a reasonable ΔC_p for the sublimation process and as the reported melting points are rather lower than would be expected from comparison with other fluorides,[3] we have undertaken a determination of the plutonium trifluoride melting point in the apparatus shown in Fig. 1. An inconclusive attempt to determine the melting point of 60 micrograms of plutonium trifluoride on a tantalum filament in purified argon yielding successive values of 1435, 1560 and 1635° has been reported by Robinson.[4] X-Ray diffraction examination indicated the formation of plutonium oxyfluoride (PuOF) in the sample. For the present work about 350 mg. of plutonium trifluoride was prepared by hydrofluorination in a platinum reactor[5] of uranium-free, spectroscopically pure plutonium dioxide. X-Ray diffraction examination and spectrochemical analyses after the measurements confirmed the purity and crystalline phase of the plutonium trifluoride and the absence of corrosion of the tantalum. The trifluoride was pelleted into an annular cylinder, placed in the tantalum crucible and a previously outgassed beryllia microfurnace. The microfurnace assembly was then placed within a bulb attached to a high vacuum apparatus. After outgassing the system, the transition temperature was then located by thermal analysis.

Continuous potential curves of the platinum *versus* platinum plus 10% rhodium thermocouple were automatically traced on a Leeds and Northrup Speedomax recorder checked against a Rubicon Type B potentiometer. These curves were essentially interpolations over ten to thirty degree ranges, the limits of which were established by direct optical pyrometer observation of the tantalum crucible at temperature equilibrium. Since essentially "black body" conditions obtain for the tantalum crucible, no emissivity correction is involved. Both optical pyrometers were calibrated against a standard lamp and also against the melting point of palladium in the present apparatus upon substitution of a beryllia liner. Direct observation of the fusion and solidification points with the optical pyrometer were found to agree with the thermocouple values and with each other regardless of the sign or magnitude of the thermal head. Corrections were applied for the transmissivity of the Pyrex window and after many transitions a compensation amounting to several degrees was required to correct for the sublimed film of plutonium trifluoride on the window. Repeated transitions were observed under various thermal heads both in high vacuum and under 10^{-2} atm. of argon, fusion temperature (11 observations): 1426 ± 2°; solidification temperature (13 observations): 1425 ± 3° the uncertainties

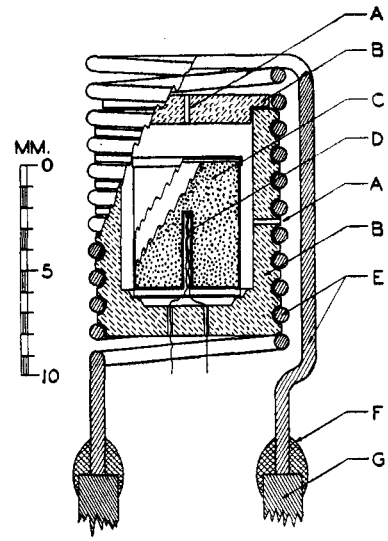


Fig. 1.—PuF_3 melting point apparatus: (A) optical pyrometric sighting ports, (B) beryllia furnace block and cover, (C) PuF_3 pellet in a covered tantalum crucible with entrant thermocouple well, (D) thermocouple, (E) 0.6 mm. diam. tungsten wire heating coil, (F) platinum weld, (G) 2 mm. diam. tungsten electrodes.

indicated are average deviations. The plutonium trifluoride had fused, and no thermal effect was detected near the temperature previously interpreted as the melting point.[1] We believe that a phase transition with a molar enthalpy change greater than two kilocalories would have been apparent.

By use of the Gaussian criterion for closeness of fit, a three constant equation fitted by weighted least squares indicated as good agreement with the vapor pressure data reported by Phipps, *et al.*,[2] as did their two similarly fitted linear equations previously reported.

The ΔC_p of sublimation corresponding to this equation was -32 cal. mole^{-1} deg.$^{-1}$. A least squares treatment with an assumed value of $\Delta C_p = -15$ cal. mole^{-1} deg.$^{-1}$ and two arbitrary constants also fits the data well and yielded the equation

$$\log_{10} P_{mm} = -24{,}917T^{-1} - 7.5513 \log T + 38.920$$

valid from 1200 to 1660°K. for the dissociation pressure and a value of 89 kcal. mole^{-1} for the heat of sublimation of 1400°.

The experimental work was performed under the auspices of the U. S. Atomic Energy Commission at the University of California Radiation Laboratory.

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RECEIVED JANUARY 26, 1951

(3) L. Brewer, L. Bromley, P. W. Gilles and N. L. Lofgren, *ibid.*, Paper No. 6.40.

(4) H. P. Robinson, Manhattan Project Metallurgical Laboratory Report CN-2159 (Oct., 1944).

(5) E. F. Westrum, Jr., and LeRoy Eyring, THIS JOURNAL, **73**, 3399 (1951).

The Condensation of Ethyl Acetoacetate to Isodehydroacetic Acid and Ethyl Ester

BY RICHARD H. WILEY AND NEWTON R. SMITH[1]

The sulfuric acid catalyzed condensation of ethyl acetoacetate to a mixture of isodehydroacetic acid

(1) The authors are indebted to the Research Corporation for a grant in support of this research.

and its ethyl ester has been known for many years.[2,3] The work of Goss, Ingold and Thorpe[4] has shown that the ester can be obtained as the major product of the reaction when dry hydrogen chloride is used as the condensing agent. As part of a study to determine the possibility of obtaining the acid as the major product, we have undertaken an investigation of the effect of varying reaction conditions on the course of the condensation. The data obtained, along with additional information on the hydrolysis of ethyl isodehydroacetate to the acid and on esterification of the acid, has established some facts about the course of the reaction and the structure of these compounds which we wish to report in this paper.

The condensation takes place at room temperature when acetoacetic ester is dissolved in a large volume of sulfuric acid. In this study the effect of the concentration of reactants, temperature, time of the reaction and type of catalyst were determined. When the ratio of sulfuric acid to the ester was varied from 1.9–6.5 to one mole, a maximum combined yield of 54% of both acid (28%) and ester (26%) was obtained at a ratio of 2.5–3.6 to one. Selected data are given in Table I. When the temperature was varied, it was found that room temperature (20–30°) was the most satisfactory for the condensation. At 0° the condensation proceeds too slowly, and at 100° the reactants are apparently destroyed. At 42° the yields are slightly lower than those obtained under comparable conditions at room temperature as indicated in Table II. The data in Table III demonstrate that there is no advantage in extending the reaction beyond 5 or 6 days. For extremely long reaction periods the yield actually decreases. The use of aluminum chloride or boron trifluoride etherate gave lower yields of the ester and no acid at all.

TABLE I

EFFECT OF CONCENTRATION OF REACTANTS[a]

Ratio[b]	Yield, % Acid	Ester	Total
1.9/1	5	48[c]	53
3.6/1	28	26	54
6.5/1	10	20[c]	30

[a] Time of runs, 15 or 20 days. [b] Moles H_2SO_4/moles acetoacetic ester. [c] Crude yield; b.p. 130–90° at 35 mm.

TABLE II

EFFECT OF TEMPERATURE[a]

Temp., °C.	Yield, % Acid	Ester	Total
0–5	1.5	6.8	8.3
20–30	18	22	40
42	14.8	19.5	34
100	0	0	0

[a] These data are for 28 hours. The mole ratio of sulfuric acid to ethyl acetoacetate is 3.2/1.

TABLE III

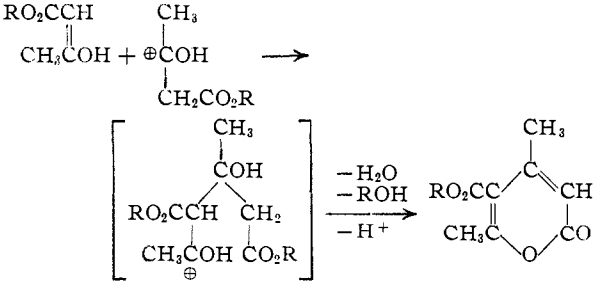
EFFECT OF TIME[a]

Time	Yield, % Acid	Ester	Total
28 hours	18	22	40
2 days	19	29	48
4 days	22	32	54
6 days	25	30	55
15 days	28	26	54
17 days	24	27	51
40 days	15	24	39

[a] Reactions run at room temperature. The mole ratio of sulfuric acid to ethyl acetoacetate varied from 2.5/1 to 3.6/1.

Under all conditions tried both isodehydroacetic acid and ester were obtained together. It was believed that additional information on hydrolysis of isodehydroacetic ester might suggest conditions under which the condensation could be carried out with simultaneous hydrolysis to give the acid as the major product. The data obtained show that isodehydroacetic ester is not easily hydrolyzed. Hydrolysis with concentrated sulfuric acid at elevated temperatures produced isodehydroacetic acid in only 40–50% yields and usually 20–30% of the ester was recovered. From attempts to hydrolyze the ester by 100% sulfuric acid at room temperature, the ester was recovered in 92% yield. When hydrolysis of the ester or esterification of acid was undertaken under the preferred conditions for the condensation, as outlined above, the starting material was recovered and none of the product could be detected. This means that under the preferred conditions for the condensation, any isodehydroacetic ester that is formed will remain unhydrolyzed and that the isodehydroacetic acid which is formed is not formed by hydrolysis of the cyclic ester but by condensation of acetoacetic acid formed by hydrolysis of acetoacetic ester prior to condensation. The best procedure thus far devised for obtaining maximum yields of isodehydroacetic acid is to carry out the condensation so as to obtain the maximum yield of both ester and acid and hydrolyze the ester thus obtained to the acid in a separate step.

The mechanism of this condensation reaction is apparently that of an acid-catalyzed aldol condensation[5] between the carbonyl group of one molecule and the methylene carbon of another molecule followed by lactonization



The formation of isodehydroacetic ester and acid proceed independently and not from one to another, for our data on hydrolysis of isodehydroacetic ester and esterification of isodehydroacetic acid show that the ester is not hydrolyzed nor the acid esterified under the conditions of the condensation. This indicates that the acetoacetic ester itself is in part hydrolyzed prior to condensation and undergoes condensation as the free acid to form isodehydroacetic acid and ester.

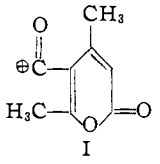
(2) A. Hantzsch, *Ann.*, **222**, 9 (1883).

(3) R. Anschutz, P. Bendix and W. Kerp, *ibid.*, **259**, 148 (1890).

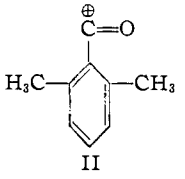
(4) F. R. Goss, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **123**, 348 (1923).

(5) L. P. Hammett, "Physical Organic Chemistry," 1st ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 347.

The fact that ethyl isodehydroacetate is not rapidly hydrolyzed and the acid not rapidly esterified in concentrated sulfuric acid provides an interesting basis for a preliminary comparison of the degree of resonance stabilization in the ion I with that in the 2,6-dimethylbenzoyl carbonium ion, II. 2,6-Di-



I



II

methylbenzoic acid is known to have a van't Hoff *i* factor of more than three in sulfuric acid[6] and this fact has been interpreted as due to partial dissociation into ions stabilized by resonance through electron-releasing characteristics of the two, one is not enough, ortho methyl groups. This effect has been used to explain the van't Hoff factor of nearly four in concentrated sulfuric acid and the ease of hydrolysis of ethyl 2,4,6-trimethylbenzoate in 100% sulfuric acid. That this effect is not necessarily steric is indicated by the fact that 2,4,6-tribromobenzoic acid is not rapidly esterified as is the corresponding trimethyl derivative.[7]

Apparently, the two ortho methyl groups in the pyrone do not contribute sufficiently to the resonance stabilization of the ion I to promote facile esterification and hydrolysis as observed in the 2,4-6-trimethylbenzoate types but one would not predict that the two methyl groups of the pyrone would produce the same ease of hydrolysis observed with ethyl trimethylbenzoate. Precise data are unavailable for comparing ease of hydrolysis or esterification or van't Hoff *i* factors of the *o,o'*-dimethyl-1,2-pyrone and the 2,6-dimethylbenzenecarboxylic acids. It appears likely, however, that such data will provide the basis for a quantitative comparison of the degree of resonance stabilization of the benzene and pyrone rings in concentrated sulfuric acid although it is recognized that the pyrone may exist as a conjugate acid or perhaps even undergoes reversible ring opening under these conditions. These, as well as data relating other heterocyclic types, are being obtained and will be reported in following papers.

Along with these studies, we have confirmed the saponification of isodehydroacetic ester to β-methylglutaconic acid[2,8] in 88% yield and observed that hydrolysis of ethyl 3-bromoisodehydroacetate is accompanied by decarboxylation with resultant formation of 3-bromo-4,6-dimethylpyrone and that hydrolysis of ethyl 3-nitroisodehydroacetate is accompanied by extensive decomposition.

Experimental

All melting points and boiling points are uncorrected.

Preparation of Isodehydroacetic Acid and Ester.—The general procedure previously described[3] was followed for the sulfuric acid condensation of ethyl acetoacetate to isodehydroacetic acid. Variations of this procedure are given in Tables I, II and III. The yields indicated therein are for isodehydroacetic acid, m.p. 155°, and ethyl isodehydroacetate boiling over a 5° range under reduced pressure except as noted. The following is a brief description of the procedure.

The sulfuric acid was cooled in an ice-bath and the acetoacetic ester added at a temperature of 10–15°. The reaction mixture was protected from atmospheric moisture and allowed to stand at the times and temperatures indicated. After pouring on ice, the products were extracted with ether and the isodehydroacetic acid separated by extracting the ether with sodium carbonate solution. Acidification with excess hydrochloric acid precipitated the crude acid, which was recrystallized from water. The ester was distilled under reduced pressure, after removal of the ether.

Attempts to use other acidic catalysts gave smaller yields of the condensation products. Using aluminum chloride, a 27.5% yield of ethyl isodehydroacetate alone was obtained, while boron trifluoride–etherate gave only a 20% yield of the ester.

Hydrolysis of Ethyl Isodehydroacetate.—The isodehydroacetic ester was hydrolyzed to isodehydroacetic acid by heating with 5 times its weight of concentrated sulfuric acid on a steam-bath for 4 to 5 hours. This was worked up to give a 40–50% yield of isodehydroacetic acid and a 20–30% recovery of the original ester. When the ester was dissolved in 100% sulfuric acid and poured onto ice after standing at room temperature, the original ester was recovered. No isodehydroacetic acid was detected.

Acid hydrolysis of 3-bromoisodehydroacetic acid ethyl ester,[2] produced a mixture consisting of 3-bromo-4,6-dimethylpyrone, m.p. 105°,[2] in 27% yield and 3-bromoisodehydroacetic acid, m.p. 160–2°,[9] in 11% yield. 3-Nitroisodehydroacetic ester under similar conditions underwent extensive decomposition from which no identifiable products were obtained.

Attempted Esterification and Hydrolysis at Room Temperature.—In order to determine whether the acid was formed from the ester or *vice versa*, in conditions used in the condensation, attempts to hydrolyze the ester at room temperature and to esterify the acid in concentrated sulfuric acid were made. When the ester was allowed to stand for 3 days in sulfuric acid at room temperature, 92% of the original ester was recovered and no acid detected. From a mixture of isodehydroacetic acid, ethanol and sulfuric acid there was obtained an 81% recovery of the acid and no ester.

(6) H. P. Treffers and L. P. Hammett, THIS JOURNAL, **59**, 1711 (1937).

(7) M. S. Newman, *ibid.*, **63**, 2432 (1941).

(8) R. P. Linstead and A. F. Millidge, *J. Chem. Soc.*, 486 (1936).

(9) F. Feist, *Ber.*, **26**, 754 (1893).

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RECEIVED MARCH 20, 1951

Preparation of Acetyl-L-leucine and Acetyl-L-glutamic Acid

BY HANS WOLFF AND ARTHUR BERGER

The use of ketene as acetylating agent for α-amino acids was proposed by Bergmann and Stern,[1] who prepared N-acetyl-*dl*-leucine from *dl*-leucine by treating its water solution with ketene and N-acetyl-*l*-glutamic acid by passing ketene through an aqueous solution of sodium *l*-glutamate. Cahill and Burton[2] have claimed that acetylation of the active amino acids *l*-leucine and *l*-glutamic acid with ketene leads to complete racemization when carried out under acid conditions but that no racemization occurs as long as the solution is kept alkaline. The acidity obtained by the generation of acetic acid from ketene and water in excess of the alkali added to the reaction mixture was found to be sufficient to cause rapid racemization. Racemization occurs on acetylating α-amino acids with excess acetic anhydride in glacial acetic acid as reported by Bergmann and Zervas[3] and confirmed in our experiments.

(1) Bergmann and Stern, *Ber.*, **63**, 437 (1930).

(2) Cahill and Burton, *J. Biol. Chem.*, **132**, 161 (1940).

(3) Bergmann and Zervas, *Biochem. Z.*, **203**, 280 (1928).

We observed, however, that *l*-leucine and *l*-glutamic acid can be acetylated with ketene even under acid conditions and at reflux temperatures without causing complete racemization. These two amino acids can also be acetylated with acetic anhydride in aqueous acetic acid to give the active acetyl amino acids. These procedures appear practical for the preparation of acetyl-*l*-leucine and acetyl-*l*-glutamic acid since they eliminate a separation of salts from the acetylated amino acids and give yields of about 50% of the pure acetylated compounds. The purity of the compounds was proved by de-acetylating them with dilute hydrochloric acid to the original amino acids of unchanged rotation. This method cannot be considered generally applicable to all active amino acids since it was found that *l*-arginine racemizes completely and *l*-cystine decomposes as observed previously (3) when treated with ketene in water solution.

Experimental

N-Acetyl-l-leucine.—Pure *l*-leucine was prepared by recrystallization of its nasylate[4] until it had a constant melting point of 189–191° and a constant rotation of $[\alpha]^{25}D$ +12.84 (4% in ethanol). On decomposing the leucine nasylate in ethanol solution with ethanolamine, *l*-leucine was obtained which was recrystallized from water to a constant rotation of $[\alpha]^{25}D$ +14.7 (9% solution in 4.5 *N* hydrochloric acid); reported $[\alpha]^{24}D$ +15.33 (4), $[\alpha]^{27}D$ +16.5 in 20% HCl (2). $[\alpha]^{25}D$ +13.91 (9.075% in 4.5 *N* HCl).[5] A stream of ketene (0.44 mole/hr.) was passed through a solution of 19 g. of *l*-leucine in 1 l. of water until a Van Slyke determination showed practically no amino nitrogen (about 9 hours were required). The solution reached a temperature of 40–50° during the passage of the ketene. The *p*H of the final solution was 3.0, and titration showed the solution to have an acidity equal to 4 *N* acetic acid. After carbon treatment the solution was concentrated *in vacuo* with repeated additions of water to drive off acetic acid. A white precipitate was obtained, weighing 16 g. after washing and drying. This material on recrystallization from ethanol yielded 10.6 g. (44% of theoretical) of acetyl-*l*-leucine, m.p. 183–184°, $[\alpha]^{25}D$ −23.3 (3% in ethanol); reported $[\alpha]^{29}D$ −21.0 (3% in ethanol)[2] and $[\alpha]_D^{29}$ −16.99.[6]

Anal. Calcd. for $C_8H_{15}O_3N$: N, 8.1; neut. equiv., 173.2. Found: N, 8.1; neut. equiv., 174.8.

Passing ketene into a water solution of *l*-leucine under reflux gave similar results. Hydrolysis with 5 *N* hydrochloric acid gave *l*-leucine hydrochloride from which *l*-leucine was obtained in 70% yield $[\alpha]^{25}D$ +14.8. Addition of 100 g. of acetic anhydride to 19 g. of *l*-leucine in 500 g. of 40% acetic acid with stirring at 60° and isolating as described above gave 16.2 g. (65% yield) of acetyl-*l*-leucine, $[\alpha]^{25}D$ −22.9. Repeating the acetylation as described above in the absence of water gave racemized acetylleucine.

N-Acetyl-*l*-glutamic Acid.—*l*-Glutamic acid, $[\alpha]^{25}D$ +31.6 (5% solution in 10% hydrochloric acid) was treated in aqueous solution with ketene as described for *l*-leucine. N-Acetyl-*l*-glutamic acid was isolated in 47% yield, m.p. 194–195°, $[\alpha]^{25}D$ −15.7 (3% in water), $[\alpha]^{25}D$ +3.97 (2% in 1 *N* sodium hydroxide); reported m.p. 198–199°,[1,2] 195°,[7] 195–197°[8] and $[\alpha]^{24.5}D$ +3.9 resp. 3.83 (2% solution in 1 *N* NaOH)[2,3] and $[\alpha]D$ −22.7 (in water).[8]

Anal. Calcd. for $C_7H_{11}O_5N$: N, 7.4; neut. equiv., 94.6. Found: N, 7.3; neut. equiv., 95.5.

Hydrolysis with 5 *N* hydrochloric acid gave 80% yield of *l*-glutamic acid $[\alpha]^{25}D$ +31.7 (5% solution in 10% hydrochloric acid). Acetylating 20 g. of *l*-glutamic acid in 500 ml. of 40% acetic acid with 100 ml. of acetic anhydride gave 14 g. (55%) of acetyl-*l*-glutamic acid of $[\alpha]^{25}D$ −15.4 (3% in water).

l-Arginine.—A solution of *l*-arginine in water was completely racemized after a stream of ketene was passed through the solution for several hours.

l-Cystine.—On passing ketene through a water solution of *l*-cystine a fine precipitate of sulfur was obtained.

A. E. STALEY MFG. CO.
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RECEIVED MARCH 10, 1950

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(8) Knoop and Oesterlin, *Hoppe-Seylers Z.*, **170**, 186 (1927).

The Preparation of Some Dialkylaminoalkylaldehydes

BY MILDRED YANDIK AND A. A. LARSEN

In the course of investigating compounds for analgesic activity two aminoaldehydes were prepared for screening. These compounds, 4-dimethylamino-2,2-diphenyl entanal and 4-dimethylamino-2,2-diphenyl-3-methylbutanal were obtained from the corresponding nitriles[1] by reduction with lithium aluminum hydride.[2] Isolation was somewhat complicated by the presence of the basic amino group in the molecule and in addition by the fact that distillation was of no benefit since the nitrile and aldehyde distill at the same temperature under reduced pressure. The presence of the quaternary carbon atom adjacent to the carbonyl group does not allow for the preparation of the more common aldehyde derivatives. Catalytic hydrogenation of the aldehydes resulted in the uptake of one mole of hydrogen and isolation of the corresponding alcohols.

Bockmühl[3] reported that 2,2-diphenyl-4-piperidinobutanal, prepared by Rosenmund reduction of the acid chloride hydrochloride, has about one-third the analgesic activity of methadone. Tests performed in this Laboratory under the direction of Dr. J. R. Lewis showed that 4-dimethylamino-2,2-diphenylpentanal has about one-fifth the activity of methadone, whereas 4-dimethylamino-2,2-diphenyl 3-methylbutanal is less active as an analgesic.

Experimental

4-Dimethylamino-2,2-diphenylpentanal Hydrochloride.—To a solution of 139 g. (0.5 mole) of 4-dimethylamino-2,2-diphenylbutanenitrile in 90 ml. of dry ether was added portionwise with stirring 5.5 g. (0.145 mole) of lithium aluminum hydride. After addition was complete the mixture was refluxed for four hours and left to stand overnight. After the addition of water, the gelatinous solid was removed by filtration and the ether layer extracted with dilute hydrochloric acid. The acid extract was washed with ether, made ammonical with concentrated ammonia and the free base extracted with ether. After drying, the ether solution was treated with alcoholic hydrogen chloride and the resultant oily solid was recrystallized from acetone–methanol to give 47 g. of aldehyde hydrochloride monohydrate, m.p. 122–124°. When dried in the vacuum oven at 100° for 96 hours the anhydrous hydrochloride was obtained, m.p. 187–189°.

Anal. Calcd. for $C_{19}H_{23}NO \cdot HCl$: C, 71.81; H, 7.61; N, 4.40; Cl, 11.15. Found: C, 71.74; H, 7.37; N, 4.41; Cl, 10.93.

Low pressure catalytic hydrogenation using platinum oxide, 1 g. of catalyst to 10 g. of aldehyde, gave 4-dimethylamino-2,2-diphenylpentanol hydrochloride,[4] m.p. 214–216°.

(1) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 2456 (1947).

(2) L. Friedman, Abstracts 116th Meeting American Chemical Society, Atlantic City, N. J., 1949, p. 5M.

(3) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 75 (1948).

(4) M. E. Speeter, W. M. Byrd, L. C. Cheney and S. B. Binkley, THIS JOURNAL, **71**, 57 (1949).

4-Dimethylamino-2,2-diphenyl-3-methylbutanal Hydrochloride.—The reduction of 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile, 27.8 g. (0.1 mole), with lithium aluminum hydride in the above manner gave 7.5 g. of aminoaldehyde hydrochloride which was recrystallized from acetone–methanol, m.p. 187.8–192°.

Anal. Calcd. for: $C_{19}H_{23}NO \cdot HCl$: C, 71.81; H, 7.61; N, 4.40. Found: C, 71.75; H, 7.34; N, 4.47.

Catalytic reduction as indicated above gave 4-dimethylamino-2,2-diphenyl-3-methylbutanol hydrochloride, m.p. 200–201°.

Anal. Calcd. for $C_{19}H_{25}NO \cdot HCl$: C, 71.34; H, 8.19; Cl, 11.08. Found: C, 71.58; H, 8.39; Cl, 11.00.

Acknowledgment.—The authors are indebted to Messrs. M. E. Auerbach and K. D. Fleischer and staff for the analyses reported here.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y. RECEIVED JANUARY 4, 1951

COMMUNICATIONS TO THE EDITOR

PYRIDOXAL PHOSPHATE, THE COENZYME OF THIOETHER-CLEAVAGE

Sir:

In a previous report[1] the activation of certain preparations of the enzyme responsible for the cleavage of thioethers (*e.g.*, cystathionine with the formation of cysteine) by relatively large amounts of folic acid was described. Since that time, it has been found that derivatives of folic acid (conjugates and citrovorum factor) were without effect. The failure of these derivatives to activate the preparations and the limited results obtained in further studies with folic acid led us to consider other possibilities as to the identity of the dialyzable component. It has been found that minute amounts of pyridoxal phosphate[2] activated all preparations of the enzyme—fresh, aged or dialyzed. Maximal activation was obtained with 0.5 γ of pyridoxal phosphate per ml. of digest. Djenkolic acid,[3] 10 mg., and 1 ml. enzyme[4] in a total volume of 10 ml. 0.1 *M* sodium citrate were incubated for 30 minutes at 37° with amounts of pyridoxal phosphate varying from 0.1 to 10 γ per ml. With the fresh enzyme, maximal activity, 1.1 mg. of cysteine was obtained with 0.5 γ of pyridoxal phosphate; the control was 0.5 mg. of cysteine. After dialysis overnight against acetate buffer, 0.1 *M*, *p*H 5.5, the activity was reduced to 0.2 mg. of cysteine and was restored to 1.0 mg. of cysteine upon the addition of 0.5 γ of pyridoxal phosphate per ml. of digest. These amounts of pyridoxal phosphate are of the same order of magnitude as required for the transamination and decarboxylation enzymes and are compatible with the amounts predicted from the absorption spectrum of the enzyme.[1] It would appear, therefore, that pyridoxal phosphate is the coenzyme of the cleavage-enzyme.

When 10 mg. of pyridoxin and 50 mg. of adenosinetriphosphate were incubated in 10 ml. of saline with 1 ml. of homogenate of liver tissue (1 g. in 10 ml.) for 15 minutes, an apparent content of 5.5 γ of pyridoxal phosphate per ml. (activation of dialyzed enzyme) was found. The addition of folic acid was found to increase markedly the amount of coenzyme formed. It would appear probable, therefore, that the effects of folic acid and of adenosinetriphosphate[5] on the cleavage will be found to be concerned with the synthesis of pyridoxal phosphate or a closely related compound. It is of interest that the ultraviolet absorption of the purified enzyme[1] may be interpreted as that of protein and pyridoxal phosphate.[6]

These and related studies will be reported in detail in the near future.

(1) F. Binkley, THIS JOURNAL, **72**, 2809 (1950).
(2) Obtained from Dr. W. W. Umbreit.
(3) M. D. Armstrong and V. du Vigneaud, *J. Biol. Chem.*, **168**, 373 (1947). Djenkolic acid is an easily prepared substrate.
(4) F. Binkley and D. Okeson, *J. Biol. Chem.*, **182**, 273 (1950).
(5) F. Binkley, *J. Biol. Chem.*, **155**, 39 (1944).
(6) W. W. Umbreit, D. J. O'Kane and I. C. Gunsalus, *ibid.*, **176**, 629 (1948).

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RECEIVED APRIL 30, 1951

"CITROVORUM FACTOR" ACTIVITY OF TETRAHYDROPTEROYLGLUTAMIC ACID

Sir:

The preparation of leucovorin (I),[1] 5-formyl-5,6,7,8-tetrahydropteroylglutamic acid,[2,3] led to speculation as to its possible role in the transfer of "single-carbon fragments," following the suggestion which has been made for folic acid in such biological mechanisms.[4] It seemed feasible that I might be reversibly transformed to tetrahydropteroylglutamic acid (II) *in vivo* during such a process in which case II should have biological properties similar to those of I. II was synthesized by hydrogenation of 14.6 mg. of pteroylglutamic acid in 10 cc. of glacial acetic acid at room temperature, using 15 mg. of platinum oxide catalyst and a standard Ogg–Cooper micro-hydrogenation apparatus.[5] After 5.75 hours, reduction was complete; hydrogen uptake was 92.5% of the theoretical 2 moles. Subsequent operations were carried out under nitrogen to prevent oxidation. The catalyst was separated from the colorless solution of II by centrifugation, then aliquots were transferred to small test-tubes and vacuum-dried to a

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(3) B. Roth, *et al.*, in preparation.
(4) M. Gordon, *et al.*, THIS JOURNAL, **70**, 878 (1948).
(5) B. L. O'Dell, *et al.*, *ibid.*, **69**, 250 (1947).