THE JOURNAL OF Organic Chemistry®

Volume 22, Number 10

October 11, 1957

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Iminotetrazolinium Salts. Identification of Sulfonic Acids

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Received April 3, 1957

Tartrates of several 1-alkyl-4-benzyl-5-iminotetrazolines are described. Excepting 1-*n*-octyl-4-*p*-nitrobenzyl-5-iminotetrazoline which forms an acid tartrate, the bases combine with two moles of tartaric acid to form hydrated complex tartrates. A number of iminotetrazolinium alkane sulfonates and arylsulfonates are described. 1-*n*-Octyl-4-benzyl-5-iminotetrazolinium ditartrate monohydrate (OBIT) is suggested as a reagent for the qualitative identification of sulfonic acids or their sodium salts. The insolubility of most of the sulfonates in water suggests that they might be adaptable to quantitative estimations.

Recently the synthesis of a series of 1,4-disubstituted 5-iminotetrazolines was described.[1] The products were isolated as the rather insoluble hydrochlorides and screened for activity against various microorganisms. Because of the insolubility of the hydrochlorides and other salts with inorganic acids, the preparation of salts with organic acids was undertaken. Salts with tartaric acid could be prepared easily by treating the bases with tartaric acid in ethyl acetate solution containing a little water. Although the iminotetrazoline bases are monoacidic and form neutral salts with one equivalent of hydrochloric acid, they form, with one exception, complex ditartrate monohydrates even when treated with only an equimolar amount of tartaric acid. The complex tartrates are soluble not only in water but in ethanol, acetone, chloroform, benzene, and hot ethyl acetate. The complex formed from 1-*n*-octyl-4-benzyl-5-iminotetrazoline and tartaric acid is extremely soluble in water; 20% solutions in water could be prepared without difficulty. Only in one case, 1-*n*-octyl-4-*p*-nitrobenzyl-5-iminotetrazoline was an acid tartrate formed, and this even in the presence of two moles of tartaric acid per mole of base.

The composition of the tartrates was established by elemental analysis and by titration with Karl Fischer reagent.[2] The base content was estimated by precipitation of the insoluble chlorides and by titration of the tartrates with perchloric acid in glacial acetic acid.[3] Attempts to estimate tartaric acid by titration of the complexes in dimethylformamide with sodium methoxide in benzene-methanol solution[4] were successful in only one instance, the acid tartrate of 1-*n*-octyl-4-*p*-nitrobenzyl-5-iminotetrazoline. In the other instances the water in the hydrates interfered with the end point of the titration. It is interesting to note that the octyl-*p*-nitrobenzyliminotetrazoline acted as a self-indicator in the titration with sodium methoxide; an intense wine-red color developed at the equivalence point, possibly due to the involvement of the *aci* form of the nitro group.

In view of the insolubility of the inorganic acid salts of the iminotetrazolines, the solubility of salts with a number of sulfonic acids was investigated. A variety of amines, quaternary pyridinium bases, and other organic compounds have been suggested as reagents for the qualitative identification of sulfonic acids. The literature has been reviewed in some detail by Chambers and Watt,[5] Dermer and

(1) R. M. Herbst and C. F. Froberger, *J. Org. Chem.*, **22**, 1050 (1957).

(2) W. Seaman, W. H. McComas, Jr., and G. A. Allen, *Anal. Chem.*, **21**, 510 (1949).

(3) P. C. Markunas and J. A. Reddick, *Anal. Chem.*, **23**, 337 (1951).

(4) J. S. Fritz, *Anal. Chem.*, **24**, 306 (1952).

(5) E. Chambers and G. W. Watt, *J. Org. Chem.*, **6**, 376 (1941).

(6) O. C. Dermer and V. H. Dermer, *J. Org. Chem.*, **7**, 581 (1942).

Dermer,[6] and Shriner, Fuson, and Curtin.[7] A reagent which will form insoluble salts with either the free sulfonic acids or their sodium salts in dilute aqueous solutions still seems to be desirable. All the complex tartrates described in Table I will cause precipitation of iminotetrazolinium sulfonates from dilute aqueous solutions of the aromatic sulfonic acids or their sodium salts. Because of its great solubility in water 1-*n*-octyl-4-benzyl-5-iminotetrazolinium ditartrate monohydrate (OBIT) was chosen for extensive investigation. With the exception of methane- and ethanesulfonic acid, insoluble sulfonates were precipitated by the reagent from aqueous solutions of all the aliphatic and aromatic sulfonic acids, or their sodium salts, listed in Table III. The methane- and ethanesulfonates could also be obtained as well-crystallized solids after extraction from their aqueous solutions with chloroform. The various iminotetrazolinium sulfonates could be recrystallized from water, aqueous ethanol, aqueous acetone, ethyl acetate, ethyl acetate–cyclohexane, benzene, benzene–petroleum ether or benzene-hexane mixtures as indicated in Table III. Many of the salts with aromatic sulfonic acids are so insoluble in water that they might lend themselves to gravimetric estimations of the sulfonic acids. Disulfonic acids form neutral salts with two moles of the OBIT reagent. Sulfocarboxylic acids and hydroxysulfonic acids form salts with only a single equivalent of the OBIT reagent. Aminosulfonic acids or their sodium salts form water-insoluble OBIT salts that crystallize readily from the indicated solvents. The melting points of the various sulfonates show a wide spread. In instances where isomeric sulfonates melt in the same temperature range, mixture melting points show depressions of 20–30°. The presence of chlorides, sulfates, and nitrates may interfere with the usefulness of the reagent due to the insolubility of the iminotetrazolinium chlorides, sulfates, and nitrates. As already noted the chlorides are sufficiently insoluble to permit their use in estimating the base content of the tartrates, and conversely, their use in the gravimetric estimation of chloride ion could be of interest. Potassium salts of the sulfonic acids may also cause difficulty due to the rather low solubility in water of potassium acid tartrate.

EXPERIMENTAL[8]

1-n-Octyl-4-benzyl-5-iminotetrazolinium ditartrate monohydrate (OBIT). A mixture of 15 g. (0.076 mole) of 1-*n*-octyl-5-aminotetrazole[1] and 11.4 g. (0.09 mole) of benzyl chloride was heated in an oil bath at 120–130° for 7 hr. A clear, homogeneous melt formed and resolidified during the first hour of heating. The crude hydrochloride was taken up in 50 ml. of 95% ethanol, diluted with 500 ml. of water, and the mixture distilled to remove ethanol and excess benzyl chloride. The hydrochloride crystallizes from the residual aqueous solution on cooling. The base was liberated with excess 10% sodium hydroxide solution and extracted with several portions of benzene. After drying over potassium carbonate the solvent was removed from the combined benzene solutions on a water bath under reduced pressure. The residual oil (22.5 g.) was taken up in 150 ml. of dry ethyl acetate and to the solution was added 22.5 g. (0.15 mole) of tartaric acid and 5 ml. of water. The solution that resulted when the mixture was heated to boiling was treated with charcoal to remove a slight turbidity. On cooling the ditartrate monohydrate separated as colorless platelets, yield 41.5 g. (92%).

The 1-*n*-nonyl and 1-*n*-decyl-4-benzyl-5-iminotetrazolinium ditartrate monohydrates were prepared in similar manner and yield from the appropriate 1-alkyl-5-aminotetrazoles.[1] The *p*-chlorobenzyl analog was prepared similarly from 1-*n*-octyl-5-aminotetrazole and *p*-chlorobenzyl chloride in equally good yield. Physical constants and analytical data for the ditartrates are given in Tables I and II.

In the first attempt to prepare a tartrate from 1-*n*-octyl-4-benzyl-5-iminotetrazoline only slightly over the equimolar amount of tartaric acid was used in the expectation that an acid tartrate would be formed. Even under these conditions only the ditartrate monohydrate could be isolated.

1-n-Octyl-4-p-nitrobenzyl-5-iminotetrazolinium acid tartrate. The base obtained from the reaction of 10 g. (0.05 mole) of 1-*n*-octyl-5-aminotetrazole and 10 g. (0.058 mole) of *p*-nitrobenzyl chloride as described in the foregoing example was treated with 15 g. (0.1 mole) of tartaric acid in ethyl acetate under the previously described conditions. The tartrate crystallized rapidly on cooling the solution, crude yield 25 g., m.p. 119–125°. One recrystallization from ethyl acetate containing a little water gave the pure acid tartrate described in Table I, yield 21.5 g. (89%).

Elemental analyses were done on the hydrates because the salts softened on attempts at drying under reduced pressure over phosphorus pentoxide at 60–65° and hardened to glassy solids on cooling. Water content of the hydrates was also estimated volumetrically with the Karl Fischer reagent.[2] The base content was estimated by titration of the tartrates with perchloric acid in glacial acetic acid solution.[3] Precipitation of the almost insoluble chlorides from aqueous, or in the case of the *p*-chlorobenzyl derivative, 10% aqueous acetone, solution gave a gravimetric estimation of the base content of the tartrates. The results of these determinations are summarized in Table II.

Attempts to estimate the tartaric acid content of the salts in dimethyl formamide solution by titration with standard sodium methoxide in 10:1 benzene-methanol solution[4] were not successful due to interference by the water. Only in the case of 1-*n*-octyl-4-*p*-nitrobenzyl-5-iminotetrazolinium acid tartrate was an acceptable result obtained. The latter acted as a self-indicator by developing an intense wine-red color at the equivalence point. Titration of the *p*-nitrobenzyl derivative gave the following results: Calcd. for $C_{16}H_{24}N_6O_2.C_4H_6O_6$: tartaric acid, 31.1. Found: tartaric acid, 31.2.

Iminotetrazolinium sulfonates. The salts of the iminotetrazolines with most alkanesulfonic acids and the aromatic sulfonic acids precipitated from aqueous solutions of the sulfonic acids or their sodium salts on addition of a concentrated aqueous solution of the iminotetrazoliuium ditartrate monohydrate. Only the salts with methane- and ethanesulfonic acid failed to precipitate and these could be extracted easily from their aqueous solutions with chloroform. In most instances commercially available sulfonic acids or their sodium salts were used without purification. The use of potassium salts may be complicated by precipitation of potassium acid tartrate. Several typical examples are described.

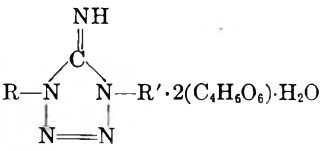
Reagent. A 0.25 molar solution of the reagent was prepared by dissolving 15.1 g. of 1-*n*-octyl-4-benzyl-5-imino-

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Edition, John Wiley and Sons, Inc., New York, 1956, p. 269.

(8) Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill.

TABLE I

1-ALKYL-4-BENZYL-5-IMINOTETRAZOLINIUM DITARTRATE MONOHYDRATES



Compound No.	R	R′	M.P., °C.	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	n-C_8H_{17}	$C_6H_5CH_2$	78–79	$C_{24}H_{39}N_5O_{13}$	47.6	6.5	11.6	47.8	6.6	11.5
II	n-C_8H_{17}	p-$ClC_6H_4CH_2$	88–89	$C_{24}H_{38}ClN_5O_{13}$[a]	45.0	6.0	10.9	45.2	6.0	10.8
III	n-C_8H_{17}	p-$NO_2C_6H_4CH_2$	153–155	$C_{20}H_{30}N_6O_8$[b]	49.8	6.3	17.4	50.1	6.4	17.5
IV	n-C_9H_{19}	$C_6H_5CH_2$	80–82	$C_{25}H_{41}N_5O_{13}$	48.5	6.7	11.3	48.4	6.6	11.4
V	n-$C_{10}H_{21}$	$C_6H_5CH_2$	70–72	$C_{26}H_{43}N_5O_{13}$	49.3	6.8	11.1	49.9	6.9	11.0

[a] Calcd.: Cl, 5.5. Found: Cl, 5.5. [b] Acid tartrate.

tetrazolinium ditartrate monohydrate (OBIT) in water and diluting to 100 ml. Solutions of the reagent have been kept for several months without outward signs of deterioration.

Benzenesulfonate. A solution of 0.9 g. (0.005 mole) of sodium benzene-sulfonate in 150 ml. of warm water was treated with 20 ml. (0.005 mole) of cold OBIT reagent, added slowly with manual agitation. The benzene-sulfonate separated as a voluminous precipitate. Since the salt melts under boiling water, it is best precipitated in warm, not hot, solution. Should the sulfonate separate as an oil, it usually solidifies promptly on cooling. The benzenesulfonate crystallized from 50% ethanol as a cottony mass of fine needles, yield 82%.

TABLE II

FUNCTIONAL GROUP ANALYSES OF 1-ALKYL-4-BENZYL-5-IMINOTETRAZOLINIUM DITARTRATE MONOHYDRATES

Compound No.	Calculated H_2O	Calculated Base	Found H_2O[a]	Found Base[b]	Base[c]
I	2.98	47.5	2.99	47.7	47.5
II	2.82	50.3	2.83	50.5	50.6
III	—	68.9	—	—	69.1
IV	2.91	48.6	2.6[d]	48.2	48.7
V	2.84	49.8	2.91	49.4	50.0

[a] By titration with Karl Fischer reagent.[2] [b] By precipitation of the chloride. [c] By titration with perchloric acid in glacial acetic acid.[3] [d] By drying to constant weight at 65° under reduced pressure over phosphorus pentoxide.

p-Nitrobenzenesulfonate. A hot solution of 1.02 g. (0.005 mole) of p-nitrobenzenesulfonic acid in 75 ml. of water was treated with 20 ml. (0.005 mole) of OBIT reagent as just described. The salt was recrystallized from 30% ethanol from which it separated as pale, straw-colored needles, yield 95%.

Naphthalene-2,5-disulfonate. Sodium naphthalene-2,6-disulfonate (0.66 g., 0.002 mole) dissolved in 100 ml. of hot water was treated with 16 ml. (0.004 mole) of OBIT reagent as just described. A voluminous precipitate separated immediately but changed to a dense solid on standing overnight. It crystallized from 50% ethanol as dense, long prisms, yield 98%. Analysis showed the product to be the neutral salt, Table III.

Sulfanilate. A solution of 0.35 g. (0.002 mole) of sulfanilic acid and 0.30 g. (0.002 mole) of tartaric acid in 50 ml. of hot water was treated with 8 ml. (0.002 mole) of OBIT reagent. The product crystallized from the hot solution as colorless needles on cooling and was recrystallized from hot water, yield 65%. The same product was also obtained from hot aqueous solution without addition of excess tartaric acid.

5-Sulfosalicylate. A warm solution of 1.27 g. (0.005 mole) of 5-sulfosalicylic acid dihydrate in 50 ml. of water was treated with 20 ml. (0.005 mole) of OBIT reagent. The salt separated as an oil with the first addition of reagent. Cooling the solution slightly induced crystallization after which the balance of the reagent was added. The product crystallized from 50% ethanol as needles that melted partially at 150–151°, resolidified and remelted at 169–170°. When plunged into a bath preheated to 150°, the salt melted completely, resolidified and melted again at 169–170°. This was the only salt that behaved peculiarly on melting. Analysis showed the product to be a 1:1 combination of the sulfosalicylic acid and the base, Table III.

Methanesulfonate. A solution of 0.53 g. (0.006 mole) of technical methanesulfonic acid in 15 ml. of water was treated with 20 ml. (0.005 mole) of OBIT reagent. The sulfonate did not crystallize on chilling but was extracted completely with several small portions of chloroform. After drying the extracts over sodium sulfate and removing the solvent by distillation, the solid residue was crystallized twice from benzene by addition of petroleum ether, colorless needles, yield 74%.

The ethanesulfonate was also isolated by extraction from aqueous solution with chloroform. The other alkanesulfonates were prepared in similar volumes of solvent and crystallized from their cold aqueous solutions.

All the sulfonates prepared as just described are recorded in Table III where melting points, molecular formulas and and analytical data are given.

1-n-Octyl-4-p-chlorobenzyl-5-iminotetrazolinium methanesulfonate was prepared by adding 1.62 g. (0.005 mole) of 1-n-octyl-4-p-chlorobenzyl-5-iminotetrazoline base[1] to a solution of 0.48 g. (0.005 mole) of methanesulfonic acid in 10 ml. of water. A clear solution formed on warming from which the salt crystallized on cooling. The product was recrystallized from benzene by addition of hexane, colorless leaflets, m.p. 126–128°, yield 1.9 g. (91%).

Anal. Calcd. for $C_{17}H_{28}ClN_5O_3S$: Cl, 8.5; N, 16.8; S, 7.7. Found: Cl, 7.8; N, 16.6; S, 7.6.

1-n-Octyl-4-p-chlorobenzyl-5-iminotetrazolinium sulfanilate was prepared by adding with manual agitation a solution of 6.39 g. (0.01 mole) of 1-n-octyl-4-p-chlorobenzyl-5-iminotetrazolinium ditartrate monohydrate in 50 ml. of warm acetone to 1.73 g. (0.01 mole) of sulfanilic acid dissolved in 300 ml. of warm water. A clear solution resulted on heat-

TABLE III

1-*n*-OCTYL-4-BENZYL-5-IMINOTETRAZOLINIUM SULFONATES

Sulfonic acid	M.P., °C.	Formula	Analyses							
			Calcd.				Found			
			C	H	N	S	C	H	N	S
Methane[a]	116–117	$C_{17}H_{29}N_5O_3S$	53.2	7.6	18.3	8.4	53.6	7.8	18.5	8.3
Ethane[a]	98–99	$C_{18}H_{31}N_5O_3S$	54.4	7.9	17.6	8.1	54.4	7.9	17.9	8.0
2-Propane[a]	108–110	$C_{19}H_{33}N_5O_3S$	55.4	8.1	17.0	7.8	55.9	8.0	17.3	7.8
1-Butane[b]	125	$C_{20}H_{35}N_5O_3S$	56.4	8.3	16.5	7.5	56.5	8.3	16.5	7.4
3-Methyl-1-butane[c]	132–133	$C_{21}H_{37}N_5O_3S$	57.4	8.5	15.9	7.3	57.3	8.7	16.0	7.3
Benzene[d]	129	$C_{22}H_{31}N_5O_3S$	59.3	7.0	15.7	7.2	59.3	6.9	16.0	7.1
p-Toluene[d]	172–173	$C_{23}H_{33}N_5O_3S$	60.1	7.2	15.2	7.0	60.0	7.1	15.3	6.9
2,4-Dimethylbenzene[a]	91–92	$C_{24}H_{35}N_5O_3S$	60.9	7.5	14.8	6.8	60.8	7.6	14.8	7.0
2,5-Dimethylbenzene[a]	102–103	$C_{24}H_{35}N_5O_3S$	60.9	7.5	14.8	6.8	61.0	7.5	14.8	7.0
p-Chlorobenzene[d,e]	159–160	$C_{22}H_{30}ClN_5O_3S$	55.0	6.3	14.6	6.9	55.2	6.5	14.7	6.8
2,4-Dichlorobenzene[d,f]	134–135	$C_{22}H_{29}Cl_2N_5O_3S$	51.4	5.7	13.6	6.2	51.3	5.7	13.4	6.0
p-Bromobenzene[d,g]	162–163	$C_{22}H_{30}BrN_5O_3S$	50.4	5.8	13.4	6.1	50.5	5.7	13.4	6.0
p-Phenol[d]	114–115	$C_{22}H_{31}N_5O_4S$	57.2	6.8	15.2	7.0	57.3	6.8	15.0	7.1
m-Nitrobenzene[d]	138–139	$C_{22}H_{30}N_6O_5S$	53.9	6.2	17.1	6.5	54.0	6.4	16.9	6.6
p-Nitrobenzene[d]	171–172	$C_{22}H_{30}N_6O_5S$	53.9	6.2	17.1	6.5	54.2	6.3	17.2	6.3
Orthanilic[d]	134–135	$C_{22}H_{32}N_5O_3S$	57.4	7.0	18.3	7.0	57.7	6.9	18.3	6.7
Metanilic[a]	107–108	$C_{22}H_{32}N_5O_3S$	57.4	7.0	18.3	7.0	57.7	7.1	18.2	6.7
Sulfanilic[h]	154–155	$C_{22}H_{32}N_5O_3S$	57.4	7.0	18.3	7.0	57.5	7.2	18.0	6.8
m-Sulfobenzoic[d]	200–201	$C_{23}H_{31}N_5O_6S$	56.4	6.4	14.3	6.6	56.4	6.5	14.3	6.6
5-Sulfosalicylic[d]	169–170[i]	$C_{23}H_{31}N_5O_6S$	54.6	6.2	13.9	6.3	54.8	6.2	13.6	6.4
m-Benzenedi-[j,k]	143–144	$C_{38}H_{56}N_{10}O_6S_2$	56.1	6.9	17.2	7.9	56.0	7.0	17.2	8.1
4,4′-Biphenyldi-[d,j]	244–245	$C_{44}H_{60}N_{10}O_6S_2$	59.4	6.8	15.8	7.2	59.4	6.6	16.0	7.3
dl-10-Camphor[b]	146–147	$C_{26}H_{41}N_5O_4S$	60.1	8.0	13.5	6.2	60.4	8.1	13.3	6.3
d-10-Camphor[b]	144–145	$C_{26}H_{41}N_5O_4S$	60.1	8.0	13.5	6.2	60.1	8.0	13.3	6.1
2-Naphthalene[d]	146–147	$C_{26}H_{33}N_5O_3S$	63.0	6.7	14.1	6.5	63.2	6.8	14.3	6.6
4-Amino-1-naphthalene[k]	131–132	$C_{26}H_{34}N_6O_3S$	61.2	6.7	16.5	6.3	61.1	6.8	16.6	6.1
4-Acetamido-1-naphthalene[d]	148–149	$C_{28}H_{36}N_6O_4S$	60.9	6.6	15.2	5.8	61.0	6.7	15.0	5.7
1,5-Naphthalenedi-[d,j]	213–214	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.5	6.7	16.2	7.5
2,6-Naphthalenedi-[d,j]	253–254	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.9	6.8	16.3	7.6
2,7-Naphthalenedi-[d,j]	210–211	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.3	6.7	16.3	7.7

[a] Recrystallized from benzene–petroleum ether or benzene–hexane [b] Recrystallized from ethyl acetate–cyclohexane [c] Recrystallized from ethyl acetate [d] Recrystallized from aqueous ethanol. [e] Calcd.: Cl, 7.4. Found: Cl, 7.4. [f] Calcd.: Cl, 13.8. Found: Cl, 13.9. [g] Calcd.: Br, 15.2. Found: Br, 15.3. [h] Recrystallized from water. [i] Melts partially at 150–151°, resolidifies and remelts at 169–170°. [j] Neutral salt. [k] Recrystallized from benzene.

ing the mixture to boiling. The product which separated in sheaf-like clusters of crystals on cooling was recrystallized from 30% aqueous acetone, yield 3.5 g. (72%), m.p. 159–161°.

Anal. Calcd. for $C_{22}H_{31}ClN_6O_3S$: Cl, 7.2; N, 17.0; S, 6.5. Found: Cl, 7.1; N, 17.0; S, 6.3.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Apparent Acidic Dissociation of Some 5-Aryltetrazoles[1]

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Received February 27, 1957

An improved procedure has been developed for the preparation of 5-aryltetrazoles in which solutions of the aryl cyanides, sodium azide, and acetic acid in *n*-butyl alcohol are heated under reflux. The isomeric 5-chlorophenyl-, 5-bromophenyl-, and 5-methoxyphenyltetrazoles were prepared, their apparent acidic dissociation constants and ultraviolet absorption spectra determined and compared with those of the correspondingly substituted benzoic acids. With the exception of the *ortho* substituted compounds, the 5-aryltetrazoles appear to be stronger acids than the correspondingly substituted benzoic acids.

Tetrazole derivatives in which the hydrogen atom attached to the ring nitrogens has not been replaced generally behave as acidic substances.[2,3,4]

(1) Based on a thesis submitted by Kenneth R. Wilson to Michigan State University in 1955 in partial fulfillment of the requirements for the degree of Master of Science.

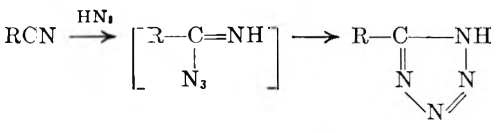
(2) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(3) E. Oliveri-Mandalà, *Gazz. chim. ital.*, **44**, II, 175 (1914).

(4) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1023, 1269 (1953).

The apparent acidic dissociation constants of 5-alkyltetrazoles (R—CN_4H) have been found to be about a fifth to a tenth as large as those of the corresponding aliphatic carboxylic acids (R—COOH) and variations in the apparent acidic dissociation due to the structure of the alkyl groups are quite parallel in both series. Apparent acidic dissociation constants have been reported for 5-phenyl-, and the 5-tolyltetrazoles[2] from which it appeared that these compounds were stronger acids than benzoic and the respective toluic acids. Furthermore, the apparent dissociation constants of the 5-tolyltetrazoles increased in the order *ortho* < *para* < *meta*, while those of the toluic acids increased in the order *para* < *meta* < *ortho*. The preparation and determination of apparent acidic dissociation constants of other 5-aryltetrazoles was undertaken to help explain this situation.

Recently it was shown that 5-substituted tetrazoles could be prepared in a single step by heating alkyl or aryl cyanides in sealed tubes at 150° with hydrazoic acid in benzene solution.[2] A similar reaction took place when the cyanide was heated under the same conditions in isopropyl alcohol solution with equivalent amounts of sodium azide and acetic acid.



The preparation would be greatly simplified if the reaction could be done in an open system and with liberation of hydrazoic acid from sodium azide in the reaction mixture. The problem was to find a solvent of sufficiently high boiling point so that the reaction would proceed at a reasonable rate and in which a weak acid such as acetic would react with sodium azide. Earlier work in closed systems[2] had shown that alcohols might be suitable. To determine the best conditions the preparation of 5-phenyltetrazole from benzonitrile, sodium azide, and acetic acid was studied in boiling isopropyl, *sec* butyl, and *n*-butyl alcohol. With all other conditions the same, the yields of 5-phenyltetrazole in the boiling alcohols were 64, 84, and 91%, respectively. The crude product obtained in *n*-butyl alcohol solution was also less pigmented and of higher melting point than when the lower boiling alcohols were used. The method eliminated the use of sealed tubes and made possible the use of larger quantities of reactants. All the 5-aryltetrazoles listed in Table III were prepared in boiling *n*-butyl alcohol from the respective aryl cyanides, sodium azide, and acetic acid; 5-phenyl-,[2,5,6,7] 5-*o*-chlorophenyl-,[8] and 5-*p*-methoxyphenyltetrazole[9] have been previously described. A 5-bromophenyltetrazole of undetermined orientation was obtained by Lossen and Statius[10] by treatment of 5-phenyltetrazole with bromine water at elevated temperature. The compound appears to be identical with the 5-*p*-bromophenyltetrazole prepared from *p*-bromobenzonitrile in this study.

The 5-aryltetrazoles listed in Table III are colorless, acidic substances; they are soluble in aqueous alkalies, alkali carbonates and bicarbonates, and aqueous ammonia. Their melting points follow the order found for substituted benzoic acids, *i.e.*, rise in the order *meta* < *ortho* < *para*. They form insoluble salts with silver nitrate in hot aqueous ethanol. Attempts to decompose the silver salts by digestion with concentrated nitric acid[11] were not successful and precluded estimation of silver by the Volhard method. Salts formed with benzylamine, ethylenediamine, 2-aminopyridine, piperidine, and *n*-hexylamine did not lend themselves to characterization of the tetrazoles since they did not crystallize well nor did they show sharp melting points.

Apparent acidic dissociation constants (Table I) and neutralization equivalents (Table III) of the 5-aryltetrazoles were determined potentiometrically in 50% or 75% aqueous methanol. Typical weak acid titration curves were obtained. For comparison apparent acidic dissociation constants of similarly substituted benzoic acids in the same solvents are included in Table I. It may be noted that the apparent acidic dissociation constant of 5-phenyltetrazole is larger than that of tetrazole[2] while

TABLE I

APPARENT ACIDIC DISSOCIATION CONSTANTS OF 5-ARYLTETRAZOLES AND THE CORRESPONDING ARYL CARBOXYLIC ACIDS

R	R—$C_6H_4CN_4H$[a] $K \times 10^6$	R—C_6H_4COOH[a] $K \times 10^6$
H	29 (13)[b]	8.0
o-CH_3	15.2[c]	9.33[c]
m-CH_3	20.0[c]	4.27[c]
p-CH_3	15.2[c]	3.55[c]
o-Cl	57 (25)[b]	70.8[d]
m-Cl	87	14.5[d]
p-Cl	(32)[b]	10.0[d]
o-Br	60	70.8[d]
m-Br	92 (42)[b]	13.5[d]
p-Br	(30)[b]	9.33[d]
o-CH_3O	1.2	6.5
p-CH_3O	14	2.8

[a] All values determined in 50% by volume methanol at 25° except as otherwise noted. [b] Values in parentheses were determined in 75% by volume methanol at 25°. [c] Reference 12. [d] Determined at 18–22°, reference 13.

(5) A. Pinner, *Ann.*, **297**, 229 (1897).
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(9) W. Lossen and J. Colman, *Ann.*, **298**, 107 (1897).
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(11) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1003 (1953).
(12) Titrations done in this laboratory by Dr. James A. Garrison.
(13) R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 3, 31 (1928).

benzoic acid appears to be weaker than formic acid. Furthermore, 5-phenyltetrazole and its *meta* and *para* substituted derivatives appear to be stronger acids than the corresponding benzoic acids while *ortho* substituted 5-phenyltetrazoles are weaker than the *ortho* substituted benzoic acids. An interpretation of these differences has been published.[14]

The ultraviolet absorption spectra of the 5-aryltetrazoles do not show the peaks of either of the components, benzene or tetrazole. The interaction of the phenyl group with the tetrazole ring produces a new chromophore that shows a single absorption band with a maximum at 241 mμ (Table II). Elpern and Nachod[15] have reported an identical absorption spectrum for 5-phenyltetrazole. Introduction of bromine or chlorine at the *para* position of 5-phenyltetrazole produces a shift of the band to longer wave lengths and an increase in the extinction coefficient while the same substituents in the *meta* position cause only a slight shift of the maximum toward longer wave lengths with a decrease in the extinction coefficient. With chlorine in the *ortho* position the band is shifted to shorter wave lengths and the extinction coefficient is lowered; bromine in the *ortho* position causes an even greater shift of the band to shorter wave lengths, maximum below 220 mμ. The hypsochromic shift caused by halogens in the *ortho* position may be a steric effect of the *ortho* substituent which makes attainment of coplanarity of the two ring systems difficult and disturbs the resonance interaction of the phenyl and tetrazoles rings. The same reasoning may explain the comparatively low apparent acidic dissociation constants of the *ortho* substituted 5-phenyltetrazoles.

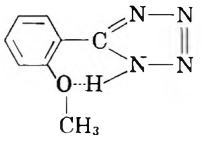

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TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF 5-ARYLTETRAZOLES

Compound	Maxima, mμ	Extinction Coefficient
5-Phenyltetrazole	241	15,900
5-*o*-Chlorophenyltetrazole	234	9,600
5-*m*-Chlorophenyltetrazole	242	14,000
5-*p*-Chlorophenyltetrazole	247	20,400
5-*o*-Bromophenyltetrazole	<220	—
5-*m*-Bromophenyltetrazole	243	13,300
5-*p*-Bromophenyltetrazole	251	21,200
5-*o*-Methoxyphenyltetrazole	294	4,900
	246	11,600
5-*p*-Methoxyphenyltetrazole	259	16,900

(14) R. M. Herbst in S. Graff, *Essays in Biochemistry*, John Wiley & Sons, Inc., New York, 1956, p. 141.

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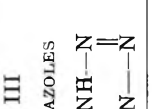
TABLE III

5-ARYLTETRAZOLES



R	Cryst. from	Yield, %[a]	M.P., °C.	Formula	Analyses								Neut. Equiv.
					Calculated				Neut. Equiv.	Found			
					C	H	Hal	N		C	H	Hal	N
H	Water	91	217–218	$C_7H_6N_4$	Ref. 2				146					147
o-Cl	20% A[b]	73	179–180	$C_8H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.7	2.9	19.7	31.3	181
m-Cl	20% A[b]	94	139–140	$C_7H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.6	3.0	19.7	31.1	181
p-Cl	80% A[b]	87	262–263	$C_7H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.7	2.9	19.6	31.1	181
o-Br	20% A[b]	74	183–184	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	35.7	25.1	225
m-Br	25% A[b]	93	154–155	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	36.0	24.9	226
p-Br	95% A[b]	84	278–279 d.	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	35.5	25.2	225
o-CH_3O	10% A[b]	52	159–160	$C_8H_8N_4O$	54.5	4.6		31.8	176	54.8	4.6		31.8	177
p-CH_3O	20% A[b]	81	238–239	$C_8H_8N_4O$	54.5	4.6		31.8	176	54.5	4.6		31.9	177

[a] Allowing for recovered nitrile. [b] Aqueous isopropyl alcohol.

The methoxyl group in the *para* position produces a large shift of the absorption band to longer wave lengths and a small increase in the extinction coefficient. However, in the *ortho* position the methoxyl group causes the appearance of a second band with maximum at 294 mμ; the strong band at 246 mμ probably corresponds to the principal band noted for the other compounds. The second band at 294 mμ may be associated with hydrogen bonding; such bonding could also account for the relatively low apparent dissociation constant of 5-*o*-methoxyphenyltetrazole (I).

EXPERIMENTAL[16]

Substituted benzoyl chlorides were prepared by refluxing the substituted benzoic acids with thionyl chloride for several hours, removing excess thionyl chloride by distillation and fractionating the product under reduced pressure. The following substituted benzoyl chlorides were prepared: *m*-chlorobenzoyl chloride, 93%, b.p. 103–104° at 14 mm.;[17] *o*-bromobenzoyl chloride, 85%, b.p. 120–122° at 14 mm.;[18] *m*-bromobenzoyl chloride, 91%, b.p. 119–122° at 13 mm.;[19] *p*-bromobenzoyl chloride, 95%, b.p. 123–126° at 15 mm.;[19] *o*-methoxybenzoyl chloride, 90%, b.p. 135–138° at 13 mm.[20]

Substituted benzamides were prepared by slow addition of the substituted benzoyl chlorides to a large excess of cold, concentrated aqueous ammonia with vigorous stirring. The following amides were prepared: *m*-chlorobenzamide, 95%, m.p. 135.5–137°;[21] *o*-bromobenzamide, 92%, m.p. 160.5–161.5°;[18] *m*-bromobenzamide, 99%, m.p. 153–155°;[22] *p*-bromobenzamide, 99%, m.p. 192–192.5°;[22] *o*-methoxybenzamide, 87%, m.p. 130–131°.[22]

Substituted benzonitriles were prepared by the method of Fahrenbach[23] by interaction of the amide with a large excess of phosphorus oxychloride in the presence of sodium metabisulfite. The following nitriles were prepared in the yields indicated; where a boiling point is given the product was distilled: *m*-chlorobenzonitrile, 76%, b.p. 99–100° at 15 mm., m.p. 40–41°;[24] *o*-bromobenzonitrile, 84%, m.p. 55–55.5°;[18] *m*-bromobenzonitrile, 81%, b.p. 112–114° at 14 mm., m.p. 39–40°;[25] *p*-bromobenzonitrile, 89%, m.p. 114–114.5°;[25] *o*-methoxybenzonitrile, 89%, b.p. 147–149° at 24 mm.[26] Other substituted benzonitriles were obtained from commercial sources.

5-Aryltetrazoles. All of the tetrazoles were prepared from the appropriate nitriles, sodium azide and acetic acid in about 3:4:4 molar ratio by heating under reflux in *n*-butyl alcohol for 6 days in a well-ventilated hood. On the fourth day small amounts of sodium azide and acetic acid were added. A typical example is described in detail.

5-p-Methoxyphenyltetrazole. A mixture of 33 g. (0.25 mole) of *p*-methoxybenzonitrile, 22 g. (0.33 mole) of sodium azide, 20 g. (0.33 mole) of glacial acetic acid and 100 ml. of *n*-butyl alcohol was boiled under reflux for 4 days at which time 5 g. of sodium azide, 10 g. of glacial acetic acid, and 10 ml. of *n*-butyl alcohol were added and heating continued for 2 days. On completion of the reaction 300 ml. of water was added and all but about 100 ml. of the solvents was removed by distillation under reduced pressure. The residual suspension was made basic by addition of 10% sodium hydroxide. A small amount of insoluble solid was removed by filtration and the filtrate was extracted twice with 50-ml. portions of benzene. From the solid and the benzene extracts about a gram of unreacted nitrile was recovered. The aqueous alkaline solution was acidified with dilute hydrochloric acid and the precipitate was collected on a filter, washed thoroughly with cold water, and recrystallized twice from 20% isopropyl alcohol to yield long, thin needles.

Physical constants, yields, and analytical data for all the 5-aryltetrazoles are given in Table III.

Two preparations of 5-phenyltetrazole were made using isopropyl alcohol and *sec* butyl alcohol in yields of 64 and 84%, respectively. The quantities of reagents, reaction periods, and isolation procedure were as just described. Both preparations gave a product, m.p. 218° after one crystallization from water, that was somewhat more discolored in the crude state than when *n*-butyl alcohol was used as solvent.

All the 5-aryltetrazoles gave precipitates with silver nitrate in ethanol solution. Attempts to decompose the silver salts by digesting them with concentrated nitric acid[11] so that the silver could be estimated by the Volhard technique were unsuccessful. None of the salts were sensitive to shock although they decomposed with a flash when heated over a flame on a spatula. Exposure to daylight did not cause discoloration of the salts. Attempts to prepare salts of several of the 5-aryltetrazoles with ethylene diamine, 2-aminopyridine, benzylamine, piperidine, and *n*-hexylamine in ethanol-ether solution gave white powdery precipitates that melted over a wide range of temperature. Recrystallization from ethanol or ethanol-hexane solution gave either oils or solids with indefinite melting points.

Apparent acidic dissociation constants of all the tetrazoles were determined potentiometrically by titration of weighed samples in aqueous methanol solutions with standard alkali at 25° ± 1° using a Beckman *p*H Meter, Model G. Apparent acidic dissociation constants and neutralization equivalents are given in Tables I and III, respectively.

Ultraviolet absorption spectra of the 5-aryltetrazoles were determined in 95% ethanol using a Beckman Model D-U spectrophotometer. Absorption maxima and extinction coefficients are given in Table II.

EAST LANSING, MICH.

(16) Analyses were done by Micro-Tech Laboratories, Skokie, Ill.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Bicyclo[3.1.0]hexane Derivatives. I. Synthesis of Bicyclo[3.1.0]-2-hexanone and Methyl Bicyclo[3.1.0]hexane-1-carboxylate[1]

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Received March 27, 1957

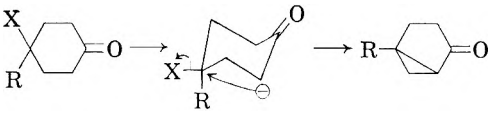
The reaction of 4-tosyloxycyclohexanone and 4-dimethylaminocyclohexanone methiodide with strong bases has been found to result in the formation of bicyclo[3.1.0]-2-hexanone. This type of intramolecular anionic displacement reaction was applied in the preparation of methyl bicyclo[3.1.0]hexane-1-carboxylate from methyl *cis*-3-brosyloxycyclohexanecarboxylate. Similar base catalyzed reactions of methyl 3,4-epoxycyclohexanecarboxylate resulted in transesterification reactions and intermolecular attack of the epoxide ring rather than an intramolecular displacement reaction. An attempted synthesis of sabina ketone is described.

The thujane terpenes[3] are unique among monoterpenes in their possession of the bicyclo[3.1.0]-hexane ring system. A number of methods of constructing this ring system have been developed which involve, in most instances, well known reactions for the preparation of substituted cyclopropanes. This paper will review briefly the known methods of preparing substituted bicyclo[3.1.0]-hexanes and will describe a study made in the preparation of new bicyclo[3.1.0]hexane derivatives involving methods which are extendable to the syntheses of thujane terpenes.

Of the numerous methods which have been described for the preparation of bicyclo[3.1.0]hexane derivatives, the following classifications can be made: the pyrolysis of substituted pyrazolines,[4] the dehalogenation of 1,3-dihalocyclohexanes[5] and related compounds[6] with zinc, internal free-radical coupling reaction[7] of iodomethylcyclopentane,[8] intramolecular anionic displacement reactions,[9] malonic ester synthesis,[10] solvolysis of cholesteryl derivatives,[11] and an intramolecular aldol condensation of a 1,2-diacylcyclopropane derivative.[12] The formation of the bicyclo[3.1.0]hexane derivatives in the present work involve intramolecular anionic displacement reactions.

The treatment of 4-tosyloxycyclohexanone (Ia) with a strong base can lead theoretically to a number of products. β-Elimination of the elements of *p*-toluenesulfonic acid would give 3-cyclohexenone (or 2-cyclohexenone by rearrangement of the double bond). An intermolecular S_N2 displacement reaction involving the base would give a 4-substituted cyclohexanone. If the strength of the base is such that enolization of the ketone can occur, the resulting enolate anion (II) could lead to the formation of bicyclo[3.1.0]-2-hexanone (IIIa) by an intramolecular anionic displacement reaction. This latter reaction is analogous to the conversion of 3-tosyloxy-6-cholestanone to *i*-cholestanone,[9a] and similar reactions have been used in the preparation of larger bicyclic ring systems.[13]

4-Tosyloxycyclohexanone was prepared by the



Ia, R = H
X = $OSO_2C_6H_4CH_3$
b, R = $CH(CH_3)_2$
X = Cl
c, R = H
X = $N(CH_3)_3{}^+I^-$

II

IIIa, R = H
b, R = $CH(CH_3)_2$

(1) This paper was abstracted from the thesis submitted by G. A. M. to the Graduate School of The Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1956.

(2) National Institutes of Health Fellow, 1955–1956.

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hydrogenation of hydroquinone to a mixture of *cis*- and *trans*-1,4-cyclohexanediols (96%), formation of the corresponding monotosylates (79–82%) and oxidation of the monotosylates to the keto tosylate (Ia) (54%)[14] using chromium trioxide in an acetic acid-water-acetone medium.

Treatment of 4-tosyloxycyclohexanone with one equivalent of potassium *t*-butoxide in hot *t*-butyl alcohol gave a product which was isolated as the 2,4-dinitrophenylhydrazone in 87% yield. This dinitrophenylhydrazone was found to be isomeric with, but otherwise different from, 2- and 3-cyclohexenone 2,4-dinitrophenylhydrazones in melting point and infrared and ultraviolet spectra (see Table I). The ultraviolet spectrum of the product is in agreement with the presence of a conjugated three-membered ring. On the basis of these data, it is concluded that the ketone formed in this reaction is bicyclo[3.1.0]-2-hexanone (IIIa).

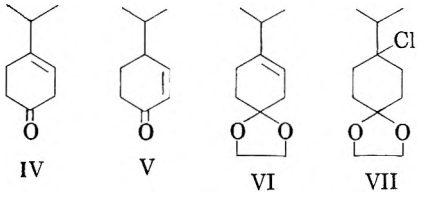
TABLE I
COMPARISON OF 2,4-DINITROPHENYLHYDRAZONES

Dinitrophenylhydrazone of	M.P.	λ_{max} in mμ	ε
Bicyclo[3.1.0]-2-hexanone	175.5–176°	369[a]	23,750
2-Cyclohexenone[15]	167.5–168°	378[a]	27,400
3-Cyclohexenone[15]	133 –134°	362[a]	22,650
Dihydroumbellulone[16]	170.5–171°[b]	369[c]	23,600

[a] In chloroform. [b] *Anal.* Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found. C, 57.86; H, 6.05; N, 16.56. [c] In ethanol.

Although the dinitrophenylhydrazone of IIIa was obtained in good yield from this reaction, it was not possible to separate the ketone by distillation from the *t*-butyl alcohol used as the solvent. However, it was possible to prepare and isolate the pure ketone (IIIa) by using a different base and solvent. When an ethereal solution of 4-tosyloxycyclohexanone was treated with triphenylmethyl sodium and heated under reflux, no bicyclic ketone was isolated. By using a higher boiling solvent (benzene) with the same base, the bicyclic ketone (IIIa) was obtained in 12% yield. When the reaction was carried out in refluxing dioxane, the yield was increased to 57%. The best yield, 64%, was achieved using sodium hydride as the base and dioxane as the solvent. The infrared spectrum of bicyclo[3.1.0]-2-hexanone[17] is different from the spectra of the two cyclohexenones which are isomeric with it and contains bands at 3.24 and 3.32 μ which are characteristic for carbon–hydrogen stretching of the methylene hydrogens in a cyclopropane ring.[18a] The pure ketone was converted in 95% yield to the same dinitrophenylhydrazone obtained in the experiment using potassium *t*-butoxide as the base.

The preparation of 4-chloro-4-isopropylcyclohexanone (Ib) was undertaken next since, if a similar intramolecular displacement reaction could be effected, sabina ketone (IIIb)[3] would be formed. 4-Isopropylanisole was reduced to 2,5-dihydro-4-isopropylanisole in 88% yield by a modification of the Birch reduction.[15] The dihydroisopropylanisole was converted in 90% yield to 4-isopropyl-3-cyclohexenone (IV) by oxalic acid in an acetone-water-methanol medium. The presence of a single band at 5.83 μ in the infrared spectrum of the ketone excluded the possibility of appreciable double-bond migration during the hydrolysis.



IV V VI VII

Direct addition of hydrogen chloride to IV to give the chloroketone Ib, was attempted, but no chlorine containing material was obtained. The product consisted of a mixture of unchanged starting material and its double bond isomer, 4-isopropyl-2-cyclohexenone (V). This result was not unexpected in view of the facile migration of β,γ-double bonds into conjugation with carbonyl groups under the influence of mineral acids.[15] To overcome the tendency for isomerization of the double bond during treatment with hydrogen chloride, the ketone function was converted to a ketal group. The ethylene ketal VI was obtained in 71% yield directly from dihydroisopropylanisole by treating it with ethylene glycol in the presence of *p*-toluenesulfonic acid, and removing the methanol formed in the reaction by distillation. The position of the double bond in the product was demonstrated by the conversion of VI in good yield into the known 2,4-dinitrophenylhydrazone of IV. Hydrogen chloride added smoothly to the unsaturated ketal to form the chloroketal VII in 78% yield. All attempts

(13) A. C. Cope and G. Holzman, *J. Am. Chem. Soc.*, **72**, 3062 (1950).

(14) R. Grewe, W. Lorenzen, and L. Vining, *Chem. Ber.*, **87**, 793 (1954), have reported higher yields for this oxidation; however, we were unable to obtain higher yields than reported here using their procedure.

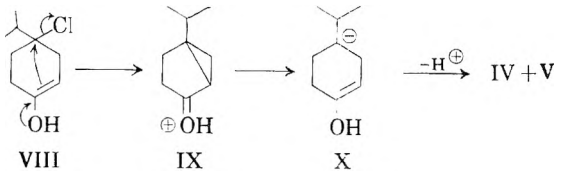
(15) (a) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953); (b) A. J. Birch, *J. Chem. Soc.*, 593 (1946).

(16) R. H. Eastman and J. C. Selover, *J. Am. Chem. Soc.*, **76**, 4118 (1954). We are indebted to Dr. Eastman for a sample of dihydroumbellulone.

(17) The infrared spectrum of IIIa is identical with that of a sample prepared by another means by J. F. Brown, Jr.; private communication.

(18) (a) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952); (b) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 2482 (1949); (c) G. Herzberg, *Infrared and Raman Spectra of Polyatomic Molecules*, D. Van Nostrand Co., New York, N. Y., 1945, p. 352.

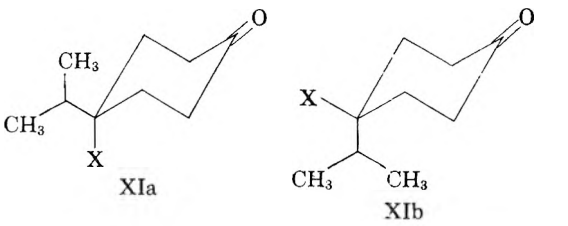
to convert VII to 4-chloro-4-isopropylcyclohexanone (Ib) were unsuccessful. Various methods of acid-catalyzed hydrolyses and ketal exchange reactions were investigated and in each case one of two results was observed; either the chloroketal was essentially unaffected or else a mixture of unsaturated ketones (IV and V) was obtained. The loss of hydrogen chloride in some of the reactions may have occurred by the usual E1 or E2 mechanism[19] or by an intramolecular displacement reaction of the enolized chloroketone (VIII) to the conjugate acid of sabina ketone (IX)[20] followed by acid-catalyzed cleavage of the three-membered ring[21] (as illustrated by X) and loss of a proton to give the observed products (after double bond migrations).



VIII IX X

It would appear that for the synthesis of sabina ketone by this type of synthetic approach to be successful, there must be placed in the tertiary 4-position of the 4-isopropylcyclohexanone molecule a group which is stable to mild conditions. This group should be sufficiently bulky to assume an equatorial configuration, and should be capable of being displaced by the enolate anion by the process illustrated in II.

It is known that the conformational arrangement of substituents on a disubstituted cyclohexane ring is controlled largely by the bulkier group, which will assume an equatorial configuration preferentially.[22] Therefore, the configuration of 4-chloro-4-isopropylcyclohexanone should be represented by structure XIa (X = axial chlorine) to a larger extent than structure XIb (X = equatorial chlorine).



XIa XIb

Structure XIa is undesirable for the preparation of a bicyclic ketone from two standpoints. The axial leaving group is oriented *trans* to β-axial hydrogen atoms and is therefore susceptible to elimination reactions. The leaving group X is not oriented properly for a backside displacement from the potential anion across the ring (as in II). Structure XIb, on the other hand, should be less susceptible to elimination reactions and the molecular orbitals are aligned for easy bond formation in an intramolecular displacement reaction. Therefore, if the leaving group in structure XI is bulkier than an isopropyl group, it would be expected that the larger percentage of molecules would have structure XIb and a displacement reaction could occur to give sabina ketone.

An example of a group which fulfills the requirement of bulkiness is the trimethylammonium ion. This group could be generated from the dimethylamino group in the last stages of a synthesis, and the latter group should exhibit no tendency to be displaced or eliminated under mild conditions as was the chloro group in the work just described.

Since the base-catalyzed decomposition of alkyltrimethylammonium ions usually goes by way of a Hofmann elimination (rather than a displacement reaction),[23] it was decided to evaluate the usefulness of the trimethylammonium ion in intramolecular displacement reactions using a readily available compound rather than XI (X = $(CH_3)_3N^+-$). The model chosen was 4-dimethylaminocyclohexanone methiodide (Ic).

The high pressure hydrogenation of *p*-dimethylaminophenol in the presence of Raney nickel gave 4-dimethylaminocyclohexanol in 19% yield. This compound was also prepared from *p*-aminophenol through the intermediates, *p*-acetamidophenol (76%), 4-acetamidocyclohexanol (*ca.* 100%) and 4-aminocyclohexanol. The latter compound was converted to 4-dimethylaminocyclohexanol in 46% yield using formaldehyde and formic acid. Oxidation of the aminoalcohol to 4-dimethylaminocyclohexanone was accomplished in 37% yield using potassium dichromate in aqueous sulfuric acid. The amino ketone was converted to the methiodide (Ic) in 97% yield.

When 4-dimethylaminocyclohexanone methiodide was treated with potassium *t*-butoxide in refluxing *t*-butyl alcohol, evolution of trimethyl amine occurred and, from the reaction mixture, bicyclo[3.1.0]-2-hexanone could be isolated as its 2,4-dinitrophenylhydrazone in 42% yield (crude product). Identification of the ketone derivative was made on the basis of its infrared and ultraviolet spectra and mixed melting point determinations. Because of the insolubility of the methiodide in nonhydroxylic solvents, the reaction could not be attempted under the other conditions described for 4-tosyloxycyclohexanone. The Hofmann pyrolysis

(19) E. R. Alexander, *Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 104.

(20) For a similar reaction, see H. L. Goering, A. C. Olson, and H. H. Espy, *J. Am. Chem. Soc.*, 78, 5371 (1956).

(21) O. Wallach, *Ann.*, 359, 265 (1908), has reported the acid-catalyzed conversion of sabina ketone to a mixture of IV and V.

(22) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).

(23) Displacement reactions yielding cyclopropanes have been observed in cases where a relatively stable anion can be formed in a position γ to the trimethylammonium group. See, for example, (a) H. Rinderknecht and C. Niemann, *J. Am. Chem. Soc.*, 73, 4259 (1951); (b) J. Weinstock, *J. Org. Chem.*, 21, 541 (1956).

of the quarternary ammonium hydroxide obtained from the methiodide Ic by the usual method[24] gave only polymeric material. In summary, the displacement reaction of Ic was not clean and was limited to hydroxylic solvents because of solubility problems. In view of these results, it has been concluded that although the trimethylammonium group can be displaced with the formation of a three-membered ring, it is not a good leaving group. Therefore, the synthesis of sabina ketone by a similar approach was not attempted.

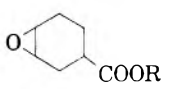
Attention was turned next to the possibility of synthesizing bicyclo[3.1.0]hexane derivatives in which the carbonyl function would not be part of the ring system itself, but adjacent to the ring. This possibility, if realized, would widen the scope of possible syntheses of thujane terpenes and could provide a handle for the introduction of an isopropyl group at the bridgehead position (the position it occupies in all terpenes of the thujane type). The synthesis of methyl bicyclo[3.1.0]hexane-1-carboxylate was therefore undertaken.

Catalytic hydrogenation of methyl *m*-hydroxybenzoate over Raney nickel gave mainly methyl *cis*-3-hydroxycyclohexanecarboxylate in 71% yield. The hydroxy ester was converted to methyl *cis*-3-brosyloxycyclohexanecarboxylate (XII) in 71% yield. When the brosylate was treated with potassium *t*-butoxide in *t*-butyl alcohol solution, a white precipitate formed quickly and the solution became neutral. The methyl bicyclo[3.1.0]hexane-1-carboxylate (XIII) isolated from the reaction mixture (83% yield) is inert to potassium permanganate solution and has bands characteristic of a cyclopropane ring[18] in the infrared spectrum. The correspondirg amide was prepared by an ammonolysis reaction and was found to be different from all of the possible cyclohexenecarboxamides (as expected).

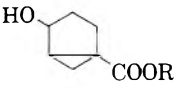
XII XIII

There have been cases reported in which epoxy ketones have undergone base-catalyzed intramolecular displacement reactions with the formation of new ring systems.[25] As an extension to our work we undertook the synthesis of the epoxy ester XIVa and a study of its reactions with base. If an intramolecular displacement reaction occurred to give XV, the product would have utility in the preparation of substituted bicyclohexanones.

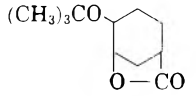
Methyl 3,4-epoxycyclohexanecarboxylate (XIVa) was prepared from methyl 3-cyclohexenecarboxylate by oxidation with peracetic acid. Treatment of



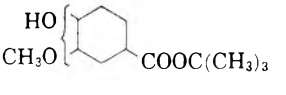
XIVa, R = CH_3
b, R = $C(CH_3)_3$



XV



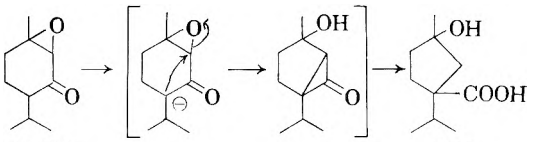
XVI



XVII

the epoxy ester with sodium hydride or triphenylmethyl sodium in dioxane gave polymeric material. When compound XIVa was treated with potassium *t*-butoxide in a refluxing solution of *t*-butyl alcohol for 1 hour, transesterification occurred and *t*-butyl 3,4-epoxycyclohexanecarboxylate (XIVb) was obtained in 71% yield. The infrared spectrum of the product excludes isomeric structures for the product, such as XVI. When the epoxy ester XIVa was treated with potassium *t*-butoxide in a refluxing solution of *t*-butyl alcohol for a longer period of time (about 8 hr.), the *t*-butyl ester (XIVb) was obtained again in addition to 22% of a higher boiling alcohol. The infrared spectrum of the alcohol did not contain bands characteristic of a three-membered ring (thus excluding structure XV) and on the basis of other evidence, structure XVII is proposed. No attempt was made to establish the relative positions of the hydroxyl and methoxyl groups in the product since it is likely that a mixture of isomers was formed.

The formation of XVII undoubtedly takes place *via* compound XIVb. The methoxide ion formed in the transesterification reaction, being a weaker base than the *t*-butoxide ion, is probably the predominant basic species in the reaction mixture and, in addition, being a less bulky entity, the methoxide ion is not as sterically hindered in its approach toward the epoxide ring. The failure to obtain any of the expected bicyclic compound XV is surprising in view of the fact that similar reactions have been reported before. For example, the rearrangement of piperitone oxide (XVIII) to the hydroxy acid XIX on treatment with methanolic potassium hydroxide solution[26] can be rationalized as proceeding through an intramolecular displacement reaction as shown.



XVIII XIX

The reactions leading to bicyclic ring systems reported in this work have occurred by a backside attack of the enolate anion on the leaving

(24) A. C. Cope, D. C. McLean, and N. A. Nelson, *J. Am. Chem. Soc.*, **77**, 1628 (1955).

(25) See, for example, D. H. R. Barton and A. S. Lindsay, *J. Chem. Soc.*, 1951, 2988.

(26) (a) W. Treibs, *Ber.*, **64B**, 2545 (1931); (b) R. H. Reitsema and V. J. Varnis, *J. Am. Chem. Soc.*, **78**, 3792 (1956).

group. The configuration of the epoxides (XIVa and b) may be such that the molecular orbital of the epoxide ring is not aligned properly for bond displacement with the enolate anion. The importance of the orientation of molecular orbitals for electron interaction across a ring has been discussed recently.[27]

EXPERIMENTAL[28]

4-Tosyloxycyclohexanone (Ia). A mixture of 611 g. of hydroquinone, 700 ml. of 95% ethanol and 6 teaspoonfuls of Raney nickel[29] was shaken in a hydrogen atmosphere (initial pressure, 1800 p.s.i.) at 140° until the hydrogen uptake ceased (4.5 hr.). The catalyst was separated by filtration from the hot reaction mixture and on cooling the filtrate, 257 g. (40%) of a mixture of 1,4-cyclohexanediols was deposited which consisted of about 90% *trans*- and 10% *cis*-diol as estimated from its melting point range of 131–141.5°.[30] Distillation of the filtrate gave an additional 363 g. (56%) of a mixture of isomers, m.p. 100.5–116°, which contained approximately 60% *trans*- and 40% *cis*-1,4-cyclohexanediol.

Eighty-two grams (0.43 mole) of *p*-toluenesulfonyl chloride was added in one portion to a solution of 50 g. (0.43 mole) of 1,4-cyclohexanediol (m.p. 100.5–116°) in 400 ml. of anhydrous pyridine. After stirring the mixture for 1 hr., it was placed in the refrigerator for 18 hr. The solid material was removed by suction filtration and the filtrate was diluted with water and extracted with ether (the ditosylate is relatively insoluble in ether and water, while the unchanged starting material is relatively insoluble in ether, but soluble in water). The ether extract was filtered and washed with dilute hydrochloric acid, water and dried.[31] Concentration of the ether, finally at reduced pressure, gave 95.8 g. (82%) of the crude semicrystalline 4-tosyloxycyclohexanol. The two isomers of this compound have been described.[32]

A solution of 38.8 g. of the crude 4-tosyloxycyclohexanol, 38 ml. of acetone, and 80 ml. of acetic acid was cooled in an ice bath to 10° and a solution of 21.0 g. of chromium trioxide in 17 ml. of water and 35 ml. of acetic acid was added dropwise with stirring over a period of 13 min. while maintaining the temperature below 20°. After 30 min. the mixture was poured into ether (1 l.) and the ether layer was washed several times with water, sodium bicarbonate solution, water, and then dried.[31] Most of the ether was removed by distillation, and crystallization of the product was induced by cooling the resulting solution with Dry Ice. Additional crops of crystals were obtained by further concentration of the mother liquor and by addition of pentane. The crude 4-tosyloxycyclohexanone (20.7 g., 54%, m.p. 90–95°) was recrystallized from ether-hexane before use, m.p. 97.2–97.8° (reported,[14] 94–95°).

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 58.15; H, 6.21.

4-Tosyloxycyclohexanone 2,4-dinitrophenylhydrazone was prepared at 0° from an ethanolic solution of 2,4-dinitrophenylhydrazine hydrochloride and was recrystallized from an ethanol-chloroform solution, m.p. 150.4–150.6°, $\lambda_{max}^{CHCl_3}$ 361 mμ, ε 23,500.

Anal. Calcd. for $C_{19}H_{20}N_4O_7S$: C, 50.88; H, 4.50; N, 12.49. Found: C, 50.67; H, 4.50; N, 12.41.

4-Tosyloxycyclohexanone semicarbazone was prepared by treating the ketone with an ethanolic solution of semicarbazide hydrochloride and pyridine. Recrystallization from absolute ethanol afforded an analytical sample, m.p. 140.3–140.7° (dec.), λ_{max}^{EtOH} 227.5 mμ, ε 26,300 [reported,[14] m.p. 145° (dec.)].

Anal. Calcd. for $C_{14}H_{19}N_3O_4S$: C, 51.68; H, 5.89; N, 12.91. Found: C, 52.05; H, 5.93; N, 12.98.

Bicyclo[3.1.0]-2-hexanone (IIIa) *from 4-tosyloxycyclohexanone.* (a) *Using sodium hydride as the base.* The reaction was carried out under a nitrogen atmosphere in a dry 200-ml. 3 necked flask equipped with a Hershberg stirrer and reflux condenser. In the flask were placed 3.8 g. of dried 4-tosyloxycyclohexanone, 0.36 g. of sodium hydride, 50 ml. of anhydrous dioxane[33] and 1 drop of absolute ethanol. The mixture was stirred and heated under reflux for 2.5 hr. and allowed to cool. The reaction mixture was diluted with 50 ml. of water and sufficient potassium carbonate was added to saturate the aqueous layer before extracting with ether. The ether extract was dried.[31] The bulk of the solvent was removed by distillation and the concentrate was distilled through a semimicro column giving 0.87 g. (64%) of bicyclo[3.1.0]-2-hexanone (IIIa), b.p. 58° (13 mm.), n_D^{25} 1.4706. An analytical sample of IIIa had b.p. 69° (20 mm.), n_D^{25} 1.4747; $\lambda_{max}^{CCl_4}$ 3.24 and 3.32μ (CaF_2 prism).

Anal. Calcd. for C_6H_8O: C, 74.97; H, 8.39. Found: C, 74.70; H, 8.45.

Bicyclo[3.1.0]-2-hexanone 2,4-dinitrophenylhydrazone was prepared from the pure ketone in 95% yield using an ethanolic solution of dinitrophenylhydrazine hydrochloride at 0°, m.p. 170.6–171.9°. An analytical sample, recrystallized from ethanol-benzene, melted at 175.5–176.1°, $\lambda_{max}^{CHCl_3}$ 369 mμ, ε 23,750.

Anal. Calcd. for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.35; H, 4.58; N, 20.35.

(b) *Using triphenylmethyl sodium as the base.* The reaction was carried out under a nitrogen atmosphere in a dry 200-ml. 3 necked flask equipped with a Hershberg stirrer, dropping funnel, and a distillation head which could be used for total reflux. To a solution of 7.1 g. of dried 4-tosyloxycyclohexanone and 100 ml. of purified dioxane[33] was added dropwise 49.5 ml. of 0.53*N* triphenylmethyl sodium in ether. The red color of the base was discharged immediately and a yellow-green precipitate formed. The solvent was distilled slowly until the boiling point reached 99° (about 2.3 hr.). The reaction mixture was cooled and 100 ml. each of water and ether were added. The aqueous layer was saturated with potassium carbonate and extracted with ether. The combined organic layers were dried.[31] The ether was removed by distillation and the residue was distilled rapidly under reduced pressure until triphenylmethane began to distil, the distillate being collected in a Dry Ice-cooled trap. The distillate was concentrated through a 20-cm. helix-packed column until most of the dioxane had been removed. The material remaining in the flask and column was dissolved in ether, the solution was concentrated, and the concentrate was distilled through a semimicro column giving 1.44 g. (57%) of bicyclo[3.1.0]-2-hexanone, b.p. 60–64° (14–15 mm.), n_D^{25} 1.4717.

(c) *Using potassium t-butoxide as the base.* The apparatus was set up as in (a). To a solution of 4.6 g. of 4-tosyloxycyclohexanone in 75 ml. of anhydrous *t*-butyl alcohol was added

(27) (a) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954); (b) E. E. van Tamelen, *J. Am. Chem. Soc.*, **77**, 1704 (1955).

(28) Melting points are corrected and boiling points are uncorrected. Ultraviolet spectra were determined with a Cary Ultraviolet Recording Spectrophotometer, Model 11MS. Infrared spectra were determined with a Baird (Model B) or Perkin-Elmer (Model 21) Double Beam Infrared Recording Spectrophotometer fitted with a sodium chloride prism unless otherwise noted. We are indebted to Dr. S. M. Nagy and his associates for analyses.

(29) Obtained from Raney Catalyst Co., Chattanooga, Tenn.

(30) R. C. Olberg, H. Pines, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **66**, 1096 (1944).

(31) Drying agent, anhydrous magnesium sulfate.

(32) L. N. Owen and P. A. Robbins, *J. Chem. Soc.*, 320 (1949).

(33) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

over a 5-min. period 0.017 mole of potassium *t*-butoxide in 25 ml. of *t*-butyl alcohol. A white precipitate formed almost immediately. The mixture was stirred and heated under reflux for 2.5 hr., at which time the reaction mixture was neutral. Water (65 ml.) and potassium carbonate were added to the flask and the organic material was extracted with ether and dried.[31] The ether was removed by distillation through a 40-cm. Vigreux column. An aliquot of the remaining solution gave 87% of bicyclo[3.1.0]-2-hexanone 2,4-dinitrophenylhydrazone, identical in m.p., mixed m.p. and ultraviolet spectrum with the sample obtained from the pure ketone. The ketone (IIIa) azeotropes (or codistils) with *t*-butyl alcohol and could not be obtained by fractional distillation.

4-Isopropyl-3-cyclohexenone (IV). The procedure described below gives higher yields than reported previously.[34] To an insulated 1-l. 3 necked flask fitted with a Hershberg stirrer and dropping funnel was added 20 g. of 4-isopropylanisole (b.p. 95–96.5° at 21 mm.; n_D^{25} 1.5004; λ_{max}^{EtOH} 223 mμ, ε 9,650, 277 mμ, ε 1,810, 284 mμ, ε 1,550: reported,[34] b.p. 81–82° at 10 mm.; n_D^{20} 1.5038) and 50 ml. of anhydrous ether. With stirring, 500 ml. of liquid ammonia was added, followed by 5.1 g. of lithium wire[15a] added in small pieces over a 5-min. period. After 10 min., 55 ml. of absolute ethanol was added dropwise over a 3-min. period. When the blue color of the reaction mixture had been discharged, 2.7 g. of lithium wire was added as before and stirred for 5 min. before 30 ml. of absolute ethanol was added dropwise. The product was isolated in the usual way[16] and gave 17.5 g. (86%) of 2,5-dihydro-4-isopropylanisole, b.p. 98–99° (21 mm.), n_D^{25} 1.4748. The ultraviolet spectrum of the distillate between 277 and 284 mμ indicated the virtual absence of unchanged starting material.

A sample of the dihydro compound was converted[15a] to *4-isopropyl-3-cyclohexenone 2,4-dinitrophenylhydrazone* in 91% yield, m.p. 114.5–117°, $\lambda_{max}^{CHCl_3}$ 364 mμ, ε 23,150 [reported, m.p. 107–108°,[15b,34] λ_{max}^{ETOH} 263 mμ,[34b] ε 22,400].

A mixture of 1.0 g. of oxalic acid, 40 ml. of water, 90 ml. of acetone, 50 ml. of methanol, and 10.0 g. of 2,5-dihydro-4-isopropylanisole was stirred at room temperature for 75 min. The reaction mixture was diluted with 600 ml. of water and extracted continuously with ether overnight. The ether solution was dried[31] and the solution concentrated. Distillation of the residue through a semimicro column gave 8.2 g. (90%) of 4-isopropyl-3-cyclohexenone, b.p. 73–75° (9 mm.) [reported,[34] b.p. 77–78° (7 mm.)]. The infrared spectrum has a single band at 5.83 μ indicating the absence of 4-isopropyl-2-cyclohexenone.

4-Isopropyl-3-cyclohexenone ethylene ketal (VI). The reaction was carried out in a distillation apparatus having a partial-reflux distillation head. A solution of 300 ml. of dry benzene, 36.7 g. of 2,5-dihydro-4-isopropylanisole, 38.1 g. of ethylene glycol, and 0.5 g. of *p*-toluenesulfonic acid was boiled gently for 2.5 hr., during which time 75 ml. of liquid distilled. The benzene solution was cooled and shaken vigorously with an excess of aqueous sodium carbonate solution. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated sodium chloride solution and dried.[31] Removal of the solvents at reduced pressure and fractional distillation of the residue through a 30-cm. Podbielniak wire-spiral column gave 31.1 g. (71%) of 4-isopropyl-3-cyclohexenone ethylene ketal, b.p. 114.5–118° (20 mm.). An analytical sample had b.p. 115–115.5° (18 mm.), n_D^{25} 1.4733.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.38; H, 9.95.

A sample of the ketal was converted at 0° to *4-isopropyl-3-cyclohexenone 2,4-dinitrophenylhydrazone* in 70% yield, m.p. 110–111°.

4-Chloro-4-isopropylcyclohexanone ethylene ketal (VII). In a 200-ml. flask equipped with a gas-inlet tube and an outlet protected with a calcium chloride-drying tube were placed 10.0 g. of 4-isopropyl-3-cyclohexenone ethylene ketal and 50 ml. of anhydrous ether. Anhydrous hydrogen chloride was bubbled through the solution at 0° until the ether was saturated (about 45 min.). The mixture was allowed to stand at room temperature overnight. The ether and hydrogen chloride were removed at reduced pressure in a dry nitrogen atmosphere. Distillation of the residue through a semimicro column (nitrogen atmosphere) yielded 9.4 g. (78%) of 4-chloro-4-isopropylcyclohexanone ethylene ketal, b.p. 63–67° (0.08 mm.). An analytical sample had b.p. 90–90.5° (0.73 mm.), n_D^{25} 1.4813.

Anal. Calcd. for $C_{11}H_{19}ClO_2$: C, 60.40; H, 8.76; Cl, 16.21. Found: C, 60.65; H, 8.82; Cl, 15.94.

This ketal did not form a dinitrophenylhydrazone at 0° when treated in the usual way.[15a] At higher temperatures (45° and above), *4-isopropyl-2-cyclohexenone 2,4-dinitrophenylhydrazone* was formed, m.p. 132–132.4°, $\lambda_{max}^{CHCl_3}$ 379 mμ, ε 27,300 (reported m.p. 135–136°, λ_{max}^{EtOH} 376 mμ, ε 28,100;[34] m.p. 136°, λ_{max}^{EtOH} 376 mμ, ε 29,300[35]).

Attempted preparation of 4-chloro-4-isopropylcyclohexanone. (a) *From 4-isopropyl-3-cyclohexenone.* The attempted Markownikoff addition of hydrogen chloride to the β,γ-unsaturated ketone in benzene solution at 10° gave a liquid (b.p. 90–91° at 14 mm.) which exhibited strong bands of equal intensity at 5.83 μ and 5.95 μ These results indicated that the product was a mixture of 4-isopropyl-2-cyclohexenone and starting material.

(b) *From 4-chloro-4-isopropylcyclohexanone ethylene ketal.* A series of experiments involving the direct hydrolysis of the chloroketal were carried out in solutions of aqueous acetone and *p*-toluenesulfonic acid, cold concentrated hydrochloric acid (short contact time), and aqueous alcoholic hydrochloric acid. Acid catalyzed transketalization reactions using acetone and pyruvic acid as acceptors were also investigated. In no instance was any of the desired product detected. Usually unchanged starting material or a mixture of unsaturated ketones was isolated.

4-Dimethylaminocyclohexanol. p-Aminophenol (500 g.) in 600 ml. of water and 100 ml. of acetic acid was acetylated by the dropwise addition of 600 ml. of acetic anhydride at 60°. The reaction mixture was heated on the steam bath for 1 hr., allowed to stand overnight at room temperature, then cooled. The *p-acetamidophenol* was collected on a filter, washed with water and dried to yield 524 g. (76%), m.p. 168–170° (reported,[36] m.p. 166°, 169°). An ethanol solution of *p*-acetamidophenol (322 g.) was hydrogenated over Raney nickel[29] at 180° and an initial pressure of 2000 p.s.i. Filtration of the reaction mixture and distillation of the solvent gave 334 g. of crystalline *4-acetamidocyclohexanol.* No attempt was made to separate the known *cis* and *trans* isomers of this compound.[37] The infrared spectrum of the product did not contain the characteristic bands of the starting phenol.

4-Acetamidocyclohexanol (50 g., 0.32 mole), potassium hydroxide (29.5 g., 0.45 mole) and 100 ml. of water were combined and heated under reflux for 18.5 hr. The solution was concentrated to a syrup and extracted with tetrahydrofuran. The solvent was then removed by distillation at reduced pressure, and to the residue were added 43 ml. (1 mole) of 98–100% formic acid and 49 ml. (0.65 mole) of 37% formaldehyde. The reaction mixture was warmed carefully until the vigorous effervescence subsided and then heated under reflux for 23 hr. Following the addition of 27 ml. (0.32 mole) of concentrated hydrochloric acid, the reaction mixture was concentrated under reduced pressure to a sirupy consistency. With cooling, the reaction mixture was made alkaline with 50% sodium hydroxide solution, ex-

(34) (a) M. D. Soffer and M. A. Jevnik, *J. Am. Chem. Soc.*, **77**, 1003 (1955); (b) Presumably this λ_{max} should be 363 mμ.

(35) K. G. Lewis, *J. Chem. Soc.*, 2765 (1951).

(36) (a) P. Friedlaender, *Ber.*, **26**, 172 (1893); (b) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 82 (1939).

(37) E. Ferber and H. Bruckner, *Ber.*, **72**, 995 (1939).

tracted with tetrahydrofuran and the extracts dried.[31] Distillation of the product under nitrogen and through a 10-cm. Vigreux column gave 18.9 g. (41%) of 4-dimethylaminocyclohexanol, b.p. 121–123° (14 mm.) (reported,[38] b.p. 126° at 19 mm.). The infrared spectra of this material and another sample prepared in 19% yield by catalytic reduction of *p*-dimethylaminophenol (using Raney nickel) were essentially the same.

4-Dimethylaminocyclohexanone. The procedure employed is similar to that of Baker and McEvoy.[39] In a 500-ml. 3 necked flask equipped with a thermometer, stirrer, and dropping funnel were placed (with cooling) 40.0 g. of 4-dimethylaminocyclohexanol, 165 ml. of ice and water and 43 ml. of concentrated sulfuric acid. When the temperature was 20°, 32.2 g. of potassium dichromate was added in one portion. The cooling bath was used as required to keep the temperature below 35°. After 30 min., stirring was discontinued, a few seeds of hydrated chromic sulfate were added, and the reaction mixture was cooled in the refrigerator for 2 days. Solids were removed by filtration and the filtrate was poured slowly, with stirring and cooling, into a solution of 300 g. of potassium hydroxide and 300 ml. of water. The mixture was shaken with 200 ml. of ether and filtered through a pad of Celite (545) to break the emulsion. The filter cake was washed with ether and the aqueous layer was separated and extracted with ether. The combined extracts were washed with saturated sodium chloride solution and dried.[31] Distillation of the product in a nitrogen atmosphere through a Vigreux column gave 12.2 g. of 4-dimethylaminocyclohexanone, b.p. 104–111° (16 mm.), n_D^{25} 1.4712 and 7.3 g. of material which was largely unchanged starting material, b.p. above 116° (16 mm.). The amino ketone darkens within a few hours when exposed to air. An analytical sample had b.p. 95° (12 mm.), n_D^{25} 1.4706.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.34; H, 10.80; N, 10.20.

4-Dimethylaminocyclohexanone 2,4-dinitrophenylhydrazone was prepared from ethanolic 2,4-dinitrophenylhydrazine hydrochloride and precipitated by the addition of sodium bicarbonate solution. An analytical sample was recrystallized from methanol, m.p. 117.5–118°, $\lambda_{max}^{CHCl_3}$ 365 mμ, ε 21,050.

Anal. Calcd. for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.60; H, 6.13; N, 21.92.

The *p-toluenesulfonic acid salt* was prepared by combining equimolar quantities of 4-dimethylaminocyclohexanone and *p*-toluenesulfonic acid in ethyl acetate. The pure derivative, recrystallized from ethyl acetate, melted at 114.2–115.6°.

Anal. Calcd. for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.40; H, 7.32; N, 4.57.

4-Dimethylaminocyclohexanone methiodide (Ic) was prepared in 97% yield by allowing a solution of 3.4 g. of the amino ketone, 7 g. of methyl iodide and 25 ml. of anhydrous ether to stand in the refrigerator overnight. A sample was recrystallized from absolute ethanol for analysis, m.p. 274° (hot stage).

Anal. Calcd for $C_9H_{18}INO$: C, 38.17; H, 6.41; I, 44.82; N, 4.95. Found: C, 38.03; H, 6.49; I, 44.75; N, 4.96.

Bicyclo[3.1.0]-2-hexanone 2,4-dinitrophenylhydrazone from 4-dimethylaminocyclohexanone methiodide. To a mixture of 3.90 g. of the methiodide (Ic) and 100 ml. of anhydrous *t*-butyl alcohol contained in a 200-ml. 3 necked flask equipped with a stirrer, dropping funnel, and condenser, was added a solution of 0.0135 mole of potassium *t*-butoxide in 25 ml. of *t*-butyl alcohol over a 5-min. period. The reaction mixture was heated under reflux for 2.5 hr. at which time the alkalinity of the solution had dropped to about *p*H 8. Water (50 ml.), potassium carbonate and ether were added to the reaction mixture and the organic layer was dried.[31] Distillation of the ether gave a solution, an aliquot of which on treatment with 2,4-dinitrophenylhydrazine reagent at 0° gave a 42% yield of crude bicyclo[3.1.0]-2-hexanone 2,4-dinitrophenylhydrazone, m.p. 151–160°, $\lambda_{max}^{CHCl_3}$ 371 mμ, ε 21,000. The mixed m.p. (155–165°) was not depressed with an authentic sample, but the mixed m.p. with 2-cyclohexenone 2,4-dinitrophenylhydrazone (m.p. 162–163.5°)[16] was depressed (135–147°). A recrystallized sample (good recovery) had m.p. 160–169° and an infrared spectrum essentially identical with the spectrum of the pure derivative of IIIa.

Methyl cis-3-brosyloxycyclohexanecarboxylate (XII). A methanolic solution of methyl *m*-hydroxybenzoate was hydrogenated with a Raney nickel catalyst[29] at 180° and 1800 p.s.i. to give 71% of crude *methyl cis-3-hydroxycyclohexanecarboxylate*, b.p. 103–110° (1–2 mm.), containing a small amount of the corresponding cyclic lactone as an impurity. The product was shown to be chiefly one isomer by its conversion (below) to a crystalline brosylate in 71% yield and by saponification of a sample to the known *cis*-3-hydroxycyclohexanecarboxylic acid (m.p. of crude sample, 121.5–125.5°) (reported,[40] m.p. 130–132°, 132°).

A mixture of 15.4 g. of methyl *cis*-3-hydroxycyclohexanecarboxylate, 100 ml. of anhydrous pyridine, and 25 g. of *p*-bromobenzenesulfonyl chloride was stirred for 1 hr. and then placed in the refrigerator overnight. The reaction mixture was filtered, the filtrate was shaken with dilute sodium carbonate solution and extracted with ether. The ether extract was washed with dilute hydrochloric acid, saturated sodium chloride solution and dried.[31] Removal of the ether at reduced pressure and recrystallization of the residue from ether-hexane gave 25.5 g. (71%) of methyl *cis*-3-brosyloxycyclohexanecarboxylate, m.p. 80–85° which was used in the next experiment. An analytical sample, recrystallized from benzene-pentane, had m.p. 89.5–90.0°.

Anal. Calcd. for $C_{14}H_{17}BrO_6S$: C, 44.57; H, 4.54; Br, 21.18; S, 8.50. Found: C, 44.82; H, 4.61; Br, 21.34; S, 8.52.

Methyl bicyclo[3.1.0]hexane-1-carboxylate (XIII). To a warm solution of 38.1 g. of dry methyl *cis*-3-brosyloxycyclohexanecarboxylate and 300 ml. of anhydrous *t*-butyl alcohol contained in a 3-necked flask equipped with a stirrer, dropping funnel, and condenser was added over a 5-min. period 0.101 mole of potassium *t*-butoxide in 100 ml. of *t*-butyl alcohol. The reaction mixture was heated under reflux for 25 min., at which time it was neutral. (The reaction mixture is nearly neutral within a few minutes after the addition of base). Water (100 ml.) and saturated sodium chloride solution (200 ml.) were added to the cooled reaction mixture and the mixture was extracted with ether. After drying the extract,[31] the solvents were removed by distillation through a Vigreux column. Distillation of the residue gave 11.72 g. (83%) of methyl bicyclo[3.1.0]hexane-1-carboxylate, b.p. 77–80° (21 mm.), n_D^{25} 1.4616. An analytical sample had b.p. 79° (22 mm.), n_D^{25} 1.4615.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.81; H, 8.71.

The product does not decolorize a 2% potassium permanganate solution in 2 min. The infrared spectrum shows two bands at 3.24 and 3.32 μ (calcium fluoride prism) attributable to the carbon-hydrogen stretching of the methylene hydrogens on a cyclopropane ring[18a] and a strong band at 9.65 μ[18a,b] attributable to the cyclopropane symmetric vibration.[18a] The vapor phase chromatogram (silicone column) shows a single sharp band, indicating the absence of olefinic isomers.

Bicyclo[3.1.0]hexane-1-carboxamide was prepared by heating 0.56 g. of the ester and 10 ml. of a saturated methanolic-ammonia solution in a sealed tube at 100° for 4 days. Removal of the solvent gave 0.33 g. (66%) of crude material which was crystallized from cyclohexane–benzene (nearly

(38) H. Heckel and R. Adams, *J. Am. Chem. Soc.*, **47**, 1712 (1925).

(39) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).

(40) (a) H. L. Goering and C. Serres, Jr., *J. Am. Chem. Soc.*, **74**, 5908 (1952) (b) W. H. Perkin, Jr., and G. Tattersall, *J. Chem. Soc.*, **91**, 486 (1907); (c) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935).

quantitative recovery) to give pure bicyclo[3.1.0]hexane-1-carboxamide having the same melting point as a sample sublimed for analysis, m.p. 161–162°, with softening at 155°. The infrared spectrum (potassium bromide pellet) contains an inflection at 3.32 μ and a band at 3.23 μ (calcium fluoride prism) as well as a strong band at 9.94 μ, characteristic of the three-membered ring.[18]

Anal. Calcd. for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.29; H, 8.98; N, 11.37.

Methyl 3-cyclohexenecarboxylate. Butadiene and methyl acrylate were condensed in a Diels-Alder reaction by a published procedure[41] to give a 91% yield of methyl 3-cyclohexenecarboxylate, b.p. 80° (20 mm.), n_D^{25} 1.4589 (reported,[41] b.p. 70° at 13 mm.).

3-Cyclohexenecarboxamide was prepared by heating 0.69 g. of the ester and 10 ml. of a saturated methanolic-ammonia solution in a sealed tube at 100° for 2 days. Removal of the solvent and crystallization of the crude product from cyclohexane-benzene gave 0.48 g. (78%) of 3-cyclohexenecarboxamide having the same melting point as a sample sublimed for analysis, m.p. 155.5–156.5°.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.43; H, 9.00; N, 11.34.

Methyl 3,4-epoxycyclohexanecarboxylate (XIVa). A solution of 0.10 mole of commercial peracetic acid in 30 ml. of methylene chloride was shaken with 4.0 g. of sodium acetate trihydrate, separated, and added dropwise with stirring over a 10-min. period to a cold solution of 7.0 g. (0.05 mole) of methyl 3-cyclohexenecarboxylate in 28 ml. of methylene chloride. When the addition was complete, the reaction mixture was allowed to stand at room temperature for 2 days. A 40% solution of sodium hydroxide was added dropwise, with cooling, to neutralize the excess acid. The solid material was separated, dissolved in water and extracted with methylene chloride. The combined methylene chloride solutions (which gave a negative starch-iodide test) were dried.[31] Distillation of the product through a semimicro column gave 2.8 g. of unchanged ester, b.p. 80–82° (22 mm.), and 3.6 g. (77%, based on recovered starting material) of methyl 3,4-epoxycyclohexanecarboxylate, b.p. 115–117° (22 mm.), n_D^{25} 1.4626. Large scale preparations gave comparable yields. An analytical sample had b. p. 109.5–110.5° (17 mm.), n_D^{25} 1.4625.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.49; H, 7.56.

Reaction of methyl 3,4-epoxycyclohexanecarboxylate with potassium t-butoxide. (a) *Short reaction time.* A solution of 0.047 mole of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol was added dropwise, with stirring, over a 5-min. period to a solution of 7.41 g. (0.047 mole) of methyl 3,4-epoxycyclohexanecarboxylate and 50 ml. of *t*-butyl alcohol. The reaction mixture was heated under reflux for 1 hr., cooled, treated with sodium chloride solution, and extracted with ether. The dried ether solution was concentrated on the steam bath and the residue was distilled through a semimicro column giving 6.63 g. (71%) of *t-butyl 3,4-epoxycyclohexanecarboxylate* (XIVb), b.p. 82.5–85.5° (1.3 mm.), n_D^{25} 1.4525–1.4534. An analytical sample had b.p. 80.5–81.5° (1.4 mm.), n_D^{25} 1.4525.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.91; H, 9.09.

The infrared spectrum of the product contains the bands characteristic of a *t*-butyl group (7.22 and 7.33 μ)[42] and does not contain bands characteristic for a hydroxyl group or a cyclopropane ring. Lithium aluminum hydride reduction gave as a product a viscous oil whose infrared spectrum did not contain the characteristic bands of a *t*-butyl group. This demonstrates that the *t*-butyl group must be present in an ester rather than an ether function.

(b) *Long reaction time.* The reaction was carried out as in part (a) using 7.91 g. (0.051 mole) of methyl 3,4-epoxycyclohexanecarboxylate in 100 ml. of anhydrous *t*-butyl alcohol and a solution of 0.052 mole of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol. The reaction mixture was stirred and heated under reflux for 8.5 hr., then worked up as in part (a). Fractional distillation through a semimicro column gave 4.38 g. (44%) of *t*-butyl 3,4-epoxycyclohexanecarboxylate, b.p. 75–105° (1.2 mm.), n_D^{25} 1.4533–1.4559 and 2.54 g. (22%) of a fraction distilling mostly at 113–114° (1.2 mm.), n_D^{25} 1.4577 which was identified as *t-butyl 3,4-methoxyhydroxycyclohexanecarboxylate* (XVII). An analytical sample had b.p. 74° (0.03 mm.), n_D^{25} 1.4575.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; OCH_3, 13.47. Found: C, 62.60; H, 9.63; OCH_3, 15.15.

The infrared spectrum (calcium fluoride prism) of the *t*-butyl 3,4-methoxyhydroxycyclohexanecarboxylate contains the characteristic bands for associated (2.88 μ, broad) and unassociated hydroxyl (2.78 μ, sharp) and for the *t*-butyl group[42] (7.22 μ and 7.34 μ).

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(41) K. Alder and W. Vogt, *Ann.*, **564**, 109 (1949).

(42) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 13, 22.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MEXICO]

Structure and Properties of Cyclic Compounds. X.[1] Dissociation Constants of Cyanohydrins of Some Bridged-Ring Ketones

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Received March 4, 1957

The dissociation constants of the cyanohydrins of norcamphor (XIII) and dehydronorcamphor (XIV) and of a number of methyl derivatives (XV–XVII) of the former have been measured. Methyl groups have a very large effect on reactivity in this system.

The bicyclo[2.2.1]heptane system of norcamphane (I) contains a cyclohexane ring (III) rigidly held in a boat form.[3] The one-carbon bridge distorts the ring and introduces considerable strain which has been estimated to amount to about 6 kcal.[4] In forming this ring from the boat form of cyclo-

(1) Part IX, *J. Am. Chem. Soc.*, **79**, 4191 (1957).

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(3) (a) C. W. Shoppee, *Chemistry & Industry*, 86 (1952); (b) D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027.

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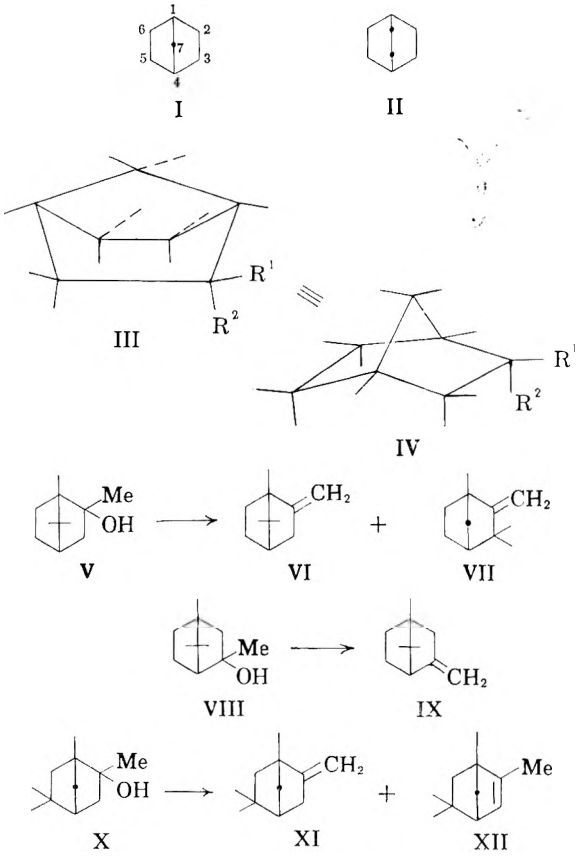
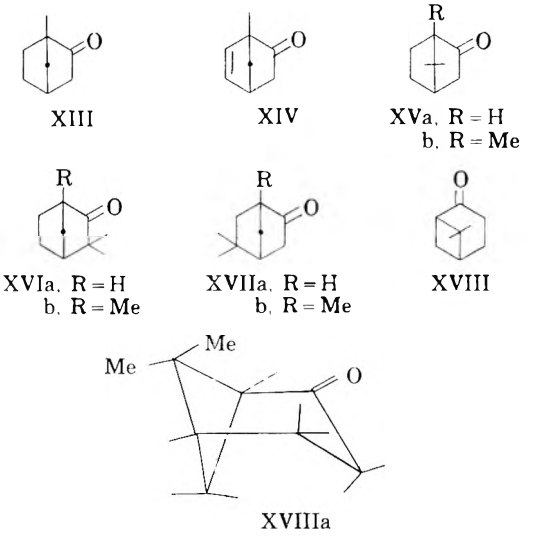
hexane by bridging the 1,4-carbon atoms (I) by a single methylene group these atoms must be brought closer together and all the internal angles of the bridge considerably opened. Bicyclo[2.2.2]-octane (II) with a two-methylene bridge is perfectly symmetrical and not strained.[5]

Placing a double bond inside a bicycloheptane ring will considerably increase the strain, since the preferred angle between carbon-carbon single and double bonds of 124° must be constrained to enter the ring and the original single bond (1.54 Å) is shortened to a double bond (1.35 Å). Chemical evidence in favor of this generalization is that the dehydration of tertiary methyl carbinols tends to take place exocyclically by loss of a primary methyl hydrogen atom rather than by loss of a secondary ring atom. Thus *tert.*-methyl borneol (V) gives β-methylcamphene (VI)[6] as well as α-methyl



camphene (VII) formed by rearrangement, 3-methylepiborneol (VIII) gives 4-methyl-α-fenchene (IX)[7] and 2-methylisofenchol (X) gives 1-methyl-β-fenchene (XI) and only a little 1-methyl-γ-fenchene (XII).[8] Moreover the enol ether of camphor is very unstable, being hydrolyzed by water[9a] and both camphor-2-carbethoxylate[9b] and camphor[9c] have very small enol contents. In these respects the bicycloheptane ring is more similar to a cyclopentane ring than to a cyclohexane ring.[10a]

A double bond exocyclic to the ring will produce a little extra strain since the preferred double bond internal angle is about 116° and this will have to be diminished to enter a ring, which has its angle a little less than the carbon tetrahedral angle. Thus addition to a ketone group might be favored since it will result in a small decrease in I-strain.[10b] However in the boat-form of cyclohexane the two pairs of bonds on either side of the ring are eclipsed and addition to the keto group in XIII will introduce unfavorable eclipsing interactions (IV). In this respect, too, the bicycloheptane ring is similar to a cyclopentane ring.[10] To test this hypothesis the dissociation constant of the cyanohydrin of norcamphor (XIII) has been measured (Table I) and found to be little different from that of cyclopentanone, but quite different from the high reactivity of cyclohexanone in its free chair-form. In the case of dehydronorcamphor (XIV) the double bond will introduce additional strain at the ketone group and facilitate an addition reaction. However there is an electronic effect of the double bond across the ring, which is manifest in the ultraviolet[11a] and infrared absorption[11b] of the ketone, and the inductive effect will decrease the ketone reactivity.[12] The net result of the opposing effects is an observed increase of about a factor of 3 in reactivity.



(5) *Cf.* W. Hückel, *Ann.*, **455**, 123 (1927).
(6) S. Nametkin and L. Brussoff, *Ann.*, **459**, 144 (1927).
(7) G. A. Nyman and A. Kuvaja, *Ann.*, **538**, 68 (1939).
(8) G. Komppa, *Ann.*, **472**, 179 (1929); G. Komppa and G. A. Nyman, *Ann.*, **523**, 87 (1936).

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(12) O. H. Wheeler and J. L. Mateos, unpublished results.

Methyl groups have a considerable effect on the reactivity of cyclohexanone[13] and in order to investigate their effect in this system a number of methylated ketones (XV–XVII) were prepared and the dissociation constants of their cyanohydrins measured (Table I). α-Fenchocamphorone (XVa), which has two methyl groups on the bridge methylene groups, is 13 times less reactive than norcamphor (XIII) and camphor (XVb), with an extra methyl group on the bridgehead adjacent to the keto-group, is 18 times less reactive. This large effect of the methyl groups results from the fact that one of them is placed over the ketone group[3a] and interferes considerably with the cyano (or hydroxyl) group of the cyanohydrin. This effect is analogous to the axial-crowding effect observed in 3-substituted cyclohexanones.[13a] When the pair of methyl groups is placed adjacent to the carbonyl group as in camphenilone (XVIa) and fenchone (XVIb) the effect is much greater, these compounds being 90 and 130 times less reactive than norcamphor. In these cases both the methyl groups will be eclipsed with the cyano and hydroxyl groups of the cyanohydrin. However when this pair of methyl groups is across the ring as in isofenchone (XVIIb) they exert no steric effect at all. The large difference in reactivity of fenchone (XVIb) and isofenchone (XVIIb) of 226/1 is noteworthy.

The large interference effect of methyl groups on the bridgehead accounts for the reversed stability of the isomeric alcohols formed by reduction of norcamphor (XIII) and camphor (XVb).[3a] Thus norisoborneol (III, IV; R^1 = OH, R^2 = H) with the hydroxyl group in the more stable exo or equatorial position, is more stable than norborneol (III, IV; R^1 = H, R^2 = OH) in which the hydroxyl group is in an endo or axial position.[14] However in the camphor series borneol (hydroxyl endo) is more stable than isoborneol (hydroxyl exo),[15] because of the *gem* dimethyl group in the latter isomer. Such interference also leads to low reactivity of camphor in a number of addition reactions. Catalytic reduction proceeds very slowly[16] giving isoborneol (exo) formed by attack from the less hindered underside of the molecule, and reduction with aluminum isopropoxide also proceeds slowly giving 70% isoborneol.[17]

Extension of these above observations allows possible steric assignments to be made to a number of pairs of alcohols of unknown configuration. Since the methyl groups in isofenchone (XVIIb) have no effect on the ketone-cyanohydrin equilibrium, the more stable of the two α and β isofenchols should have an exo hydroxyl group as in the norcamphor series. α-Isofenchol is uneffected by sodium ethoxide in xylene, whereas β-isofenchol is partially converted to the α-isomer.[14,18] Also reduction of isofenchone with sodium in alcohol gives largely the α-isomer.[18] Such procedures give the more stable isomer[3b] and this α-isomer must have the hydroxyl group exo.[19] Catalytic reduction proceeds by absorption of the ketone grouping on the catalyst from the less hindered side,[3b] which in this case is from the exo direction, and it is observed that β-(endo)-isofenchol is formed in over 90%.[18] Similarly since reduction of β-fenchocamphorone (XVIIa) with sodium and alcohol gives β-fenchocamphorol with less than 10% of iso-β-fenchocamphorol,[20a] these must be the exo- and endo-isomers respectively.

Reduction of epicamphor (3-ketocamphane) with sodium and alcohol gives epiborneol,[16b,20b] while catalytic hydrogenation gives epi-isoborneol,[16b] and by analogy with camphor these should have the endo and exo configurations respectively. In the case of the fenchols (from XVIb) one of the methyl groups in position 3 interferes with the hydroxyl group in either configuration and since at position 7 there is only hydrogen atom, there will probably be little difference between the isomers, and sodium catalyzed isomerization of either alcohol gives a mixture of both.[21a] Infrared evidence[19] suggests that β-fenchol is the exo-isomer.

The camphenilols, I and II, derived from camphenilone (XVIa) are probably the exo and endo isomers since they are formed by sodium-ethanol reduction[22a] and catalytic hydrogenation respectively.[22b]

An additional manner of bridging a cyclohexane ring is with a 1,3-bridge as in bicyclo[3.1.1]heptane derivatives (XVIII) and in this case the cyclohexane ring has the form of a distorted chair.[23] However in the case of nopinone (XVIII), because of the distortion of the ring and the shielding effect of one of the methyl groups on the ketone grouping, the reactivity will be less than that of cyclohexanone and it in fact has the same reactivity towards cyanohydrin formation as norcamphor (XIII). Of the corresponding nopinols, the α-

(13) (a) O. H. Wheeler and J. Z. Zabicky, *Chemistry & Industry*, 1388 (1956); (b) O. H. Wheeler, *J. Am. Chem. Soc.*, 79, 4191 (1957).

(14) K. Adler and G. Stein, *Ann.*, 525, 183 (1936).

(15) Y. Asahina, M. Ishidate and T. Sano, *Ber.*, 69, 343 (1936).

(16) (a) G. Vavon and P. Peignier, *Bull. soc. chim. France*, 39, 924 (1926); *cf.* G. Vavon, *Bull. soc. chim. France*, 49, 337 (1941). (b) M. Lipp and E. Bund, *Ber.*, 68, 249 (1935).

(17) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 1949, 2641.

(18) K. Alder and G. Stein, *Ann.*, 525, 221 (1936). *Cf.* G. Komppa and S. Beckmann, *Ann.*, 522, 137 (1936).

(19) This assignment is confirmed by infrared measurements. P. Hirsjarvi, *Suomen Kemistilehti*, 29B, 138 (1956).

(20) (a) G. Komppa and S. Beckmann, *Ann.*, 537, 140 (1939); (b) M. Lipp, *Ber.*, 74, 6 (1941).

(21) (a) W. von E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, 71, 838 (1949); (b) *Cf.* W. Hückel and H. Kindler, *Ber.*, 80, 202 (1947).

(22) (a) W. Hückel, *Ann.*, 549, 186 (1941); (b) W. Hückel and W. Tappe, *Ber.*, 69, 2769 (1936).

(23) (a) O. H. Wheeler, *Chemistry & Industry*, 1020 (1954); (b) A. K. Bose, *J. Org. Chem.*, 20, 1003 (1955).

isomer has been shown to be equatorial and the β-isomer axial,[24a] and as expected sodium reduction gives principally the α-isomer.[24b]

EXPERIMENTAL

Ketones. Norcamphor was prepared by chromic acid oxidation[25] of norborneol[26] and dehydronorcamphor by oxidation of dehydronorborneol[26] using only a slight excess (10%) of oxidant.

Camphor was an Eastman Kodak White Label sample and fenchone an Eastman Kodak Technical sample which was fractionated in a 20-plate column.

Camphenilone was prepared by ozonolysis of camphene in acetic acid[27] and nopinone by ozonolysis[28] of a fractionated sample (95% pure) of β-pinene.

Fenchone was reduced with lithium aluminum hydride to α-fenchol which was dehydrated with phthalic anhydride[29] to α-fenchene. Part of this was ozonized to α-fenchocamphorone[30] and part rearranged with acetic-sulfuric acid to isofenchyl acetate,[31] which was hydrolyzed and oxidized to isofenchone.[31]

Several ketones were purified through their semicarbazones and regenerated by steam distillation with phthalic anhydride.[32] The physical constants are given in Table II.

Cyanohydrins. The ketones were dissolved in purified 96% ethanol and an excess of hydrogen cyanide in the same solvent added together with 2% by volume of a 2% solution of tri-*n*-propylamine in ethanol. The solutions were allowed to equilibrate in a constant temperature bath mantained at 25.0 ± 0.2° for 24–30 hr. Samples were withdrawn, added to excess 0.1*N* aqueous silver nitrate, containing 0.5% nitric acid and the excess titrated with standardized potassium thiocyanate using ferric alum as indicator.

In the case of the more reactive ketones, samples of 0.4–0.2 g. were reacted in 50 ml. of solution and 10 ml. samples used for titration. The substituted ketones were very unreactive[33] and their dissociation constants were determined by using samples of 0.4–0.5 g. in 10 ml. of solution and titrating 2 ml. samples with a microburette. All the determinations were repeated 3 or more times and the mean values are reported in table I. Because of the small amount of reacted hydrogen cyanide in the cases of the substituted ketones, the results are only accurate to 5–8%, relatively.

TABLE I
DISSOCIATION CONSTANTS OF CYANOHYDRINS[a]

	$K_D \times 10^5$	Ratio[b]
Cyclopentanone	2.05[c]	0.67
Cyclohexanone	0.059[c]	.019
Norcamphor (XIII)	3.07	1.0
Dehydronorcamphor (XIV)	1.11	.36
α-Fenchocamphorone (XVa)	38.5	13
Camphor (XVb)	54.0	18
Camphenilone (XVIa)	285	90
Fenchone (XVIb)	397	130
Isofenchone (XVIIb)	1.76	.58
Nopinone (XVIII)	3.07	1.0

[a] In 96% ethanol at 25.0 ± 0.2°. [b] Ratio of dissociation constants to norcamphor = 1.0. [c] O. H. Wheeler and J. Z. Zabicky, ref. 13a, and unpublished results.

TABLE II
PHYSICAL CONSTANTS OF KETONES[a]

	M.P.	B.P.	n_D^{25}
Norcamphor (XIII)[b]	88–89°(92°)[c]	80°/25 mm.	
Dehydronorcamphor (XIV)[d]	—	72–76°/22 mm.	1.4834
		(59–59.3°/18 mm.)[e]	(1.4839)[e]
α-Fenchocamphorone (XVa)	108° (110°)[f]	95–100°/27 mm.	
Camphor (XVb)	174–175°	—	—
Camphenilone (XVIa)		85–88°/18 mm.	1.4669
		(78°/12 mm.)[g]	
Fenchone (XVIb)		82–84°/25 mm.	1.4605
			(1.4635)[h]
iso-Fenchone (XVIIb)		90–93°/21 mm.	1.4625
			(1.4619)[i]
Nopinone (XVIII)[j]		98–99°/25 mm.	1.4775
		(77–78.5°/8 mm.)[k]	(1.4769)[k]

[a] Literature values in parenthesis. [b] From semicarbazone, m.p. 192.5–193°. Ref. 26 gives m.p. 198°. [c] Ref. 26. [d] From semicarbazone, m.p. 207–208°. P. D. Bartlett and B. E. Tate, Ref. 11b., give m.p. 205–206.8°. [e] Bartlett and Tate, *Loc. Cit.* [f] From semicarbazone, m.p. 218°, Ref. 30 gives m.p. 220°. [g] Ref. 22a. [h] At 18°. O. Wallach, *Ann.*, *263*, 131 (1891); [i] At 20°. Ref. 31. [j] From semicarbazone, m.p. 174.5–176°. [k] Ref. 24a.

Acknowledgments. The work was supported by financial grants from the Rockefeller Foundation, New York.

MÉXICO, 20. D. F.

(24) (a) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 3054 (1955); (b) O. Wallach, *Ann.*, **356**, 227 (1907).

(25) L. T. Sandborn, *Org. Syn.*, Coll. Vol. I., 340 (1941).

(26) K. Alder and H. F. Rickert, *Ann.*, **543**, 1 (1939).

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(28) H. Schmidt, *Angew. Chem.*, **42**, 126 (1929).

(29) G. Komppa and G. A. Nyman, *Ann.*, **535**, 252 (1938).

(30) G. Komppa and R. H. Raschier, *Ann. Acad. Sci. Fennicae*, **10**, 1 (1917); G. Komppa and S. V. Hintikka, *Ber.*, **47**, 936 (1914).

(31) O. Wallach and P. Vivek, *Ann.*, **362**, 191 (1908).

(32) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, **1949**, 1890.

(33) A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, **1928**, 2533, report that camphor cyanohydrin has an immeasurably large dissociation constant.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Reaction of Ketones with Peroxides in Alkaline Solution

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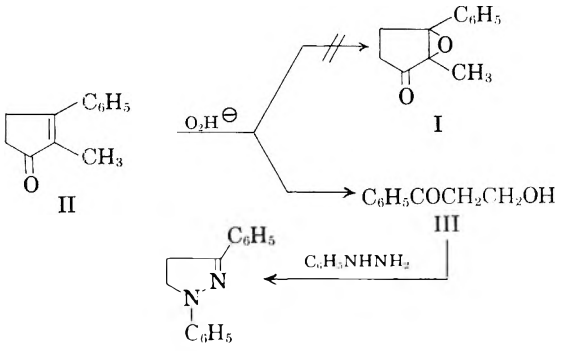
Received May 3, 1957

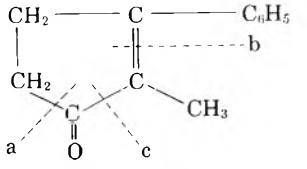
The reaction of 2-methyl-3-phenyl-2-cyclopentenone with alkaline hydrogen peroxide yielded β-hydroxypropiophenone. The cleavage of four ketones, butyrophenone, 2-pentanone, 2-octanone, and 2-methyl-3-hexanone, with sodium hydroperoxide was studied. A possible explanation for the results is suggested.

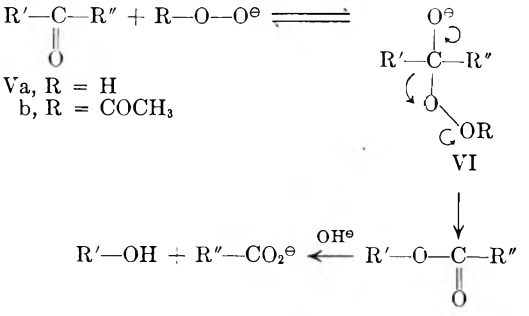
In an attempt to prepare 2,3-epoxy-2-methyl-3-phenylcyclopentanone (I) the corresponding unsaturated ketone II was treated with alkaline hydrogen peroxide. However, the product isolated from this reaction clearly was not the expected oxide I. The infrared and ultraviolet spectra of the product indicated the presence of conjugated carbonyl and hydroxyl functions; the composition of the material, $C_9H_{10}O_2$, established the loss of three carbon atoms in the reaction. These data suggested that the product was the previously unknown β-hydroxypropiophenone (III). This structural assignment was confirmed by treatment of the hydroxy ketone III with phenylhydrazine. The product, 1,3-diphenyl-2-pyrazoline (IV), was identical with an authentic sample prepared from β-dimethylaminopropiophenone and phenylhydrazine.



Since no other product was isolated the fate of the three carbon atoms lost in the reaction is unknown. The most reasonable course for the reaction involves cleavage of the unsaturated ketone II at positions designated as *a* and *b* in Figure 1. The carbon-carbon bond cleavage at position *a* can be likened to a Baeyer-Villiger reaction in which a ketone is cleaved in the presence of a peracid to yield an ester or, after hydrolysis, an alcohol and a carboxylic acid. A possible base-catalyzed counterpart of the Baeyer-Villiger reaction is illustrated in the accompanying equation.[1] Reaction of a ketone with the hydroperoxide anion Va to form the intermediate VI is in accord with the pronounced nucleophilic character of the hydroperoxide anion.[2]

FIGURE 1





The assumption of such a reaction path offers an explanation as to why the unsaturated ketone II underwent oxidative cleavage rather than base-catalyzed epoxidation. The first step in the epoxidation, the conjugate addition of the hydroperoxide anion to the unsaturated ketone II,[3] would be impeded by the presence of an α-alkyl substituent which would destabilize the intermediate carbonion.[4] In addition, the carbonyl group, being part of a five-membered ring, should be particularly reactive in carbonyl addition reactions. A combination of these factors could easily account for the fact that the predominant reaction with the ketone II is cleavage and not epoxidation. The relatively poor yields obtained in the epoxidation of other cyclic unsaturated ketones[5] is perhaps best attributed to this side reaction rather than a retrograde

(1) A similar mechanism has been proposed for the Dakin reaction [J. Hine, *Physical Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 324].

(2) K. B. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); *J. Am. Chem. Soc.*, **77**, 2519 (1955).

(3) C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 665 (1949).

(4) For example, the epoxidation of both α-ethyl- and α-methyl-*trans*-benzalacetophenone is appreciably slower than the corresponding reaction with α-phenyl-*trans*-benzalacetophenone or *trans*-benzalacetophenone [H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, in press, and earlier work cited therein]. Similarly, the conjugate addition of methoxide ion is inhibited by the presence of an α-alkyl substituent [J. E. Dubois and R. Luft, *Compt. rend.*, **242**, 905 (1956)].

(5) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

aldol condensation as we had previously supposed.

The cleavage of ketones by alkaline hydrogen peroxide is not without precedent, the reaction having been observed previously with cyclohexanone,[6,7] cyclopentanone,[8,9] and one substituted cyclopentanone.[9] Related reactions include the cleavage of certain aromatic aldehydes[10] and of α-diketones.[11] In each of these previous examples the cleavage products are the same as those formed when the carbonyl compounds are treated with peracids. However, the reaction of one α-diketone with alkaline hydrogen peroxide has been found[12] to yield products different from those obtained when the diketone was cleaved with a peracid.[3] The interesting cleavage of certain α,β-unsaturated ketones recently reported by Southwick and coworkers[13] also represents a marked departure from the reaction to be expected with peracids and may be similar to the cleavage reported here.

Although the cleavage of the unsaturated ketone II at position *a* (Figure 1) bears a resemblance to the Baeyer-Villiger reaction, one point of difference is readily apparent. In previous studies[14-16] of the reaction of α,β-unsaturated ketones with peracids cleavage has invariably occurred at the bond joining the carbonyl group to the carbon-carbon double bond. Consequently, reaction of the unsaturated ketone II with a peracid would be expected to result in cleavage at position *c* (Figure 1). These considerations, which suggested that the base-catalyzed reaction of ketones with peroxides differed both in mechanism and direction of cleavage from the acid-catalyzed[17] reaction, prompted us to study the reaction of several simple ketones with peroxides in alkaline solution.

Butyrophenone reacted very slowly with sodium hydroperoxide in methanol solution at room temperature to form benzoic acid. Even after a reaction period of 118 hr. the bulk of the ketone was recovered, the yield of benoic acid being 5.8%. In an effort to increase the yield of cleavage products, the reaction was run at the boiling point of methanol. Under these conditions the reaction time was limited to about 2 hr. by the instability of the sodium hydroperoxide; the yield of benzoic acid was 11%. The necessity of base in the reaction was demonstrated by treatment of butyrophenone with a methanolic solution of hydrogen peroxide which contained no alkali. Only the unchanged ketone was isolated from the mixture. The amount of benzoic acid formed was estimated to be 0.3%.

The possible mechanism outlined previously for the base-catalyzed cleavage suggested that the reaction might be accelerated if the hydroxide ion (or water) eliminated from the intermediate VI were replaced by a more favorable leaving group. To explore this possibility butyrophenone was treated with sodium peracetate in methanol. As in a previous experiment the reaction time was limited by the instability[18] of sodium peracetate. However the reaction was definitely more rapid than the corresponding reaction with sodium hydroperoxide under comparable conditions, the yield of benzoic acid being 7.2% after a reaction time of 22 hr. at room temperature.

In no instance could butyric acid be detected in the reaction mixtures obtained from butyrophenone. Each of the alkaline reaction mixtures contained *n*-propyl alcohol; unfortunately the amounts of *n*-propyl alcohol were too small to permit reliable yield estimates. In one case, the reaction of the ketone with sodium hydroperoxide in boiling methanol, a small amount of propionic acid was also formed. This acid may have resulted either from further oxidation of propyl alcohol or by direct oxidation of the enolate anion derived from butyrophenone.[19] The absence of butyric acid in these experiments is in marked contrast to the results expected with peracids. Both acetophenone[20,21] and propiophenone[20] yield as major products the phenyl esters of the corresponding aliphatic acids when treated with peracids.[22]

To investigate the behavior of aliphatic ketones, 2-pentanone, 2-octanone, and 2-methyl-3-hexanone were treated with sodium hydroperoxide in boiling methanol. The neutral and acid components of the reaction mixtures were analyzed by vapor-phase chromatography. The results are outlined in Table I. The expected alcohols could be detected in each of the neutral fractions of the reaction mixtures;[23] however, reliable estimates of the quantities of the alcohols formed were not possible except in the case

(6) S. W. Fox, E. H. Polak, M. W. Bullock, and Y. Kobayashi, *J. Am. Chem. Soc.*, **73**, 4979 (1951).

(7) H. W. Heine and H. Jones, *J. Am. Chem. Soc.*, **73**, 1361 (1951).

(8) M. Fling, F. N. Minard, and S. W. Fox, *J. Am. Chem. Soc.*, 69, 2466 (1947).

(9) W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

(10) H. D. Dakin, *Am. Chem. J.*, 42, 477 (1909).

(11) C. A. Bunton, *Nature*, **163**, 444 (1949).

(12) A. H. Blatt and A. W. Rytina, *J. Am. Chem. Soc.*, **72**, 403 (1950).

(13) P. L. Southwick, H. L. Dimond, M. S. Moores, and D. I. Sapper, *J. Am. Chem. Soc.*, **78**, 101 (1956).

(14) J. Boeseken and A. L. Soesman, *Rec. trav. chim.*, 52, 874 (1933).

(15) N. Prilejaeff, *Bull. soc. chim. France*, [4] 41, 687 (1927).

(16) J. Boeseken and J. Jacobs, *Rec. trav. chim.*, 55, 786 (1936).

(17) S. L. Friess and A. H. Soloway, *J. Am. Chem. Soc.*, **73**, 3968 (1951).

(18) D. Swern, *Chem. Revs.*, **45**, 1 (1949).

(19) W. von E. Doering and J. D. Chanley, *J. Am. Chem. Soc.*, **68**, 586 (1946); W. von E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954).

(20) S. L. Friess, *J. Am. Chem. Soc.*, **71**, 14 (1949).

(21) W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

(22) A comprehensive study of this reaction, reported by M. F. Hawthorne at the Sixth Reaction Mechanisms Conference, Swarthmore College, Sept. 12–15, 1956, supported the previously reported (ref. 20 and 21) observations.

(23) The presence of methanol has no meaning since it was the reaction solvent.

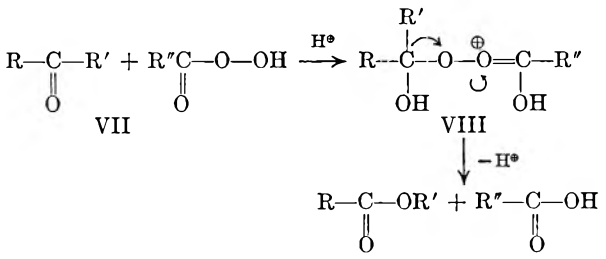
TABLE I
REACTION OF KETONES WITH SODIUM HYDROPEROXIDE IN BOILING METHANOL

Ketone	Recovered Ketone, %	Acidic Products (% Yield)
$C_6H_5COCH_2CH_2CH_3$[a]	80.8	$C_6H_5CO_2H$ (11.1%)[b]
$CH_3COCH_2CH_2CH_3$[c]	...	CH_3CO_2H (6.1%) + $CH_3CH_2CO_2H$ (1.6%) + $CH_3(CH_2)_2CO_2H$ (0.5%)
$CH_3CO(CH_2)_5CH_3$[c,d]	81	CH_3CO_2H (12%) + $CH_3(CH_2)_4CO_2H$ (1.6%) + $CH_3(CH_2)_5CO_2H$ (1.2%)
$CH_3CH\ CH_2COCH(CH_3)_2$[c]	82	$(CH_3)_2CHCO_2H$ (5.4%) + $CH_3(CH_2)_2CO_2H$ (1.9%)

[a] The yields were determined by isolation. [b] A small amount of propionic acid was also detected. [c] The yields were determined by vapor-phase chromatography. [d] The yield of *n*-hexyl alcohol from this reaction was estimated to be 8.8%.

of *n*-hexyl alcohol. It is apparent that the poor yields obtained in these reactions preclude the use of this reaction synthetically unless more favorable reaction conditions can be found.

Previous studies of the reaction of peracids with ketones[17,20,21,24,25] have indicated that the cleavage reaction involves migration of an alkyl or aryl group to an electron-deficient oxygen atom as shown in the accompanying equation. These studies have



further suggested that the migratory aptitudes of the groups R and R′ in the ketone VII are in the order: tertiary alkyl > secondary alkyl > phenyl > primary alkyl > methyl. This order has been rationalized by the assumption that the group which can better tolerate a positive charge in the transition state is the more favorable migrating group. The results of this study (Table I) indicate that the ease of cleavage (and migratory aptitude if the assumed mechanism is correct) of groups from ketones with alkaline peroxides is in the order: primary alkyl > secondary alkyl > methyl and phenyl. There is no compelling reason for the requirements of the migrating group to be similar in the base-catalyzed and acid-catalyzed reactions VI and VIII. The requirements of the migrating group in the base-catalyzed cleavage process represented by VI can be compared more appropriately with the requirements of the migrating group in the benzilic-acid rearrangement.[26] Presumably, the same migrating group requirements would also be applicable to the rearrangement of certain 1,3-dihalides.[27] These investigations as well as the results reported here all suggest that the migratory aptitudes to be expected in base-catalyzed rearrangements differ from the order established for the migration of groups to electron deficient atoms. The studies of certain substituted benzils[12,26] further imply that the migration of aryl groups is facilitated by electron-withdrawing substituents. One possible method for learning whether this implication is correct would be the reaction of various substituted benzophenones with sodium hydroperoxide. However, this study does not appear to be profitable because of the experimental difficulties arising from the very poor yields obtained. The question might also be answered by a study of the rearrangement of 2,2-diaryl-1,3-dihalopropanes as suggested by Schubert and Leahy.[27]

EXPERIMENTAL[28]

2-Methyl-3-phenyl-2-cyclopentenone (II). The unsaturated

(24) W. von E. Doering and E. Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).

(25) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(26) The migration of a phenyl group in the benzilic-acid rearrangement is retarded by a *p*-methyl or *p*-methoxyl group and accelerated by a *m*- or *p*-chloro substituent [for leading references see M. T. Clark, E. C. Hendley, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955); D. G. Ott and G. G. Smith, *J. Am. Chem. Soc.*, **77**, 2325 (1955)] whereas the reverse substituent effect is observed in symmetrical pinacol rearrangements and related reactions [W. E. Bachmann and F. H. Mosher, *J. Am. Chem. Soc.*, **54**, 1124 (1932); J. G. Burr, Jr., and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5426, 5431 (1952)]. Unfortunately, these results are not definitive of migratory aptitudes since the results may be explained in terms of the concentrations of the two possible intermediates prior to rearrangement [see J. D. Roberts, C. R. Smith and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 619 (1951)].

(27) W. M. Schubert and S. M. Leahy, Jr., *J. Am. Chem. Soc.*, **79**, 381 (1957). In this study no products were isolated which would correspond to the migration of a phenyl group. This might be taken (and was by the authors) to mean that the migration of a phenyl group is unfavorable in this kind of rearrangement.

(28) All melting points are corrected and all boiling points are uncorrected. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model 11 MS. The infrared spectra were determined either with a Baird, model B, or a Perkin-Elmer, model 21, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates. The vapor-phase chromatographic analyses were obtained with a 8 mm. × 215 cm. column packed with di-(2-ethylhexyl) sebacate suspended on 50–80 mesh firebrick. The fractions from the chromatogram, eluted with helium, were detected with a thermal conductivity cell.

ketone, m.p. 49–50°, b.p. 90–91° (0.6 mm.) [lit.[29] m.p. 50–51°, b.p. 136–137° (6 mm.)], was obtained in poor yield by the base-catalyzed cyclization procedure of Koebner and Robinson.[29] In our hands the major product obtained from this reaction was β-benzoylpropionic acid. The unsaturated ketone II formed a 2,4-dinitrophenylhydrazone, m.p. 232–232.5° (lit.[29] 232–233°), in 95% yield. The infrared spectrum[30] of the unsaturated ketone has bands at 1695 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1610 cm.$^{-1}$ (conj. C=C); the ultraviolet spectrum has maxima at 242 mμ (ε 1,500) and 279.5 mμ (ε 10,300).

Reaction of 2-methyl-3-phenyl-2-cyclopentenone (II) *with alkaline hydrogen peroxide.* A solution of 0.50 g. (0.0042 mole) of the ketone, 3 ml. (0.031 mole) of 30% aqueous hydrogen peroxide and 1 ml. (0.006 mole) of 6*N* aqueous sodium hydroxide in 20 ml. of methanol was stirred at room temperature (20–25°) for 4 hr. The reaction time was determined by measuring periodically the optical density of the reaction mixture at 279.5 mμ; after 4 hr. the optical density at 279.5 mμ had fallen to 1.8% of its initial value. However, the optical density of the reaction mixture at 240 mμ, examined several times during the reaction mixture, did not diminish in intensity. The reaction mixture was diluted with water and extracted with two 50-ml. portions of ether. After the combined extracts had been dried over magnesium sulfate and concentrated, the residual oil was crystallized from petroleum ether at Dry Ice temperatures. *β-Hydroxypropiophenone* separated as white crystals, m.p. 22–24°, yield 0.35 g. (58%). The infrared spectrum[31] of the product has bands at 3400 cm.$^{-1}$ (associated O—H) and 1690 cm.$^{-1}$ (conj. C=O); the ultraviolet spectrum has a maximum at 242 mμ (ε 10,000).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.29; H, 6.99.

No acidic material was isolated from the alkaline aqueous solution from the reaction mixture.

A solution of 0.05 g. (0.00033 mole) of β-hydroxypropiophenone, 0.05 g. (0.00033 mole) of phenylhydrazine hydrochloride, and 0.1 g. of sodium acetate in 10 ml. of ethanol was refluxed for 30 min. The resulting cold solution deposited 0.05 g. (70%) of *1,3-diphenyl-2-pyrazoline* as light yellow needles, m.p. 150–152°. Recrystallization from ethanol sharpened the melting point of the pyrazoline to 151–151.5° (lit.[32] 151–153°). The material was shown to be identical with an authentic sample of pyrazoline, prepared as subsequently described, both by a mixed melting point determination and by comparison of the infrared spectra[33] of the two samples.

1,3-Diphenyl-2-pyrazoline (IV). A mixture of 2.13 g. (0.01 mole) of the hydrochloride of β-dimethylaminopropiophenone, 1.45 g. (0.01 mole) of phenylhydrazine hydrochloride, 2 ml. of 10% aqueous sodium hydroxide, 3 ml. of acetic acid, and 50 ml. of ethanol was boiled under reflux for 30 min. The pyrazoline separated from the cold solution as yellow needles, m.p. 148–152°, yield 1.6 g. (75%). Recrystallization from ethanol sharpened the melting point of the product to 151–151.5° (lit.[32] 151–153°).

Cleavage of butyrophenone with alkaline peroxides. Procedure A. A mixture of 14.8 g. (0.1 mole) of butyrophenone, 4 g. (0.1 mole) of sodium hydroxide,[34] 20 ml. (0.208 mole) of 30% aqueous hydrogen peroxide, and 100 ml. of methanol was boiled under reflux for 2 hr. at which time the solution gave a negative test for peroxides. After the bulk of the methanol had been distilled from the reaction mixture, the residue was diluted with water and extracted with ether. By the appropriate manipulations 11.95 g. (80.8%) of unchanged butyrophenone, b.p. 95–96° (6 mm.), n_D^{27} 1.5167, was recovered from the ether extract. The vapor phase chromatogram of the forerun from the distillation indicated the presence of *n*-propyl alcohol.

The aqueous, alkaline layer was concentrated and acidified. Benzoic acid, identified by a mixed melting point with an authentic sample, separated as white needles, m.p. 120.5–122.5°, yield 1.35 g. (11.1%). After the aqueous mother liquor had been extracted with ether, the extract was dried over magnesium sulfate and concentrated. Examination of the residual solution by vapor phase chromatography indicated the presence of a small amount of propionic acid; no butyric acid could be detected.

Procedure B. The same mixture of reagents as used in procedure A was stirred at room temperature for 118 hr., diluted with water and worked up as previously described. The yield of benzoic acid was 0.712 g. (5.8%) and the recovered butyrophenone amounted to 9.8 g. (66%). *n*-Propyl alcohol could be detected in the neutral fraction. The acidic residue, after removal of the bulk of the benzoic acid, was neutralized and treated with α,*p*-dibromoacetophenone. The infrared spectrum[30] of the resulting crude organic material has bands at 1705 and 1730 cm.$^{-1}$ attributable to the *p*-bromophenacyl ester of benzoic acid but lacks the absorption bands at 1715 and 1755 cm.$^{-1}$ found in the spectrum of the *p*-bromophenacyl ester of butyric acid.

As a control experiment a solution of 14.8 g. (0.1 mole) of butyrophenone and 20 ml. (0.208 mole) of 30% aqueous hydrogen peroxide in 100 ml. of methanol was stirred for 116 hr. The recovered butyrophenone amounted to 12.87 g. (86.9%). Since no benzoic acid could be isolated, the acid fraction was neutralized and treated with α,*p*-dibromoacetophenone. The infrared spectrum[30] of the resulting organic material indicated the presence of a small amount (estimated yield 0.3%) of the *p*-bromophenacyl ester of benzoic acid in the recovered α,*p*-dibromoacetophenone (C=O band at 1690 cm.$^{-1}$).

Procedure C. To a cold solution of 28 g. (0.7 mole) of sodium hydroxide in 200 ml. of methanol was added, dropwise and with stirring, 30 ml. of a solution of 0.2 mole of peracetic acid in acetic acid. The temperature was kept below 20° throughout the addition. The resulting mixture was treated with 14.8 g. (0.1 mole) of butyrophenone and then stirred at room temperature for 22 hr. The reaction mixture, which no longer gave a positive test for peroxides, was worked up as previously described. The yield of benzoic acid was 0.872 g. (7.2%) and the recovered butyrophenone amounted to 10.96 g. (74.2%). As in former cases *n*-propyl alcohol could be detected in the reaction mixture but butyric acid could not be detected.

Cleavage of the aliphatic ketones. The aliphatic ketones listed in Table I were all cleaved according to procedure A used for butyrophenone. The neutral and acidic fractions were weighed and then analyzed by vapor phase chromatography. The products listed in Table I were identified by demonstrating that their retention times corresponded to those of authentic samples of the various components. For the purpose of the yield estimates listed in Table I the response factors for the various components of the mixtures were all assumed to be unity.

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(29) A. Koebner and R. Robinson, *J. Chem. Soc.*, 566 (1941).

(30) Determined in chloroform solution.

(31) Determined in carbon tetrachloride solution.

(32) T. L. Gresham, J. E. Jansen, F. W. Shaver, and R. A. Bankert, *J. Am. Chem. Soc.*, 71, 2807 (1949).

(33) Determined as a suspension in a potassium bromide pellet.

(34) It was found advantageous to prepare the sodium hydroperoxide from a methanolic solution of sodium hydroxide rather than by the usual technique of adding aqueous sodium hydroxide. Apparently the additional water introduced by the use of an aqueous solution facilitates decomposition of the sodium hydroperoxide, since the peroxide content of the reagent prepared with aqueous sodium hydroxide had fallen almost to zero at the end of 24 hr. at room temperature [see H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, 76, 6525 (1955)]. However, the reagent prepared as described here retained an appreciable peroxide content even after 5 days at room temperature.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Reaction of Peroxyacetic Acid with α-Aralkylidenecyclanones

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Received February 22, 1957

The reaction of peroxyacetic acid with α-aralkylidenecyclopentanones and α-aralkylidenecyclohexanones in acetic acid media of different acidity resulted in the intrusion of an oxygen atom between the carbonyl and methylidene carbon atoms, with the formation of new 5-enoic-5-hydroxy acid δ-lactones and 6-enoic-6-hydroxy acid ε-lactones. In the presence of massive amounts of potassium acetate further oxidation of the enol lactones under conditions of their formation was effectively suppressed. α-Furfurylidenecyclohexanone reacted similarly.

As part of a program investigating the antimicrobial activity of α,β-unsaturated ketones, a series of α-aralkylidene and α-furfurylidenecyclanones (I) was prepared by the condensation of the requisite aldehydes with cyclopentanone, cyclohexanone, and 3-methylcyclohexanone.

In the course of chemical studies aiming at further utilization of cyclanones (I), their reaction with peroxyacetic acid was investigated. The reagent used in most cases was commercial peroxyacetic acid.[1]

α-Aralkylidene- and α-furfurylidenecyclanones (I) are commonly prepared by condensation of cyclopentanones and cyclohexanones with aldehydes in the presence of basic catalysts.[2a-e] This method of preparation is complicated by the tendency of cyclanones (I) to condense with a second molecule of aldehyde at the remaining activated methylene group to form 2,5- and 2,6-disubstituted products.[3] This tendency is especially pronounced in the preparation of cyclanones (I) from cyclopentanone.[4] In order to minimize the second condensation reaction, it is customary to use the ketone in one- to fourfold molar excess.[2a,5] However, a method by Poggi[2c,d] permits the preparation of I in satisfactory yields on a small scale from equimolecular quantities (0.05-0.1 mole) of benzaldehydes and cyclohexanones. With modifications this method proved capable of extension to larger scale preparations. It also proved possible to prepare α-furfurylidenecyclopentanone and a series of aralkylidenecyclopentanones (I) from the requisite aldehydes and cyclopentanone in equimolecular amounts or slight excess, by stirring the reactants in a mixture of ether and dilute alkali at room temperature. Yields ranging from 24% (*o*-chlorobenzaldehyde) to 72% (*p*-anisaldehyde) were obtained. A series of new cyclanones (I), in addition to known ones, was prepared by these methods; several of these have since been described by other workers.[3,6] Table I lists α-aralkylidenecyclopentanones which apparently have not been described to date.

TABLE I
α-ARALKYLIDENECYCLOPENTANONES (I)

Substituent in R	M.P., °C. or B.P., °C./mm.	Analyses C Calcd.	C Found	H Calcd.	H Found
o-Cl	128/0.15	59.20[a]	59.02[a]	5.35[a]	5.25[a]
p-Cl	82[b,c]	69.73	69.66	5.37	5.33
p-OCH_3	68–69[b]	77.20	77.22	6.98	6.79

[a] Analysis of semicarbazone, m.p. 230° dec., from aq. dioxane. [b] From isopropyl alcohol. [c] Semicarbazone, m.p. 213–218° dec., placed on block at 200° and heated 4°/min., from aq. dioxane. *Anal.* Calcd.: C, 59.20; H, 5.35. Found: C, 59.04; H, 5.20.

The primary oxidation of cyclanones (I) by peroxyacetic acid, with the uptake of one oxygen atom, may *a priori* take three different directions:[7] It may proceed with the addition of an oxygen atom to the ethylenic double bond and formation of oxido compounds II, or with rupture of the bond between the carbonyl group carbon and an adjacent carbon atom, with formation of the lactone structures III and IV. The reaction of peroxidic reagents with ethylenic double bonds has been widely studied. It is recognized that ethylenic bonds in conjugation with carbonyl groups may resist the attack of peroxyacids. Scission of the carbon-to-

(1) Commercial peroxyacetic acid results from the equilibration of 1.5 moles acetic acid with 1.0 mole 90% hydrogen peroxide in the presence of 1% sulfuric acid; it contains about 45% peroxyacetic acid, 6% hydrogen peroxide, and 13% water. *Cf.* F. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947); U. S. Patent **2,490,800**, *Chem. Abstr.*, **44**, 2013c (1950).

(2a) D. Vorländer and K. Hobohm, *Ber.*, **29**, 1836 (1896); (2b) D. Vorländer and K. Kunze, *Ber.*, **59**, 2081 (1926); (2c) R. Poggi and V. Guastalla, *Gazz. chim. ital.*, **61**, 405 (1931); *Chem. Abstr.*, **26**, 105 (1932); (2d) R. Poggi and M. Gottlieb, *Gazz. chim. ital.*, **64**, 852 (1934); *Chem. Abstr.*, **29**, 2152 (1935); (2e) R. Poggi and P. Saltini, *Gazz. chim. ital.*, **62**, 678–86 (1932); *Chem. Abstr.*, **27**, 65 (1933).

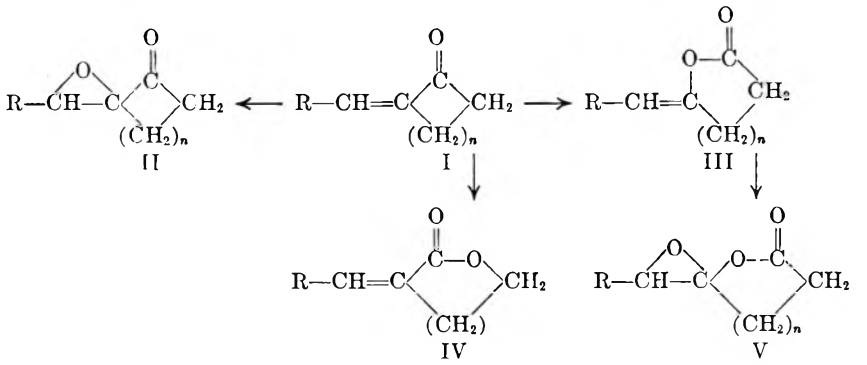
(3) *Cf.* A. C. Huitric and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 614 (1956).

(4) A. Maccioni and E. Marongui, *Gazz. chim. ital.*, **85**, 1570 (1955); *Chem. Abstr.*, **50**, 10702f (1956).

(5) E. Braude and W. F. Forbes, *J. Chem. Soc.*, 1755 (1951).

(6) G. Vavon and J. M. Conia, *Compt. rend.*, **234**, 526 (1952); R. Baltzly, E. Lorz, P. B. Russell, and F. M. Smith, *J. Am. Chem. Soc.*, **77**, 624 (1955).

(7) J. Böeseken and C. O. Vermij, *Rec. trav. chim.*, **50**, 1023 (1934), found that peroxyacetic acid reacts with furfural with cleavage of the carbonyl group from the furan nucleus. Hence in the case of furfuralcyclanones (I) the possibility must also be considered that they may undergo a similar side-chain cleavage at the furan α-carbon atom.



R = phenyl, substituted phenyl, 2-furyl; n = 3,4.

FIGURE 1.

carbon bond between the carbonyl and an adjacent methylene group in cyclohexanone by means of persulfuric acid has been described by Baeyer and Villiger[8] who obtained ϵ-caprolactone. In formal analogy the reaction of hydrazoic acid with cyclohexanone leads to the formation of ϵ-caprolactam.[9] The formation of lactones from cyclohexanones may also be caused by alkaline hydrogen peroxide.[10] Finally, Böeseken[11] has shown that peroxyacetic acid reacts with benzalacetone and related ketones with the intrusion of an oxygen atom between the carbonyl and styryl groups, resulting in the formation of enol esters of phenylacetaldehyde and benzyl ketones, respectively. Testa[12] has comprehensively surveyed oxidations by hydrogen peroxide and peroxyacids involving cleavage of carbon-carbon bonds. Wenkert and Rubin[13] have advanced a unifying mechanistic interpretation for the main paths that the reaction of peroxyacids and benzalacetone and related ketones might take; their interpretation appears applicable to the present case.

The reaction of peroxyacetic acid with cyclanones (I) was studied at about 30° using the cyclanones in slight molecular excess. Orienting experiments indicated that the nature of the reaction products was strongly affected by the acidity of the reaction medium. Consequently the effect of acidity on the reaction of peroxyacetic acid with cyclanones (I) was studied in three media of different acidity using acetic acid as the solvent. The most acidic media contained 0.1–0.2% sulfuric acid which was introduced *via* the peroxyacetic acid reagent. Less acidic media were obtained by the addition of small amounts of sodium or potassium acetate to the solvent in order to neutralize the sulfuric acid introduced *via* the reagent. Media of repressed acidity involved the use of saturated solutions of potassium acetate in acetic acid as the solvent. This solvent, containing about 20% of potassium acetate, gave color phenomena with various indicators, which corresponded to those obtained at *p*H 4.3–4.5 in water.

The addition of the peroxyacetic acid reagent to acetic acid resulted in the expected formation of additional peroxyacetic acid at the expense of the hydrogen peroxide in the reagent.[1] Addition of the reagent to acetic acid saturated with potassium acetate caused the decomposition of the hydrogen peroxide. The decomposition was substantially complete in several hours at room temperature and was accompanied by a slower decomposition of peroxyacetic acid

Cyclohexanone in acetic acid and peroxyacetic acid reacted with formation of ϵ-caprolactone,[14] indicating the possibility of reaction (I) → (VI).[15] Benzalcyclanones (I, R = phenyl, n = 2,3) in acetic acid reacted vigorously with peroxyacetic acid; at the same time the hydrogen peroxide in the reagent was consumed rapidly. Complex reaction mixtures resulted and it was difficult to isolate primary oxidation products, even though the reaction was quenched when only molecular or slightly smaller proportions of active oxygen had been consumed.

When the reaction was carried out under less acidic conditions (addition of small amounts of alkali acetate to the solvent), benzalcyclopentanone yielded products which apparently resulted from further oxidation of primary oxidation products. Benzalcyclohexanone, used in 25% excess

(8) A. v. Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900).

(9) J. v. Braun and A. Heymons, *Ber.*, **63**, 502 (1930).

(10) J. Reese, *Ber.*, **75**, 384 (1942).

(11) J. Böeseken, *et al.*, *Rec. trav. chim.*, **50**, 827 (1931); **52**, 874 (1933); **55**, 786 (1936).

(12) E. Testa, *Oxydationen durch Wasserstoffperoxyd und Persäuren die zur Spaltung von C-C-Bindungen führen*, Juris Verlag, Zurich (1950).

(13) E. Wenkert and M. Rubin, *Nature*, **170**, 708 (1952).

(14) Recently reported by P. S. Starcher and B. Phillips, *Abstracts, 130th Meeting, American Chemical Society*, Atlantic City, N. J., p. 16P, September 1956.

(15) During this reaction the hydrogen peroxide contained in the reagent tended to persist although one might have expected it to be consumed, at least through continued equilibration with the acetic acid as the peroxyacetic acid was consumed. The observed protective effect of cyclohexanone on hydrogen peroxide might be ascribed to their tendency to form addition compounds, of which several are known; *cf.* R. A. Raphael, in *Chemistry of Carbon Compounds*, E. H. Road, ed., IIa, Elsevier Publishing Company, N. Y., 1953, pp. 196–7.

under the same conditions, afforded a moderate yield of the primary oxidation product of structure III.

When the reaction of peroxyacetic acid with (I) was conducted in acetic acid saturated with potassium acetate, peroxyacetic acid was consumed more rapidly than in the more acidic media, and hydrogen peroxide consumption was slowed. Primary oxidation products of structure III were easily isolated in yields of 60–80%. Lactones of structure III obtained by this method are listed in Table II. This table also lists lactones of structure V which were isolated from mixtures obtained by using acetic acid containing small amounts of alkali acetate as the solvent.

positive Legal test[16] and their ready saponification with the formation of ketoacids which were characterized as semicarbazones. These semicarbazones are listed in Table III.

Saponification of 6-phenyl-5-hydroxy-5-hexenoic acid δ-lactone (lactone 1, Table II) yielded 85% of 6-phenyl-5-oxohexanoic acid. Structure III was further supported by potassium permanganate oxidation of 7-phenyl-6-heptenoic acid ε-lactone (lactone 8, Table II) which afforded benzoic and adipic acid.

For purposes of comparison, commercial peroxyacetic acid was treated with acetic anhydride, resulting in a 26% peroxyacetic acid reagent which contained less than 0.4% hydrogen peroxide. Benzalcyclopentanone reacted with this reagent under conditions of different acidity with results which were similar to those obtained with commercial peroxyacetic acid. In acetic acid saturated with

TABLE II

LACTONES III AND V[a]

Lactone No.[b]	Substituent in R	n	M.P. or B.P., °C./mm.	Recrystallized from[c]	Analyses C Calcd.	C Found	H Calcd.	H Found	Sapon. Equiv. Calcd.	Sapon. Equiv. Found
1[2a]	None	2	79–80	E	76.57	76.39	6.43	6.29	188	189
2	None[a]	2	80	E	70.57	70.72	5.93	5.99	204	207
3[d]	*o*-Cl	2	113.5–114.5	A	64.72	64.91	4.98	5.10	222.7	223
4[d]	*p*-Cl	2	111–112	A	15.92[e]	15.82[e]				
5[d]	*p*-CH_3O	2	72–73	A	71.54	71.30	6.54	6.49		
6	*p*-CH_3O[a]	2	64	A	66.65	66.81	6.02	6.12		
7[f]	3,4-OCH_2O	2	96–97	E + A	67.23	66.99	5.22	5.30		
8[g]	None	3	70–71	E	77.20	76.99	6.98	6.94	202	202
9[h]	*p*-Cl	3	103–104	A	65.96	65.49	5.53	5.6		
10[2c]	*p*-CH_3O	3	67	E	72.39	72.35	6.94	6.92		
11[2e]	None	[i]	63.5	E	77.75	77.40	7.46	7.33		
12[j]	*o*-Cl	3	88–89	A	Analyzed as semicarbazone of saponification product; cf. Table III					
13[18]	R = 2-furyl	3	137/1.5		68.73	69.10	6.30	6.33	192	192

[a] Lactones V are listed following the corresponding lactones III and designated [a]. [b] Properties of the parent α-aralkylidene- and α-furfurylidenecyclanones (I) are described in the references given in this column. [c] E = isopropyl ether; A = isopropyl alcohol. [d] See Table I. [e] Cl. [f] G. Vavon and J. M. Conia, *Compt. rend.*, **234**, 526 (1952). [g] O. Wallach, *Ber.*, **40**, 71 (1907). [h] A. C. Huitric and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 1150 (1956). [i] From 3-methyl-6-benzalcyclohexanone. [j] R. Baltzly, E. Lorz, P. B. Russell, and F. M. Smith, *J. Am. Chem. Soc.*, **77**, 624 (1955).

TABLE III

SEMICARBAZONES OF KETOACIDS $RCH_2CO(CH_2)_nCO_2H$

From Lactone No.	M.P., °C.	Recrystallized from[a]	Analyses C Calcd.	C Found	H Calcd.	H Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
1	162–163.5	A	59.30	59.65	6.56	6.70	263	264
5	157	A	57.31	57.31	5.62	5.62		
8	158–159	A	60.63	60.83	6.90	6.70	277	271
9	163–163.5	D	13.48[b]	13.76[b]				
12	188–189 dec.	D	11.37[b]	11.35[b]				
13	150	M	53.92	53.52	6.41	6.11	267	269

[a] A = aqueous alcohol; D = aqueous dioxane; M = aqueous methanol. [b] Cl.

The lactones (III) were obtained as solids generally having higher melting points than the antecedent ketones. They were stored in the dark under nitrogen. Without these precautions the lactones, especially the lower melting ones, tended to decompose on storage.

The structure of the new lactones follows from elemental analysis, positive tests for unsaturation,

(16) *Cf.* H. Meyer, *Analyse und Konstitutionsbestimmung Organischer Verbindungen*, 5th ed., Julius Springer Verlag, Vienna, 1938, p. 550.

potassium acetate, the corresponding lactone (III) was formed in somewhat higher yield than by the reaction of commercial peroxyacetic acid.

The reaction of benzalacetone, in acetic acid saturated with potassium acetate, with the 26% peroxyacetic acid reagent afforded a 65% yield of once-distilled phenylacetaldehyde enol acetate, b.p. 88–89°/1.4 mm., n_D^{20} 1.5615.[17]

Lactones of structure III, containing a double bond not conjugated with a carbonyl group, could be expected to react readily with peroxyacetic acid, a reaction which was previously inferred from the isolation of more highly oxygenated lactones presumed to have structure V (Table I). This oxidation was also effected by treating 6-phenyl-5-hydroxy-5-hexenoic acid δ-lactone (Lactone 1, Table II) with peroxyacetic acid in solutions of different acidity. In this case, too, the presence of massive amounts of potassium acetate in the reaction mixture proved beneficial in channeling the reaction toward a clearly defined product containing an additional atom of oxygen; presumably it had the oxido structure V.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point block; the thermometer was calibrated with Keufler "Testsubstanzen." Boiling points are uncorrected.

Preparation of cyclanones (I). *p-Anisalcyclopentanone.* A mixture of *p*-anisaldehyde (28.5 g., 0.208 mole), cyclopentanone (18.0 g., 0.214 mole), ether (200 ml.), and 1*N* sodium hydroxide solution (200 ml.) was stirred for 64 hr. at room temperature. The aqueous layer was separated and extracted with ether. The combined ethereal solutions were washed to neutrality, dried briefly over magnesium sulfate, and concentrated by distillation. Vacuum distillation of the residue yielded the product, b.p. 175°/25 mm., as a light yellow oil which crystallized (30.0 g., m.p. 63–65°). Recrystallization from isopropyl alcohol afforded light yellow crystals, m.p. 68–69°.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.22; H, 6.79.

A somewhat higher yield was obtained when the same reactants in ether (100 ml.) and 1*N* sodium hydroxide solution (450 ml.) were shaken for 15 hr. at room temperature. More reactive aldehydes required less stirring time.

Furfurylidenecyclopentanone. A mixture of redistilled furfural (32.0 g., 0.33 mole), cyclopentanone (28.0 g., 0.33 mole), ether (150 ml.), and 0.1*N* sodium hydroxide solution (300 ml.) was stirred with external cooling to moderate the exothermic reaction. After about 30 min., yellow crystalline material (presumably difurfurylidenecyclopentanone) began to separate in rapidly increasing amounts. After having been stirred for a total of 45 min., the mixture was filtered with suction. The filtered solid material as well as the separated aqueous layer of the filtrate were extracted with ether. The combined ethereal solutions were washed twice with water and concentrated on the steam bath. The residue was distilled *in vacuo*. After distillation of unreacted starting material, the product was obtained as a yellow oil having b.p. 154°/15 mm., which readily crystallized (55 g., 60% yield). After recrystallization from isopropyl ether it had m.p. 59–60°; reported m.p. 60.5°.[4]

Benzalcyclohexanone. A mixture of benzaldehyde (212 g., 2.0 moles), cyclohexanone (218 g., 2.2 moles), and 1*N* sodium hydroxide solution (1000 ml.) was stirred and heated under reflux for about 3 hr., allowed to cool and stand at room temperature overnight. Methylene chloride was added to the mixture; the aqueous layer was separated and extracted with the same solvent. The combined methylene chloride solutions were washed with water and then with water containing a few drops of acetic acid. After drying over magnesium sulfate the combined solutions were concentrated and distilled *in vacuo*. The product was obtained as a yellow oil, b.p. 173–183°/10 mm. (273 g., 73% yield). It was taken up in low boiling petroleum ether (90 ml.) and seeded. Crystallization was allowed to proceed for several hours. The liquid was decanted from the coarse crystalline material and the material was then washed with a small amount of low boiling petroleum ether. After air-drying, it had the reported melting point, 54°.[2b]

When substituted benzaldehydes were condensed with cyclohexanones, heating under reflux was applied for 5–6 hr. With less reactive aldehydes (*o*- and *p*-chlorobenzaldehyde), twofold molar quantities of cyclohexanone gave improved yields.

Furfurylidenecyclohexanone. Furfural (196 g., 2.0 moles), in two equal portions, was added to a stirred mixture of cyclohexanone (200 g., 2.05 moles) and 1*N* sodium hydroxide solution (2000 ml.). After addition of the first half-portion, the reaction mixture warmed up gradually to 34°. After 2 hr., when the temperature of the mixture had dropped to 30°, the remainder of the furfural was added and stirring continued for a total of 21 hr. A yellow precipitate was obtained which was separated by filtration and washed by slurrying with water and filtering. When this washing procedure was repeated twice, a neutral filtrate was obtained. The filter cake was washed with low boiling petroleum ether and subjected to distillation *in vacuo*. The oil obtained at 103°/0.2 mm. represented a yield of 60.5% (217 g.). The oil solidified rapidly; yellow crystals were obtained which had m.p. 46–47°, reported m.p. 47°.[18]

Peroxyacetic acid oxidation of cyclanones (I). *General procedure.* The peroxyacetic acid reagent was added rapidly with stirring to a slight molecular excess of cyclanone (I), dissolved or suspended in a five- to sixfold amount of the appropriate solvent system. The ensuing reaction was strongly exothermic. By means of external cooling the reaction mixture was maintained at 30 ± 2°. The disappearance of peroxyacetic acid and of hydrogen peroxide was followed by titration of 1-ml. samples of the mixture.[19] After 20–30 min., the reaction usually slowed down, as was shown by spontaneous cooling of the reaction mixture [chlorinated cyclanones (I) reacted more slowly]. When the temperature of the reaction mixture had returned to within 2 degrees of room temperature, 93–95% of the peroxyacetic acid had usually been consumed. At this point or, alternately, when 1.0 atom of active oxygen had been consumed, the reaction was quenched by the addition of ether and water and the product was isolated from the ethereal solution.

When the ethereal solutions that were obtained from reaction mixtures containing massive amounts of potassium acetate were evaporated on the steam bath, the evaporation residue usually crystallized on cooling, furnishing crude lactones (III); in a few cases partial purification of the crude product by vacuum distillation was necessary to bring about crystallization.

Characterization of the lactones (III) by saponification and semicarbazone formation involved saponification of the lactones in a slight excess of aqueous-alcoholic alkali and

(17) J. Böeseken and A. Kremer, *Rec. trav. chim.*, **50**, 827 (1931), using distilled peroxyacetic acid, obtained a yield of 38% of twice-distilled material, n_D^{20} 1.555; as obtained by means of peroxybenzoic acid the ester had b.p. 144°/24 mm., n_D^{25} 1.559.

(18) N. Wolff, *Compt. rend.*, **174**, 1469 (1922).

(19) The method of F. P. Greenspan and D. G. Mackellar, *Anal. Chem.*, **20**, 1061 (1948) was used.

treatment of the saponification mixture with semicarbazide reagent.

6-Phenyl-5-hydroxy-5-hexenoic acid δ-lactone (Lactone 1, Table II) from (I) (*R* = *phenyl*, *n* = *2*). Commercial peroxyacetic acid[20] (12 ml. containing 0.076 mole peracid) was added with stirring during 10 min. to benzalcyclopentanone (14.05 g., 0.082 mole) in glacial acetic acid saturated with potassium acetate (70 ml.). After 40 min., about 93% of the peroxyacetic acid and 53% of the hydrogen peroxide content of the reagent had been consumed; after 70 min. about 95% and 68%, respectively, had been consumed. Ether and water (100 ml. each) were added to the reaction mixture. The aqueous layer was separated and extracted twice with ether (50 ml.). The ethereal solutions were combined, washed consecutively with water (3 × 50 ml.), sodium carbonate solution (2 × 25 ml.), and again with water (2 × 50 ml.). After filtration through magnesium sulfate and concentration on the steam bath, a residue was obtained which solidified on cooling. By recrystallization from isopropyl ether it yielded colorless flakes, m.p. 79–80° (8.4 g.).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.58; H, 6.43. Found: C, 76.39; H, 6.29.

Somewhat less pure additional material (1.0 g.) was isolated from the recrystallization mother liquors. Total yield obtained: 67% on the basis of peroxyacetic acid, 62% on the basis of the ketone used.

Potassium permanganate oxidation of 7-phenyl-6-hydroxy-6-heptenoic acid ε-lactone (VII). The lactone (2.02 g., 0.01 mole) was oxidized by stirring it with 2% potassium permanganage solution (450 ml.) for 16 hr. at room temperature. Potassium carbonate (5.0 g.) was added and stirring continued for 2 hr. Several small portions of oxalic acid were added to the mixture with warming on the steam bath, until the purple color of the solution was discharged. The resulting mixture was filtered and the filtrate evaporated on the steam bath. The solution of the residue in water (50 ml.) was acidified to *p*H 5. Solid benzoic acid separated and was removed by filtration. The filtrate was extracted twice with ether (15.10 ml.). On concentration, the ethereal extracts yielded adipic acid. Both acids were identified by their neutralization equivalents and melting points, taken separately and admixed with authentic specimen.

Peroxyacetic acid oxidation of lactones (III). A solution of 6-phenyl-5-hydroxy-5-hexenoic acid δ-lactone (Lactone I, Table II) in acetic acid saturated with potassium acetate (12 ml. solution containing 1.30 g., 5.9 millimoles, of lactone) was treated with peroxyacetic acid (2 ml. containing 6.8 millimoles of peracid and less than 0.24 millimole of hydrogen peroxide). After 1 hr., the peroxyacetic acid had been consumed. The reaction mixture was poured into water (30 ml.) and the precipitated oil was allowed to crystallize. The crystallized material was separated by filtration, washed with water and low boiling petroleum ether; after recrystallization from isopropyl ether it had m.p. 80° (0.73 g., 52% yield). Additional material was obtained by working up the recrystallization mother liquors.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93; Sapon. equiv. 204. Found: C, 70.72; H, 5.99; Sapon. equiv. 207.

Saponification of lactone (V). The above lactone (0.10 g.) was saponified in 0.2*N* potassium hydroxide in 50% alcohol (3 ml.) at room temperature. The saponification mixture was acidified with hydrochloric acid; the precipitated organic acid was filtered and washed with water, after air-drying, the acid was recrystallized from a mixture of carbon tetrachloride and petroleum ether and then from carbon tetrachloride; it had m.p. 62° and neut. equiv. 221 (calcd., 222).

Acknowledgment. The author is indebted to S. J. Tassinari for the microanalyses reported.

OAKDALE, N. Y.

(20) "Becco 40% Peracetic Acid" was obtained from the Becco Chemical Division, Food Machinery and Chemical Corp., Buffalo 7, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Preparation and Stability of Some Organolithium Compounds in Tetrahydrofuran

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Received April 15, 1957

Methyl-, *n*-butyl-, and phenyllithium have been prepared in tetrahydrofuran by the interaction of methyl chloride, *n*-butyl chloride, *n*-butyl bromide, and bromobenzene, respectively, with lithium wire. The stability of these reagents in tetrahydrofuran at several temperatures has been studied. The order of stability was found to be: methyl- > phenyl- > *n*-butyllithium.

A number of studies concerned with the cleavage of ethers by organometallic reagents have been reported;[1] however, only three of these studies[1i, 1s, 1t] involved reactions of tetrahydrofuran

(1) (a) K. Ziegler and A. Colonius, *Ann.*, **479**, 135 (1930); (b) J. W. Cook, C. L. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, **1936**, 71; (c) W. Huckel and H. Bretschneider, *J. prakt. Chem.*, **151**, 61 (1938); (d) A. Lüttringhaus and G. Wagner-v. Sääf, *Angew. Chem.*, **51**, 915 (1938); (e) A. H. Haubein, *Iowa State Coll. J. Sci.*, **18**, 48 (1943) [*Chem. Abstr.*, **38**, 716 (1944)]; (f) A. A. Morton, *Chem. Revs.*, **35**, 21 (1944); (g) A. Lüttringhaus, G. Wagner-v. Sääf, E. Sucker, and G. Borth, *Ann.*, **557**, 46 (1947); (h) B. C. McKusick, *J. Am. Chem. Soc.*, **70**, 1976 (1948); (i) G. Wittig and A. Rückert, *Ann.*, **566**, 101 (1950); (j) K. Ziegler and H. G. Gellert, *Ann.*, **567**, 185 (1950); (k) S. J. Cristol, J. R. Douglass, and J. S. Meek, *J. Am. Chem. Soc.*, **73**, 816 (1951); (l) D. H. Gould, K. H. Schaaf, and W. L. Ruigh, *J. Am. Chem. Soc.*, **73**, 1263 (1951); (m) R. L. Letsinger, A. W. Schnizer, and E. Bobko, *J. Am. Chem. Soc.*, **73**, 5708 (1951); (n) R. L. Letsinger, J. H. Traynham, and E. Bobko, *J. Am. Chem. Soc.*, **74**, 399 (1952); (o) P. D. Bartlett, S. Friedman, and M. Stiles, *J. Am. Chem. Soc.*, **75**, 1771 (1953); (p) R. L. Letsinger and E. Bobko, *J. Am. Chem. Soc.*, **75**, 2649 (1953); (q) A. A. Morton and E. Brachman, *J. Am. Chem. Soc.*, **76**, 2973 (1954); (r) H. Gilman, A. H. Haubein, and H. Hartzfeld, *J. Org. Chem.*, **19**, 1034 (1954); (s) H. Normant, *Compt. rend.*, **239**, 1510 (1954); (t) R. L. Letsinger and D. F. Pollart, *J. Am. Chem. Soc.*, **78**, 6079 (1956).

with organometallic reagents. Wittig and Rückert[1i] reported that tetrahydrofuran, when complexed with triphenylboron, could be cleaved by triphenylmethylsodium. Letsinger and Pollart[1t] reported that tetrahydrofuran was fairly stable toward cleavage by propylsodium at 50°, and Normant[1s] reported that the tetrahydrofuran-Grignard complex can be cleaved at temperatures above 200°.

Recently tetrahydrofuran has been used as a solvent for a number of reactions involving organolithium reagents.[2] These reactions either do not proceed in diethyl ether or they proceed at a much slower rate and in appreciably lower yields. Among these reactions are the preparation of some dihalobiphenyls from dihalobenzenes and *n*-butyllithium[2a] (prepared in diethyl ether); the preparation of aryllithium compounds from aryl chlorides and fluorides;[2b, 2c] the cleavage of a number of heterocyclic compounds by lithium;[2d] and the metalation of dibenzofuran and aryl fluorides with *n*-butyllithium.[2e, 2f] The pronounced effect of tetrahydrofuran in facilitating metalation reactions and displacement reactions in a mixed solvent system (tetrahydrofuran—diethyl ether), and the desire to investigate some of these reactions in tetrahydrofuran alone, led to the present study involving the preparation and chemical stability of methyl-, *n*-butyl-, and phenyllithium in tetrahydrofuran.

Phenyllithium can be prepared from bromobenzene and lithium wire in tetrahydrofuran at −60° in yields up to 98%. The preparation of organolithium compounds in diethyl ether at such low temperatures has not been reported. Higher reaction temperatures consistently resulted in lower yields of phenyllithium in tetrahydrofuran. In contrast to the preparation of *n*-butyllithium in diethyl ether, this same organolithium compound could be prepared in higher yields from *n*-butyl chloride than from *n*-butyl bromide in tetrahydrofuran. Methyllithium could not be prepared in tetrahydrofuran from methyl iodide and lithium at temperatures ranging from 0° to −30°, but it could be prepared in yields up to 77% from liquified methyl chloride at −10°.

The decreased yields of phenyllithium at temperatures above −60°, the lower yields of *n*-butyllithium obtained from the bromide as compared to the chloride and the inability to prepare methyllithium from the iodide in tetrahydrofuran can be rationalized on the basis of previous results. The coupling reaction, a nucleophilic displacement of a halide in the organic halide by the anion of the organolithium compound, appears to be enhanced in tetrahydrofuran, *e.g.*, dihalobiphenyls are readily formed at low temperatures by the interaction of *n*-butyllithium with dihalobenzenes;[2a] also certain Grignard reagents and organolithium compounds couple smoothly with chlorosilanes at low temperatures.[3] The marked effect of tetrahydrofuran on facilitating displacement reactions, together with the decreasing ease of displacement in a bimolecular, nucleophilic substitution reaction for the series I, Br, and Cl, can be correlated with the dependence of the organolithium yields on the particular alkyl or aryl halide employed. Although methyllithium could not be prepared from methyl iodide in tetrahydrofuran, presumably because of coupling, the organolithium compound can be prepared in 64–70% yields from liquified methyl chloride and lithium in the same solvent. When gaseous methyl chloride was bubbled through a mixture of lithium and tetrahydrofuran until all of the lithium was consumed, the yield of methyllithium dropped to 23%. It is not necessary for lithium to participate in the coupling reaction because it has been observed that methyllithium, prepared in tetrahydrofuran at −10° in the presence of an excess of methyl chloride, upon warming to 0°, gives a negative Color Test I.[4] Methyllithium in the absence of an excess of organic halide is quite stable at room temperature (see Table III).

Methyl-, *n*-butyl-, and phenyllithium have been found to be less stable in tetrahydrofuran than in diethyl ether.[1e,1r] As expected, the order of stability of the three organolithium reagents investigated was the same as the order found in diethyl ether,[1e,1r] namely, methyl- > phenyl- > *n*-butyllithium. Examination of the stability data (Tables I and III), indicates that workable temperatures for methyl-, *n*-butyl-, and phenyllithium in tetrahydrofuran are 0°, below −35°, and 0 to −30°, respectively.

It is interesting to note that the sensitivity of Color Test II[5] appears to be much lower in tetrahydrofuran than in diethyl ether. When the concentration of *n*-butyllithium, as determined by the double titration procedure,[6] had decreased to about 0.2*M*, the solution no longer gave a positive Color Test II in tetrahydrofuran; however, Color

(2) (a) H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 447 (1957); (b) H. Gilman and T. Soddy, *J. Org. Chem.*, **22**, 565 (1957), (c) H. Gilman and T. Soddy, *J. Org. Chem.*, **22**, 1121 (1957); (d) H. Gilman and J. J. Dietrich, *J. Org. Chem.*, **22**, 851 (1957); (e) H. Gilman and R. D. Gorsich, *J. Org. Chem.*, **22**, 867 (1957); (f) H. Gilman and T. Soddy, *J. Org. Chem.*, in press. See, also, H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **77**, 3134 (1955); G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); H. Heaney, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 4692 (1956).

(3) (a) Allylmagnesium chloride has been found to couple instantaneously at −35° with triphenylchlorosilane in tetrahydrofuran (unpublished studies of B. J. Gaj); (b) triphenylsilyllithium couples readily with triphenylchlorosilane below −60° in good yield in tetrahydrofuran (unpublished studies of G. D. Lichtenwalter); (c) in this study, methyllithium coupled smoothly with triphenylchlorosilane at −35° in tetrahydrofuran.

(4) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(5) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).

(6) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

TABLE I
STABILITY OF METHYLLITHIUM IN TETRAHYDROFURAN

Size Aliquot	Hr. at t, °C.	t, °C.	Triphenylmethylsilane,[a] Wt.	Yield,[b] %
25	0	−10	4.78	71.1
50	1	0–3	8.95	66.6
50	1	0–3	8.40	62.5
50	2.5	0–3	8.00	59.5
—	2	0–3	—	—
50	2	25	5.87	43.7
50	12	25	4.97	37.0
80	13	65	2.97	13.8

[a] These fractions all melted within the range 65–68°. [b] The yields are based on the titration yield taken as 100%.

TABLE II
PREPARATION OF RLi COMPOUNDS IN TETRAHYDROFURAN[a]

RX	RX, Mole	Lithium, g.-atoms	t,°C	Yield,[b,c] %
Bromobenzene	0.3	1.5	−35	77
Bromobenzene	0.3	1.5	−40	81
Bromobenzene	0.3	1.5	−50	82
Bromobenzene	0.6	1.5	−60	92
n-Butyl chloride	0.25	1.0	−30	75
n-Butyl chloride	0.5	1.25	−25	77
n-Butyl bromide	0.2	1.0	−60	56
Methyl chloride	0.37	0.89	−10	70

[a] Reactions described in the experimental part have been excluded from this table. [b] The yields of phenyllithium and methyllithium were determined by acid titration. [c] The yields of *n*-butyllithium were determined by the double titration method.

TABLE III
STABILITY OF PHENYL- AND *n*-BUTYLLITHIUM IN TETRAHYDROFURAN[a]

RLi	Time at t°C., Hr.	t,°C.	Molarity	Yield,[b,c] %	Color Test I	Color Test II
1. Phenyllithium	0	−20	0.77	100	+	
	7[d]	65	—	1.0	+	
2. Phenyllithium	0	0	0.88	100	+	
	10	25	—	67	+	
	2	65	—	18	+	
3. *n*-Butyllithium	0	−30	0.99	100	+	+
	12	−30	0.94	95	+	+
	10	10	0.20	20	+	−
	2	27	0.00	0.00	−	−
4. *n*-Butyllithium	0	0	1.04	100	+	+
	22.5	0	0.62	60	+	+
	15	0	0.20	19	+	−
	9.5	0	0.00	0.00	−	−

[a] Reactions described in the experimental part have been excluded from this table. [b] The yields are based on the titration yield taken as 100%. [c] The decrease in yield of phenyllithium was followed by carbonation of aliquots, while for *n*-butyllithium the double titration procedure was used. [d] In another run, Color Test I became negative after refluxing for 11 hr.

Test I persisted until all of the *n*-butyllithium had been utilized, as indicated by a double titration of an aliquot. The minimum concentration of *n*-butyllithium necessary to give a positive Color Test II is 0.03*M* in diethyl ether.[5] This suggests that Color Test II, if used at all to detect alkyllithium reagents in tetrahydrofuran, should be used with discretion.

EXPERIMENTAL[7]

Phenyllithium, Run I. A solution of 94.2 g. (0.6 mole) of bromobenzene in 400 ml. of anhydrous tetrahydrofuran[8] was added over a 3-hr. period to a suspension of 10.4 g. (1.5 g.-atoms) of finely cut lithium wire in 200 ml. of tetrahydrofuran. The reaction was initiated and maintained at a temperature of −60 ± 5° during the entire addition by means of a Dry Ice-acetone bath. A pale pink color developed after the first 5 ml. of the bromobenzene solution was added. The color progressively darkened to deep red at the end of the addition. Upon completion of the addition, the reaction mixture was stirred at −50° for 1 hr., then stirred overnight while being cooled by a Dry Ice-acetone bath. The temperature was allowed to rise to 0° and the unreacted lithium was removed by filtration through a plug of glass wool into a calibrated addition funnel. The yield, as determined by acid titration,[9] was 655 ml. of 0.8*M* phenyllithium (87.5%).

The red solution was stirred at room temperature for 24 hr. A 100-ml. aliquot was removed and carbonated by pouring jet-wise onto a Dry Ice-ether slurry. The carbonation mixture was worked up in the usual manner to give 4.74 g. (48%) of crude benzoic acid, m.p. 114–123°. Sublimation of this material under reduced pressure gave 3.73 g. (38%) of pure benzoic acid, melting point and mixed melting point with an authentic sample, 122–123°, and 0.15 g. (1.8%) of less pure acid, m.p. 118–122°. No attempt was made to purify the dark-brown, sublimation residue.

The remaining phenyllithium solution was refluxed for 1.5 hr. and a 200-ml. aliquot was carbonated. Work-up in the usual manner yielded 6.57 g. of a brown, sticky material which appeared to melt over the range 107–124° to a dark-brown liquid. Sublimation of this material yielded 2.31 g. (12%) of benzoic acid, melting point and mixed melting point with an authentic sample, 122–123°, and a non-sublimable, dark, amorphous residue which was not purified or identified. The remaining 355 ml. of phenyllithium was carbonated after refluxing an additional 1.5 hr. Sublimation of the dark-brown, tarry material obtained by work-up in the usual manner, gave about 1 g. (3%) of benzoic acid, m.p. 120–123° and 8 g. of an amorphous, dark solid similar to that obtained from the previous aliquots.

Run II. In order to determine how close the titration yield agreed with the yield upon carbonation, this reaction was repeated on a smaller scale and the mixture was carbonated after filtration and titration. The quantities of materials used were 3.5 g. (0.5 g.-atom) of lithium in 25 ml. of tetrahydrofuran and 15.7 g. (0.1 mole) of bromobenzene in 75 ml. of tetrahydrofuran. The addition was made over a 2-hr. period at −60 ± 5°. The reaction mixture was stirred at this temperature for 3 hr. after the addition, at which time it was noticed to be green. Upon warming the mixture to −35°, the lithium began to clump together and the red

(7) All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen, and all melting points are uncorrected. The Color Test II referred to in these experiments is the one involving *p*-bromo-*N*,*N*-dimethylaniline.

(8) The tetrahydrofuran used in these experiments was dried and purified by preliminary refluxing over sodium wire for at least 24 hr. followed by distillation into a receiver containing lithium aluminum hydride from which it was distilled immediately before use.

(9) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).

color returned. The solution was cooled to the minimum temperature afforded by a Dry-Ice-acetone bath and held at this temperature overnight. The mixture was warmed to −35°, filtered and a 2-ml. aliquot was titrated.[9] The yield was 97%. Carbonation of the red solution, followed by work-up in the usual manner, yielded 11.9 g. (97.5%) of crude acid, m.p. 118–120°. Recrystallization from an ethanol-water pair gave 5.5 g. of benzoic acid, m.p. 122–123° and 5.6 g. of less pure acid, m.p. 121–123° (91%).

Several additional preparations of phenyllithium were made in tetrahydrofuran, the essentials of which are given in Tables II and III.

n-Butyllithium. (*a*). *From n-butyl chloride.* A solution of 64.8 g. (0.7 mole) of *n*-butyl chloride in 300 ml. of tetrahydrofuran was added over a 1.66-hr. period to a stirred suspension of 13.94 g. (2 g.-atoms) of finely cut lithium wire in 300 ml. of tetrahydrofuran. The reaction mixture was maintained at −25 ± 5° during the addition and for 1 hr. thereafter by means of a Dry Ice-acetone bath. The excess lithium was removed by filtration in the manner described for phenyllithium. The yield, as determined by the double titration method,[6] was 658 ml. of 0.79*M* *n*-butyllithium (74%). The solution was warmed to room temperature[10] during a 10-min. period. An aliquot was titrated by the double titration procedure[6] after stirring for 1 hr. at room temperature. The molarity of the solution had decreased to 0.23. Color Test II[6] was found to be negative 15 min. later, at which time the molarity was 0.20. After stirring at room temperature for an additional 3.75 hr., Color Test I became negative, and titration of an aliquot indicated that all of the *n*-butyllithium had been consumed.

The results of several additional preparations of *n*-butyllithium from *n*-butyl chloride are given in Tables II and III.

(*b*). *From n-butyl bromide. Run I.* *n*-Butyllithium was prepared from 3.5 g. (0.5 g.-atom) of lithium in 70 ml. of tetrahydrofuran and 27.4 g. (0.2 mole) of *n*-butyl bromide in 130 ml. of tetrahydrofuran. The addition was made at −60 ± 5° over a 2-hr. period. The mixture was stirred for 1 hr. at the same temperature before it was filtered and titrated. The yield was 56% by double titration.

Run II. The reaction was repeated under the same conditions except that 6.94 g. (1.0 g.-atom) of lithium metal was used. There was no increase in yield.

Methyllithium. (*a*). *From liquified methyl chloride.* The apparatus used for this preparation consisted of a 500-ml., four-necked flask which was fitted with a Dry Ice-acetone condenser, low-temperature thermometer, Trubore stirrer, and a jacketed, addition funnel containing a Dry Ice-acetone mixture in the outer jacket.

A suspension of 9.3 g. (1.33 g.-atoms) of lithium wire in 300 ml. of tetrahydrofuran was introduced into the flask and cooled to −10 ± 2° by means of a Dry Ice-acetone mixture. A solution of 27.6 g. (0.545 mole) of liquid[11] methyl chloride in 50 ml. of tetrahydrofuran, cooled with a Dry Ice-acetone bath, was added over a 45-min. period. After completion of the addition the gray suspension was stirred at −10 ± 2° for 30 min. The mixture was cooled to −35°, filtered to remove unreacted lithium and rewarmed to −10°. Acid titration[9] indicated a yield of 355 ml. of 0.986*M* methyllithium (64%). The solution was transferred, while still at −10°, to a three-necked flask which had been cooled previously to −10°. Aliquots were removed at various times and temperatures, and these were derivatized at −35° with triphenylchlorosilane. Each derivatized aliquot was hydrolyzed with saturated ammonium chloride. The organic layer was evaporated to remove tetrahydrofuran and the residue was dissolved in a 1:1 mixture of benzene and petroleum ether (b.p. 60–70°). The resulting solution was chromatographed through an alumina column. The eluant was passed through until evaporation of a 2-ml. portion of the eluate indicated the absence of triphenylmethylsilane. The eluate was evaporated and the yield of triphenylmethylsilane determined. After recrystallization from petroleum ether (b.p. 28–38°), the product was identified by a mixed melting point with an authentic sample. The melting point and mixed melting point of the recrystallized product with an authentic sample, was 67–68°, lit.[12,13] 67°. The results of this experiment are given in Table I.

(*b*). *From gaseous methyl chloride.* Methyllithium was prepared in 23% yield when gaseous methyl chloride was bubbled through a suspension of 0.56 g. (0.08 g.-atom) of lithium wire in 50 ml. of tetrahydrofuran at −10°. The methyl chloride was bubbled through the mixture until all of the lithium was consumed, and the yield was determined by isolating triphenylmethylsilane from the reaction of the methyllithium with an excess of triphenylchlorosilane. The yield was 2.48 g. (23%) of triphenylmethylsilane, m.p. 67–68°.

In a similar reaction, gaseous methyl chloride was bubbled through a mixture of lithium and tetrahydrofuran at −10° for 5 min. after all of the lithium had been consumed. A single acid titration of an aliquot indicated a yield of 12%. Color Test I became negative upon warming to 0° indicating the absence of any organolithium compound.

Attempted preparation of methyllithium from methyl iodide. Several attempts were made to prepare methyllithium from methyl iodide and lithium in tetrahydrofuran at 0° to −30°. A reaction did occur, as was evidenced by the bright surface on the metal, gas evolution at 0° to −10°, and the formation of a gray suspension in the reaction mixture. However, Color Test I was negative throughout the reaction.

Acknowledgment. This work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59, incidental to a study concerned with organic liquid solution scintillators.

AMES, IOWA

(10) Cooling was required to hold the temperature at 25°, since the reaction became exothermic as soon as room temperature was reached.

(11) The gaseous methyl chloride was liquified by passing the compressed, dry gas through a 50-ml., long-necked, glass-stoppered flask, whose bulb was immersed in a Dry Ice-acetone bath. The cold flask was weighed before and after transfer to the addition funnel.

(12) C. A. Kraus and H. Eatough, *J. Am. Chem. Soc.*, **55**, 5008 (1933).

(13) H. Marsden and F. S. Kipping, *J. Chem. Soc.*, **93**, 198 (1908).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE AND THE LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

Some Derivatives of Aza-aromatic Heterocycles as Liquid Scintillator Solutes

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Received May 27, 1957

A wide variety of polyaryls containing an aza-aromatic heterocycle have been screened as liquid scintillator solutes. In general this heterocycle appears to be less effective than other nitrogen heterocycles, but some striking effects of the dialkylamino derivatives are observed. A number of the compounds are previously unreported, and details of their syntheses are given.

Among the numerous interesting systems suggested, but thus far not investigated, by previous reports[1] of liquid scintillator solutes is the series of polyaryls involving the pyridine nucleus. Most of these compounds are more soluble in aromatic solvents than their benzene analogs, and a wide variety is readily accessible by way of addition of aryllithium reagents to the azomethine linkage and subsequent oxidation of the dihydro intermediate by a method first reported by Ziegler[2] and later refined by many investigators.

This mode of preparation restricts one to α-substituted derivatives, but this series appears to be most promising on the basis of the three 2-pyridyl-5-phenyloxazole isomers previously reported.[1b] In that instance the α-isomer registered a relative pulse height of 0.94, the β-isomer 0.93, and the γ-isomer 0.79, as compared with a value of 1.00 for 2,5-diphenyloxazole, the commonly accepted arbitrary standard.

Included in Table I are a number of dialkylamino derivatives, some of which have rather high values, which seems to confirm the view that this group makes a definite, positive contribution to the scintillation ability of a solute. The first suggestion of the striking influence of this function was noted in the report by Arnold[1d] of high values for 7-diethylamino-4-methylcoumarin and 2-(*p*-dimethylaminophenyl)benzothiazole (0.93 and 0.90, respectively). In the first of these compounds there is a carbonyl function and in the second a sulfur atom in the heterocyclic ring. Both of these are generally believed to give rise to marked decreases in the scintillation ability of a solute.

Of particular interest among the dialkylamino derivatives in Table I is the rather pronounced difference between 2-(*p*-diethylamino and *p*-dimethylaminophenyl)pyridine (0.45 and 0.80, respectively). Although a direct analogy is not available among the quinoline derivatives, corresponding compounds with different nuclear substituents are available. 6-Chloro-2-(*p*-dimethylaminophenyl)quinoline gives a slightly higher value (0.63) than the corresponding diethylamino derivative with the methoxyl group in the 6-position (0.59), and this latter value is higher than the diethylamino derivative of the bare nucleus (0.50). This difference is again favorable to the dimethylamino group in view of previous values,[1b] which show a marked and consistent superiority of methoxy derivatives over the corresponding chloro derivatives of oxazole and oxadiazole. A final observation with respect to dialkylamino compounds is the two instances in which the dimethylaminophenyl moiety is separated from the quinoline nucleus by a vinyl group, 2-(*p*-dimethylaminostyryl)quinoline and 4-(*p*-dimethylaminostyryl) quinoline. There is obviously no ready explanation for the failure of these compounds to scintillate that would also admit the possibility of the corresponding *m*-amino compound having a value of 0.51. It appears necessary to test a greater variety of this type of compound in order to make a more definitive statement with regard to the vinyl group.

The compounds without functional groups seem to indicate that the aza-aromatic heterocycles are clearly inferior to other nitrogen heterocycles. As evidence of this 2-(4-biphenylyl)pyridine, 2,5-diphenylpyrazine,[1b] 3,6-diphenylpyridazine[1b] and 1-(4-biphenylyl)isoquinoline fail to give a significant response, even though all are closely related to *p*-terphenyl. 2,6-Diphenylpyridine, which may be thought of as an analog of 2,5-diphenylpyrrole as well as *m*-terphenyl, fails to give a measurable response. The latter two have been reported as 0.97[1b] and 0.44,[1a] respectively.

The values reported in Table I were measured in the pulse height analyzer previously described,[1b] and all were measured at a concentration of 3 g./l. in toluene except 7, 21, 24, 32, 39, and 41 which, due to limited solubility, were measured as saturated solutions. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

(1) (a) H. Kallman and M. Furst, *Nucleonics*, 8, No. 3, 32 (1951); (b) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, 13, No. 12, 38 (1955); (c) F. N. Hayes, D. G. Ott, and V. N. Kerr, *Nucleonics*, 14, No. 1, 44 (1956); (d) J. R. Arnold, *Science* 122, 1139 (1955).

(2) K. Ziegler and H. Zeiser, *Ann.*, 485, 174 (1931).

TABLE I

PRIMARY-SOLUTE RELATIVE PULSE HEIGHTS

Compounds	Relative Pulse Height	Ref.
Substituted Pyridine		
1. 2-Phenyl	<0.10	[a]
2. 2-(4-Biphenylyl)	0.12	[a]
3. 2,6-Diphenyl	<0.10	[b]
4. 6-(4-Biphenylyl)-2-phenyl	0.47	[c]
5. 2-(*p*-Dimethylaminophenyl)	0.80	[b]
6. 2-(*p*-Diethylaminophenyl)	0.45	[d]
7. 2,6-Bis(*p*-diethylaminophenyl)	0.15	[d]
8. 2-(9-Carbazolyl)	0.20	[e]
9. 2-(10-Phenothiazinyl)	<0.10	[f]
10. 2-(5-Oxo-10-phenothiazinyl)	<0.10	[f]
11. 2-(5,5-Dioxo-10-phenothiazinyl)	<0.10	[f]
12. 4-(*m*-Aminostyryl)	0.49	[g]
Substituted Quinoline		
13. 2-Phenyl	<0.10	[a]
14. 4-Methyl-2-phenyl	<0.10	[h]
15. 4-(1-Hydroxy-1-methylpropyl)-6-methoxy-2-phenyl	0.13	[i]
16. 4-(α-Hydroxy-α-methylbenzyl)-6-methoxy-2-phenyl	0.13	
17. 4-(α-Hydroxy-α-methyl-*p*-dimethylaminobenzyl)-6-methoxy-2-phenyl	<0.10	[i]
18. 2-Mesityl	<0.10	[j]
19. 4,7-Dichloro-2-(*p*-tolyl)	<0.10	[k]
20. 4,7-Dichloro-2-(*p*-methoxyphenyl)	0.17	[k]
21. 2-(*p*-Dimethylaminophenyl)-6-chloro	0.63	[d]
22. 2-(*p*-Diethylaminophenyl)	0.50	[d]
23. 2-(*p*-Diethylaminophenyl)-6-methoxy	0.59	[d]
24. 2-(*m*-Diethylaminophenyl)	<0.10	[d]
25. 2-(*m*-Diethylaminophenyl)-8-methyl	0.57	[d]
26. 2-[*p*-(Trimethylsilyl)phenyl]	<0.10	[c]
27. 2-(9-Carbazolyl)	0.14	[e]
28. 2-[*m*-(Trifluoromethyl)styryl]	<0.10	[g]
29. 2-(*m*-Aminostyryl)	0.51	[g]
30. 2-(*p*-Dimethylaminostyryl)	<0.10	[g]
31. 4-(*p*-Dimethylaminostyryl)	<0.10	[g]
32. 2-(*p*-Terphenyl-4-yl)	0.12	[c]
Substituted Isoquinoline		
33. 1-Phenyl	<0.10	[a]
34. 1-(2-Biphenylyl)	<0.10	[c]
35. 1-(4-Biphenylyl)	<0.10	[c]
Benzoquinolines		
36. Benzo[*h*]quinoline	<0.10	[l]
37. 2-Phenylbenzo[*g*]quinoline	0.27	[m]
38. 6-Phenylphenanthridine	<0.10	[n]
39. 9-(*p*-Dimethylaminophenyl)acridine	0.26	[d]
Bisaza-aromatics		
40. 2,3-Diphenylquinoxaline	<0.10	[n]
41. 2,3-Bis(*p*-hydroxyphenyl)quinoxaline	<0.10	[n]
42. 6-Amino-2,3-bis(*p*-methoxyphenyl)-quinoxaline	<0.10	[n]
43. 2,3-Bis(*p*-methoxystyryl)quinoxaline	0.18	[n]
44. 2,3-Bis(3,4-dimethoxystyryl)quinoxaline	0.29	[n]
45. Phenazine	<0.10	[o]

[a] J. Evans and C. Allen, *Org. Syntheses*, **18**, 70 (1938). [b] H. Gilman and J. T. Edwards, *Can. J. Chem.*, **31**, 464 (1953). [c] See Experimental. [d] H. Gilman and D. Shirley, *J. Am. Chem. Soc.*, **72**, 2181 (1950). [e] H. Gilman and J. B. Honeycutt, *J. Org. Chem.*, **22**, 226 (1957). [f] H. Gilman and R. O. Ranck, *J. Org. Chem.*, in press. [g] H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945). [h] D. Tarbell, J. Burnett R. Carlin, and V. Wystrach, *J. Am. Chem. Soc.*, **67**, 1584 (1945). [i] R. A. Benkeser, Doctoral dissertation, Iowa State College, Ames, Iowa, 1947. [j] W. Oldham and I. Johns, *J. Am. Chem. Soc.*, **61**, 3291 (1939). [k] H. Gilman and R. A. Benkeser, *J. Am. Chem. Soc.*, **69**, 124 (1947). [l] H. Skraup, *Monatsh.*, **2**, 163 (1881). [m] H. Gilman and R. D. Nelson, *J. Am. Chem. Soc.*, **70**, 3316 (1948). [n] H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2620 (1948). [o] H. Waterman and D. Vivian, *J. Org. Chem.*, **14**, 289 (1949).

EXPERIMENTAL[3]

6-(4-Biphenylyl)-2-phenylpyridine. A. From 4-biphenylyllithium and 2-phenylpyridine. A solution containing 0.073 mole of 4-biphenyllithium[4] in 200 ml. of ether was added in rapid drops (30 min.) to a solution of 11.3 g. (0.073 mole) of 2-phenylpyridine in 100 ml. of toluene. After refluxing 12 hr., Color Test I[5] was negative. The ether was removed, and the remaining toluene solution was refluxed 8 hr., cooled and carefully poured over crushed ice. The layers were separated and the aqueous layer was washed with 50 ml. of benzene. The combined organic layer was filtered from a small amount of quaterphenyl (formed in the preparation of 4-biphenylyllithium) and dried over potassium hydroxide pellets. Removal of solvents and recrystallization of the residue from benzene gave 4.2 g. (18.7%) of white plates, m.p. 147–148.5°. The analytical sample melted at 150–151°.

Anal. Calcd. for $C_{23}H_{17}N$: C, 89.86; H, 5.57; N, 4.57. Found: C, 89.17; H, 5.87; N, 4.66.

B. From phenyllithium and 2-(4-biphenylyl)pyridine. The previous preparation was repeated using phenyllithium and 2-(4-biphenylyl)pyridine The yield was 27.2%, and the products were shown to be identical by both mixed melting point and superposition of the infrared spectra.

2-[p-(Trimethylsilyl)phenyl]quinoline. To a stirred solution of 13.0 g. (0.10 mole) of quinoline in 100 ml. of ether was added dropwise a solution of 0.082 mole of *p*-(trimethylsilyl)phenyllithium.[6] When addition was complete the orange mixture was refluxed overnight, and then hydrolyzed with saturated ammonium chloride solution. The ether extract was dried over anhydrous sodium sulfate and the ether distilled. The residue was treated with 20 ml. of nitrobenzene for 15 min. at 180°. After removal of the nitrobenzene at reduced pressure, the remaining viscous liquid was distilled at 165–166° (0.005 mm.). The product, which solidified in the receiver, was recrystallized from ethanol and melted 69–70°. Yield 9.4 g. (42%).

Anal. Calcd. for $C_{18}H_{19}NSi$: Si, 10.13. Found: Si, 10.25.

1-(4-Biphenylyl)isoquinoline. To a stirred solution of 13.0 g. (0.10 mole) of isoquinoline in 150 ml. of ether was added dropwise a solution of 0.085 mole of 4-biphenylyllithium[4] over a period of 45 min. At the completion of the addition the mixture was red-brown, and Color Test I[5] was negative. The reaction mixture was worked up as described for 2-[*p*-(trimethylsilyl)phenyl]quinoline. The residue after distillation of the ether was treated with nitrobenzene for 30 min. at 190°. The nitrobenzene was removed by distillation at reduced pressure, and the residue crystallized from ethanol. The yield was 7.0 g. (45%), melting at 169–170°. The infrared spectrum showed no band at 2.9–3.1 μ indicating the absence of N—H bond.

Anal. Calcd. for $C_{21}H_{15}N$: N, 4.98. Found: N, 4.74.

(3) All melting points are uncorrected. Reactions involving organolithium reagents were carried out under an atmosphere of dry, oxygen-free nitrogen in sodium-dried solvents.

(4) H. Gilman, E. A. Zoellner, and W. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932).

(5) H. Gilman and J. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(6) H. Melvin, Doctoral dissertation, Iowa State College, Ames, Iowa, 1954.

1-(2-Biphenylyl)isoquinoline. The compound was prepared in the same manner as described for the *para*-isomer. The yield was 2.0 g. (14%), melting at 220-221°. The infrared spectrum showed no N—H bonding.

Anal. Calcd. for $C_{21}H_{15}N$: N, 4.98. Found: N, 4.98.

2-(p-Terphenyl-4-yl)quinoline. To a stirred solution of 1.3 g. (0.01 mole) of quinoline in 100 ml. of ether was added a solution of *p*-terphenyl-4-yllithium[7] in 100 ml. of ether. Upon completion of the addition the reaction mixture was yellow and Color Test I[5] was negative. The mixture was worked up and the intermediate oxidized as before. The product, after recrystallization from benzene, melted at 274-275°. The yield was 1.2 g. (37%). The infrared spectrum again showed the absence of N—H bonding.

(7) H. Gilman and E. A. Weipert, *J. Org. Chem.*, **22**, 446 (1957).

Anal. Calcd. for $C_{27}H_{19}N$: N, 3.90. Found: N, 3.73.

Acknowledgments. This work was supported by the United States Atomic Energy Commission under Contract No. AT(11-1)-59. The authors are indebted to E. Miller Layton of the Institute for Atomic Research, Ames, Iowa, for the infrared spectra, to Drs. Wright H. Langham and Donald G. Ott of the Los Alamos Scientific Laboratory for their interest and helpful suggestions and to Elizabeth Hansbury and Vernon N. Kerr also of the Los Alamos Scientific Laboratory for technical assistance.

AMES, IOWA

[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

The Dinitriles of Acetylenedicarboxylic and Polyacetylenedicarboxylic Acids.[1] I.[2] Dicyanoacetylene and Dicyanodiacetylene

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Received April 22, 1957

The synthesis of dicyanoacetylene, C_4N_2, and dicyanodiacetylene, C_6N_2, is described. The pure compound C_6N_2 is stable at room temperature in the absence of oxygen. Vapor pressure, infrared spectral data, and other physical properties are presented and discussed.

A phase of high temperature research currently under investigation in our laboratories is the production of ultrahigh temperatures by means of chemical reactions. The attainment of such temperatures depends upon the exothermicity of the reaction and the thermodynamic stability of the products of combustion. A flame temperature of slightly over 5000°K. has been reached by burning cyanogen with oxygen under pressure to CO and N_2.[3]

It was obvious that higher flame temperatures could be attained with compounds possessing a higher endothermic heat of formation than cyanogen and could also be burned to the same thermally stable products, *i.e.*, CO and N_2. A series of such compounds exists in the dinitriles of acetylenedicarboxylic and polyacetylenedicarboxylic acids or dicyanoacetylene and dicyanopolyacetylene, having the general formula

$$N{\equiv}C{-}(C{\equiv}C)_n{-}C{\equiv}N$$

where $n = 1, 2, 3\ldots$.

The importance of these compounds in the production of high temperatures has led us to conduct a study of the preparative methods and comparative properties of the individual members in this series. This paper will present and discuss the synthesis and properties of dicyanoacetylene and dicyanodiacetylene.

Kirshenbaum and Grosse[4] found that the first member of the series ($n = 1$), carbon subnitride[5] (C_4N_2) burned with oxygen produces a temperature of 5260°K. at 1 atm. and should produce 5750°K. at 40 atm. With the substitution of ozone for molecular oxygen a temperature of 5520°K. at 1 atm. is expected. C_4N_2 was prepared by the slightly modified method of Moureu and Bongrand.[5]

$$H_3COOC{-}C{\equiv}C{-}COOCH_3 \xrightarrow{NH_4OH} \underset{CONH_2}{H_2NOC{-}C{\equiv}C{-}} \xrightarrow{P_2O_5} N{\equiv}C{-}C{\equiv}C{-}C{\equiv}N$$

The dinitrile, dicyanoacetylene, is a clear colorless liquid, b.p. 76.5°, which solidifies into mono-

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF 18(600)-1475, Project No. 7-7968. Reproduction in whole, or in part, is permitted for any purpose of the United States Government.

(2) Technical Note No. 3, Report Control No. AFOSR-TN-57-33, Contract No. AF 18(600)-1475, Project No. 7-7968, December 19, 1956, Air Force Office of Scientific Research, Air Research and Development Command, U. S. Air Force, Washington 25, D. C.

(3) J. B. Conway, W. F. R. Smith, W. J. Liddell, and A. V. Grosse, *J. Am. Chem. Soc.*, **77**, 2026 (1955).

(4) A. D. Kirshenbaum and A. V. Grosse, *J. Am. Chem. Soc.*, **78**, 2020 (1956); Technical Note No. 1, Report Control No. AFOSR-TN-56-13, Contract No. AF 18(600)-1475, Project No. 7-7968, December 15, 1955.

(5) C. Moureu and J. C. Bongrand, *Bull. soc. chim.*, (V), 846 (1909); *Ann. chim.*, **14**, 5 (1920).

clinic crystals, m.p. 20.5°. Hannan and Collin[5] have reported that C_4N_2 is a symmetrical linear molecule displaying the bond lengths C≡N 1.14, C—C 1.37 and C≡C 1.19 Å. The solid compound can be stored indefinitely at Dry Ice temperatures and is easily handled at room temperature. It is, of course, much more sensitive in the presence of oxygen, a polymerization or condensation reaction probably taking place. A simple vacuum sublimation or atmospheric distillation will separate pure unreacted dicyanoacetylene from the mixture of condensation and polymerization products.

In 1920 Moureu and Bongrand[7] reported trace quantities of a solid with characteristic properties from the action of aqueous potassium ferricyanide on the cuprous derivative of propiolonitrile (cyanoacetylene). Brockman[8] recently firmly established this product as dicyanodiacetylene (C_6N_2) by elementary analysis, molecular weight determinations, and by conversion on hydrogenation to hexamethylenediamine. The C_6N_2 utilized in this work was prepared according to the scheme illustrated.

$$\mathrm{KOOC{-}C{\equiv}C{-}COOH \xrightarrow[\text{reflux}]{H_2O} H{-}C{\equiv}C{-}COOH \xrightarrow[H_2SO_4]{CH_3OH}}$$

$$\mathrm{H{-}C{\equiv}C{-}COOCH_3 \xrightarrow{NH_4OH} H{-}C{\equiv}C{-}CONH_2 \xrightarrow{P_2O_5}}$$

$$\mathrm{H{-}C{\equiv}C{-}C{\equiv}N \xrightarrow[NH_4OH]{CuCl} Cu{-}C{\equiv}C{-}C{\equiv}N \xrightarrow{K_3Fe(CN)_6}}$$

$$\mathrm{N{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}N}$$

Dicyanodiacetylene is formed as fine white elongated needles, m.p. 64.5–65°. Brockman describes this unique compound as an *unstable* white solid which he obtained by sublimation in a stream of carbon dioxide. Pure stable crystalline dicyanodiacetylene has been successfully produced in this laboratory through the use of careful distillation and sublimation techniques under low pressures of dried prepurified nitrogen. Samples of our product were maintained *in vacuo* and under a nitrogen atmosphere at room temperature. After 3 months substantial amounts of white crystalline C_6N_2 were recovered from the samples. Only slight discoloration of the water-white liquid dinitrile occurred after several hours under nitrogen. Even at 100° only partial decomposition took place. In addition, freshly prepared dicyanodiacetylene gave an infrared spectral absorption curve identical with that of a sample which had been stored for several weeks below 0°.

It seems evident from the foregoing that dicyanodiacetylene is a relatively more stable compound than other systems of comparable multiple conjugated bonds and, hence, can be stored for long periods of time. The compound is, of course, much less stable in the presence of oxygen. Nevertheless, the pure compound can be handled for a time in an atmosphere of oxygen at room temperature although a slow polymerization or condensation reaction takes place.

Dicyanodiacetylene is unique in that it combines both a linear chain of eight atoms and a system of four conjugated triple bonds. This symmetrical molecule, N≡C—C≡C—C≡C—C≡N probably displays bond lengths the same as dicyanoacetylene. Hannan and Collin[6] have found the single bond length of C_4N_2 to be virtually the same as that found in monocyanoacetylene, diacetylene, and cyanogen (Table I) indicating that the addition of the triple bond to the conjugated system has only a minor effect upon the structure. This suggests that one might expect the bond distances of dicyanodiacetylene to be in close agreement with those in Table I.

TABLE I

BOND LENGTHS (Å) OF RELATED CONJUGATED SYSTEMS[6,9]

Compound	C—C	C≡C	C≡N
H—C≡C—C≡N	1.382	1.203	1.157
H—C≡C—C≡C—H	1.36	1.19	...
N≡C—C≡N	1.37	...	1.16
N≡C—C≡C—C≡N	1.37	1.19	1.14

The physical properties of the members in the series N≡C—$(C{\equiv}C)_n$—C≡N where n = 0, 1, 2, 3, etc., conform reasonably well with the trends in vapor pressure, boiling point, density, etc., that are consistent with increasing molecular weight in a homologous series. Table II illustrates the effect of an additional C≡C group upon the boiling point and melting point of adjacent members in several homologous acetylenic series. For instance, the boiling point rises with the addition of an acetylenic group. However, the difference in boiling point of two adjacent members, becomes proportionately smaller as the homologous series is ascended. The melting point also increases with the increasing molecular weight. In this case, too, the difference between the melting points of two adjacent members becomes, in general, smaller. Similar relationships are found in many other homologous series. From these regularities the boiling point estimated for C_6N_2 is in fair agreement with the extrapolated value of 154° obtained from the vapor pressure data. In this fashion properties of subsequent members (*e.g.* C_8N_2, $C_{10}N_2$) may be approximated.

The vapor pressures of dicyanodiacetylene and dicyanoacetylene were studied as a function of temperature over the ranges 21–96° and −11 to 76.5°, respectively (Table III). The method employed was an isotensimetric one with the use of a Kel-F polymer oil as the confining liquid. A semilog plot of the experimental values for P (mm.) *vs.* $1/T$°K.

(6) R. B. Hannan and R. L. Collin, *Acta Cryst.*, **6**, 350 (1953).

(7) C. Moureu and J. Bongrand, *Ann. chim.*, **14**, 47 (1920).

(8) F. J. Brockman, *Can. J. Chem.*, **33**, 507 (1955).

(9) A. A. Westenberg and E. B. Wilson, Jr., *J. Am. Chem. Soc.*, **72**, 199 (1950).

TABLE II
REGULARITIES IN THE PROPERTIES OF ACETYLENIC COMPOUNDS

Compound	Boiling Point, °C.	Δ^a	Melting Point, °C.	Δ^a
HC≡CH	−83.6		−81.8	
		93.9		45.4
H(C≡C)$_2$H	10.3		−36.4	
		74.7		16.4
H(C≡C)$_3$H	*ca.* 85[b]		−20	
H$_3$C—CH$_3$	−88.3		−172	
		115.5		140
H$_3$C—C≡C—CH$_3$	27.2		−32.5	
		102		97
H$_3$C—(C≡C)$_2$—CH$_3$	129		64.5	
N≡C—C≡N(C_2N_2)	−20.7		−34.4	
		97.2		54.9
N≡C—C≡C—C≡N(C_4N_2)	76.5		20.5	
				44.0
N≡C—(C≡C)$_2$—C≡N(C_6N_2)	*ca.* 155–160[c]		64.5	
N≡C—(C≡C)$_3$—C≡N(C_8N_2)	*ca.* 230[c]		*ca.* 100[c]	

[a] Δ signifies the difference in a property between adjacent members. [b] Calculated from vapor pressure data reported by W. Hunsmann, *Ber.*, **83**, 213 (1950). [c] Values are approximately those one would expect of subsequent members.

was essentially linear for the solid and liquid vapor pressure curves of C_6N_2 and C_4N_2 (Fig. 1).

TABLE III
MOST PROBABLE VALUES OF THE VAPOR PRESSURE OF DICYANODIACETYLENE AND DICYANOACETYLENE

State	C_6N_2 Temperature °C.	°K.	Experimental Vapor Pressure in Mm. Hg
Solid	21.7	294.9	15.0
	24.2	297.4	16.5
	40.3	313.5	33.5
	57.4	330.6	67.5
	62.0	335.2	80.0
Liquid	68.0	341.2	97.5
	96.2	369.4	220
	154[a]		760
	C_4N_2		
Solid	−10.6	262.6	16.1
	0.0	273.2	35.4
Liquid	22.8	296.0	140.4
	32.5	305.7	200
	76.5	349.7	760

[a] Extrapolated value of the boiling point of C_6N_2.

The vapor pressure of the crystalline solid hexacarbon dinitride can be expressed by the equation:

$$\log_{10} P_{mm} = 4.30827 + 151.654 \times \frac{1}{T} - 321{,}008 \times \frac{1}{T^2}$$

and from the experimental values there has been derived the following vapor pressure equation for the liquid:

$$\log_{10} P_{mm} = 6.6174 - 1579.2 \times \frac{1}{T}$$

where T = °K.

From the vapor pressure equations for C_6N_2 it follows that:

Heat of sublimation, ΔH_{sub} = 8590 cal./mole

Heat of vaporization, ΔH_{vap} = 7230 cal./mole

Heat of fusion, ΔH_{fus} = 1360 cal./mole

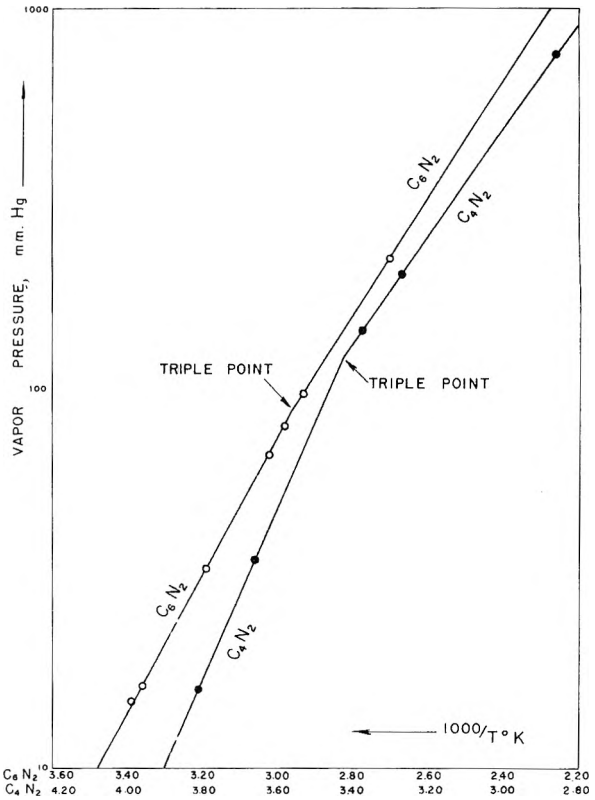

FIG. 1. VAPOR PRESSURE OF C_6N_2 AND C_4N_2

From the vapor pressure equation for solid C_4N_2

$$\log_{10} P_{mm} = 10.0115 - 2312 \times \frac{1}{T}$$

and for liquid C_4N_2

$$\log_{10} P_{mm} = 6.4308 - 1093.4 \times \frac{1}{T} - 51707 \times \frac{1}{T^2}$$

the following values were obtained:

ΔH_{sub} = 10,575 cal./mole

ΔH_{vap} = 6,875 cal./mole

ΔH_{fus} = 3,700 cal./mole

In the infrared the C≡C absorption is weak and often undetectable in symmetrically disubstituted acetylenes.[10] Additional bands may arise, however, in the disubstituted alkynes as the result of overtones. The frequency of C≡C absorption is usually displaced in a conjugated system from the normal region of 4.42–4.76 microns to lower frequencies. Likewise, the position of the C≡N stretching vibration in conjugated systems (4.48–4.50 microns) has also been shown to undergo displacement from the higher frequencies found in saturated mono- and dinitriles. It is clear from the related conjugated systems in Table IV that the absorptions in the infrared by the molecules dicyanoacetylene and dicyanodiacetylene correspond well with the expected absorption regions based upon the preceding generalizations.

A Baird Associates Recording Spectrophotometer of Samuel P. Sadtler and Sons, Inc., was used to obtain the infrared spectra of monocyanoacetylene, dicyanoacetylene, and dicyanodiacetylene (Fig. 2). Attempts to prepare a KBr disk of C_6N_2 resulted in extensive decomposition of the sample. An appropriate carbon tetrachloride solution of dicyanodiacetylene was utilized with a solvent compensating cell of 0.2 mm. thickness. The spectra of liquid C_3NH and C_4N_2 were recorded at cell thicknesses of 0.2 and 0.1 mm., respectively. The absorption bands appearing at ca. 2.5–3.2 and 6.0–6.5 microns in the spectra of C_4N_2 are believed to be due to slight traces of moisture.

TABLE IV

INFRARED ABSORPTION BANDS IN RELATED CONJUGATED SYSTEMS[16]

Compound	C≡C	I^a	C≡N	I^a
$C_5H_{11}C{\equiv}C{-}C{\equiv}N$	4.71 μ	w	4.4 μ	s
$H{-}C{\equiv}C{-}C{\equiv}N$	4.88	m	4.46	s
$N{\equiv}C{-}C{\equiv}C{-}C{\equiv}N$	4.41 (Raman)[b]	w	4.52	m
$N{\equiv}C{-}(C{\equiv}C)_2{-}C{\equiv}N$	4.84	w	4.47	m
$HC{\equiv}C{-}C{\equiv}C{-}H$	4.94			
$H_2C{=}CH{-}C{\equiv}C{-}H$	4.76			

[a] The intensities, I, of the absorptions are represented as w = weak, m = medium and s = strong.

[b] A detailed discussion of the infrared and Raman spectra of dicyanoacetylene is presented by F. A. Miller and R. B. Hannan, Jr., *J. Chem. Phys.*, **21**, 110 (1953).

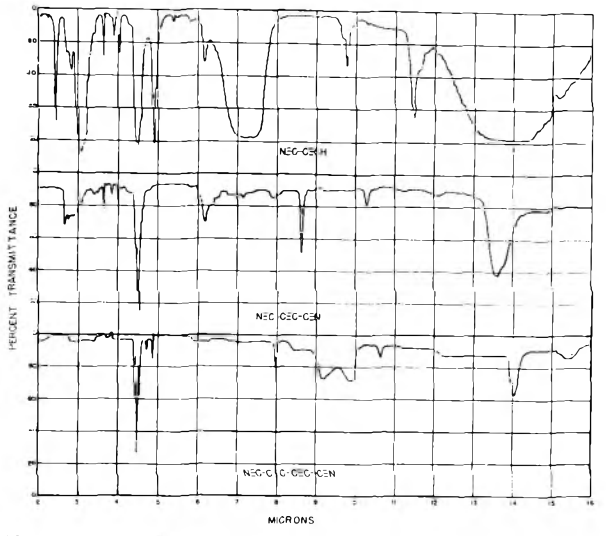

FIG. 2. INFRARED ABSORPTION SPECTRA OF MONOCYANOACETYLENE, DICYANOACETYLENE, AND DICYANODIACETYLENE.

(10) For a discussion of the infrared absorption of substituted acetylenes see L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, page 48.

EXPERIMENTAL[11]

Monocyanoacetylene.[7] Propiolic acid was prepared from monopotassium acetylenedicarboxylate and then esterified with methanol in the presence of sulfuric acid. Reaction with ammonium hydroxide produced propioloamide. Dehydration of the latter with phosphorus pentoxide yielded monocyanoacetylene (propiolonitrile).

Dicyanodiacetylene. Cuprous propiolonitrile, prepared by passing the nitrile in a slow stream of nitrogen through an ammoniacal cuprous chloride solution, was treated with potassium ferricyanide in water at 2–5°C. The suspension was extracted with carbon tetrachloride and the mixture centrifuged. Measures were taken to insure a temperature of <5°. The bottom carbon tetrachloride layer was withdrawn by means of a pipette. This procedure was carried out several times. The combined extracts were dried over anhydrous sodium sulfate and distilled at atmospheric pressure in helices-packed column to remove most of the solvent. The cold residue was then placed in a 10–20° bath under a 20–25 mm. pressure of dried prepurified nitrogen. The residual solvent was collected in a Dry Ice-acetone cooled trap. The light brown crystalline residue was then slowly allowed to sublime. There was obtained pure white crystalline dicyanodiacetylene, m.p. 64.5–65° in 33% yield.

Stability of C_6N_2 at room temperature. Dicyanodiacetylene was sublimed into several tubes *in vacuo*. Samples were sealed in Pyrex brand glass No. 7740 tubes in atmospheres of nitrogen, oxygen, *in vacuo*, and with a trace of organic material (benzene). The tubes were kept at room temperature (22–26°), in the absence of light for 3 months. Periodic microscopic examinations were made. After 1 month only slight discoloration of the crystalline compound under nitrogen and *in vacuo* had occurred. No crystalline material was apparent, however, in the brown oxygen tube. Crystals were apparent in the tube containing traces of benzene.

The tubes were opened *in vacuo* after three months. Considerable white crystalline dicyanodiacetylene from the nitrogen and vacuum-sealed tubes was recovered. The sample sealed under pure oxygen produced no crystalline material. Only a dark brown residue remained. The same results were obtained from the sample sealed with traces of benzene under nitrogen.

Stability of C_6N_2 above room temperature. Samples were sealed under oxygen and dried prepurified nitrogen. Upon heating for 3 hr. at 40°, only slight discoloration occurred. The oxygen tube became very dark after an additional 5 hr. at 40°. Droplets of liquid were observed. The tube was opened and no recovery was made of crystalline dicyanodiacetylene.

The nitrogen tube was only slightly discolored after 3 hr. at 60–70°. The liquid dinitrile upon cooling melted at 62–64°. The tube was then heated at 90–100° for 0.5 hr. The liquid dinitrile became very dark. However, upon cooling some crystalline dicyanodiacetylene was still present in the

(11) All melting and boiling points reported herein are uncorrected.

dark tube. After a period of time the tube was opened with recovery of trace amounts of C_6N_2.

Diamide of acetylenedicarboxylic acid. Dimethyl acetylenedicarboxylate (Madison Laboratories) (100 g., 0.705 mole) was added dropwise with stirring to 400 ml. ammonium hydroxide at −10°. After 2 hr. the precipitated diamide was filtered, washed with several portions of absolute ethanol and dried under vacuum for 2 days. There was obtained a light tan product (70 g., 89%), m.p. 190–192° (lit.[5] m.p. 290–292°). A nitrogen analysis indicated 0.5 molecule of water.

Anal. Calcd. for $C_4H_4N_2O_2 \cdot {}^1/_2H_2O$: N, 23.13. Found: N, 23.35.

Dicyanoacetylene. An intimate mixture of diamide (6 g.), fine sea sand (Calcined) (100 g.) and P_2O_5 (50 g.) was divided into four test tubes and connected to a glass apparatus. The system contained a Dry Ice–acetone-cooled receiver and was evacuated, refilled with dry nitrogen and then re-evacuated. This procedure was carried out several times. The evacuated system of test tubes was then placed in a preheated bath at 215° whereupon distillation of C_4N_2 took place. After *ca.* 45 min. the cooled receiver contained 1.4 g. of fairly pure product which gave upon atmospheric distillation in a glass helices-packed column under prepurified nitrogen, pure dicyanoacetylene, m.p. 20.5–21°.[5] A discussion of the critical features of this dehydration and the system employed is found in ref. (5).

Acknowledgment. The author wishes to express his gratitude and deep appreciation to Dr. Aristid V. Grosse and E. A. Nodiff for their invaluable suggestions during the course of this work.

PHILADELPHIA 44, PA.

[CONTRIBUTION FROM THE PHYSICAL RESEARCH LABORATORY AND THE SPECTROSCOPY LABORATORY, THE DOW CHEMICAL COMPANY]

Preparation of Cyclohexanone Dimethyl Acetal[1,2]

ROBERT E. McCOY, ALVIN W. BAKER,[3] AND ROLAND S. GOHLKE

Received August 22, 1956

Cyclohexanone dimethyl acetal was identified by infrared absorption and mass spectrometry among the products of reaction of salts of *aci*-nitrocyclohexane with methanol and acid, with methyl sulfate, and with ethyl sulfate when methanol was used as solvent. Direct preparation from cyclohexanone and methanol, even without addition of a catalyst, was found feasible. The ease of obtaining this compound in contrast to ketals in general is believed explainable from steric considerations. Attempts to prepare cyclohexanone diethyl acetal directly indicate an unfavorable equilibrium, but the mass spectrometer showed an appreciable conversion.

During an investigation of conversion of nitroparaffins to oximes,[4] an unexpected by-product was discovered in several reactions of *aci*-nitrocyclohexane salts.

Acidification of methanolic solutions or suspensions of *aci*-nitrocyclohexane salts produced cyclohexanone oxime in yields of 35% or less. Infrared and mass spectra of the crude reaction mixtures showed the presence of nitrocyclohexane, cyclohexanone, and a component not immediately identified, in addition to the oxime. Reaction of methyl sulfate with salts of *aci*-nitrocyclohexane gave the same products, although the yield of oxime was higher. Substitution of ethyl sulfate for methyl sulfate gave similar results if methanol was used as solvent, but in other solvents no fourth product was found. Likewise only nitrocyclohexane, cyclohexanone, and cyclohexanone oxime were observed on acidifying salts of *aci*-nitrocyclohexane in ethanol.

When a mixture of cyclohexanone and the unknown was diluted with a large volume of water, ultraviolet and mass spectra revealed no large molecule other than cyclohexanone.

The infrared spectrum (discussed below), the mass spectrum (Table 1), and the facts presented above show clearly that the unexpected product is cyclohexanone dimethyl acetal. Preparation of this compound has been reported previously only by reaction of methyl orthosilicate[5] or methyl sulfite[6] with cyclohexanone. Direct preparation of cyclic ketals from 1,2- and 1,3-glycols is known,[7,8] but it is commonly stated that simple ketals can be prepared only by indirect methods.[9] This opinion is probably correct for most ketals, but the frequent occurrence of cyclohexanone dimethyl acetal in the above reactions suggests that its direct preparation is feasible. This was confirmed by mixing cyclohexanone and methanol, as described in the experimental section.

The successful direct preparation of cyclohexanone dimethyl acetal, contrasted to the usual ex-

(1) Presented in part at the 129th meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956.

(2) For specific compounds we have followed Chemical Abstracts' nomenclature, but generically we have used the more popular term "ketal" as a matter of convenience.

(3) Present address: The Dow Chemical Company, Pittsburg, Calif.

(4) R. E. McCoy and R. S. Gohlke, *J. Org. Chem.*, 22, 286 (1957).

(5) B. Helferich and J. Hausen, *Ber.*, 57B, 795 (1924).

(6) W. Voss, *Ann.*, 485, 283 (1931).

(7) J. Boeseken and F. Tellegen, *Rec. trav. chim.*, 57, 133 (1938).

(8) E. J. Salmi, *Ber.*, 71, 1803 (1938).

(9) For example: (*a*) H. W. Post, *The Chemistry of the Aliphatic Orthoesters*, ACS Monograph 92, Reinhold Publishing Corp., New York, 1943, Chapter 3. (*b*) C. A. Mackenzie and J. H. Stocker, *J. Org. Chem.*, 20, 1695 (1955).

TABLE I
RELATIVE MASS SPECTRUM (PRINCIPAL PEAKS) OF CYCLOHEXANONE DIMETHYL ACETAL

$\frac{M}{e}$	Peak Height[a]	Explanation or Comment
144	11.2	Molecular ion
113	50.4 + 0.4[b]	Loss of CH_3O
101	100.00[c]	Loss of $(CH_2)_3$ and H from ring
88	8.2	Loss of CH from 101
81	23.7	Loss of 2 CH_3O + H
69	23.5	Loss of C from 81?
55	32.0	Fragment of ring
53	6.0	
45	11.9	
43	18.9	
42	13.5	
41	5.8	
39	7.3	
27	5.8	

[a] Relative to mass 101. [b] Average of three runs. [c] Actual peak height is 1/5.52 that of the parent peak of an equal weight of toluene, 1/1.85 that of the 98 peak of the same weight of cyclohexanone, or on an equimolar basis 1/1.26 that of the 98 peak of cyclohexanone. (Conversions are most readily calculated using the molar factor.)

perience with ketals, probably results from the fact that the *exo* double bond in cyclohexanone is unstable relative to tetrahedral bonding[10] for each of the six carbons. This is sufficient to place the equilibrium on the side of the ketal. Moreover, the carbonyl group of the cyclic ketone is considerably less hindered than that in most ketones, and this may contribute to the ease of reaction.

Relative to cyclohexanone, the *exo* double bond in cyclopentanone is comparatively stable. Therefore, despite the smaller steric hindrance of the carbonyl group in the latter compound[11] one would expect that the ketal of cyclopentanone would be more difficult to prepare than that of cyclohexanone. Experiments verify this prediction. Under conditions where cyclohexanone will react almost completely (excess methanol, a trace of HCl, room temp.) no reaction is observed with cyclopentanone.

Ketals of cyclohexanone with alcohols other than methanol can also be prepared directly, but the equilibria are distinctly less favorable. For example, equal volumes of cyclohexanone and ethanol with a trace of HCl catalyst gave a conversion to the ketal of only approximately 10%, (with methanol 78%). This reduction in reaction equilibrium is probably caused by an external steric hindrance which is greater in the ethyl than the methyl compound.

Identification of compound from spectra. Cyclohexanone dimethyl acetal was first detected (but not identified) by means of the $\frac{m}{e}$ 101 peak in the mass spectra of the reaction mixtures. After determining that both this compound and cyclohexanone oxime[4] contribute to the $\frac{m}{e}$ 113 peak, the main features of the spectrum (Table 1) were obtained. The presence of the parent peak and the 113 peak, representing the loss of one methoxyl group, provide strong evidence that the compound is correctly identified. The 101 peak is less easily explained but is probably due to a fragment which retains both methoxyl groups while a portion of the ring has been lost. A similar fragment $\left(\frac{m}{e}\ 129\right)$ is observed in the mass spectrum of cyclohexanone diethyl acetal, and unpublished data show that the same type of fragment is obtained from the bicyclic ketals formed from cyclohexanone and glycols.

In the infrared spectrum, two strong, typical ether bonds occur at 9.06 μ and 9.48 μ. These bands have approximately equal absorption coefficients and may correspond respectively to the antisymmetric and symmetric carbon-oxygen stretching frequencies. A third band occurring at 11.81 μ appears to be characteristic of acetals in general and is confirmation that the structure is correctly assigned.

The methoxyl groups are detected by an increased absorption at 3.5 μ (C—H stretching) and by a band at 7.4 μ (CH_3—O methyl deformation). Neither carbonyl nor C=C groups are present. Cyclohexyl structure is preserved as indicated by a typical, weak band at 3.7 μ. The remaining bands do not provide *a priori* evidence of structure and are not discussed.

EXPERIMENTAL

Distilled cyclohexanone and methanol were used in the direct preparation of the acetal. The catalyst, when used, was generally methanolic HCl.

The reaction of cyclohexanone and methanol is comparatively rapid in the absence of an inhibitor, particularly at 100°. Thus, the mass spectra, obtained from a mass spectrometer having a heated inlet system at 100°,[12] of catalyzed and uncatalyzed mixtures are essentially the same regardless of the time between mixing and introduction to the heated inlet. At room temperature infrared spectra of samples show that equilibrium is approached within a very few hours without a catalyst. The reaction is accelerated by a trace of soluble acid or by insoluble acids such as the hydrogen form of an ion exchange resin. Reaction under catalyzed conditions occurs with liberation of appreciable amounts of heat. By adding a small amount of base or cyclohexanone oxime after a selected reaction time, the mass spectrometer could be used to determine the conversions at room temperature. With such inhibitors, no measurable reaction occurs at 100° for several hours or at room temperature for several days. At 25° a stoichiometric mixture (2:1 mol. ratio) of methanol and cyclohexanone gives a conversion to the ketal of more than 50%. The conversion can be increased easily by using an excess of methanol or a drying agent. Concentrated sulfuric acid, however, gives considerable bimolecular dehydration to a product identified as 2-(1-cyclohexenyl)-cyclohexanone.[13] At 100° equilibrium is somewhat less

(10) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, 76, 467 (1954).

(11) A .W. Baker, *J. Phys. Chem.*, 60, 1660 (1956).

(12) V. J. Caldecourt, ASTM Committee E-14 Conference on Mass Spectrometry, New Orleans, May 1954.

(13) *Cf.* J. Reese, *Ber.*, 75*A*, 384 (1942).

favorable to the ketal. Equal volumes of cyclohexanone and methanol give only a 28% conversion. From equal volumes at 25°, about 78% conversion was obtained. The conversion could be increased to 92% from a mixture of 23.1% by weight cyclohexanone, or to more than 95% from a mixture of 12.1% cyclohexanone.

By distillation, a sample of the ketal was obtained which had only a trace of ketone. It had a boiling point of 73.0° at 50 mm. and a refractive index n_D^{25}, of 1.4372. This compares reasonably well with the value $n_D^{17.5}$ of 1.4416 for a sample prepared from methyl orthosilicate.[6]

Acknowledgment. The authors wish to thank R. F. Lind, R. F. Hamilton, S. A. Schrader, and their associates for the distillation work, E. R. Hopke for the ultraviolet analyses, and R. B. Duvall, D. S. Early, and R. A. Nyquist for assisting with the infrared work after one of us (A.W.B.) had left Midland near the conclusion of this research.

MIDLAND, MICH.

[CONTRIBUTION FROM THE APPLIED SCIENCE DEPARTMENT, UNIVERSITY OF CINCINNATI]

Selenium-catalyzed Isomerization of *cis*-Stilbene

J. D. FITZPATRICK[1] AND MILTON ORCHIN

Received March 4, 1957

The isomerization of *cis* to *trans*-stilbene can be achieved by elemental selenium at 200–210°. The reaction is homogeneous and depends upon the formation and decomposition of a *pi* complex between selenium and the stilbene. The reaction is pseudo first order with respect to *cis*-stilbene. The catalyst dependence appears to involve the concentration of selenium to the one-third power and suggests that, as in the case of the oleic-elaidic acid transformation, a dissociation of Se_6 to $3Se_2$ is involved.

In previous work in this laboratory[2] it was shown that the selenium-catalyzed interconversion of oleic (*cis*) and elaidic (*trans*) acids is a homogeneous reaction, the first step of which consists of the formation of a *pi* complex between the unsaturated fatty acid and selenium. The reversible formation and decomposition of the complex results in the isomerization. It was further shown that most other olefinic substrates complex reversibly with selenium at 200°. If the substrate contains a hydrogen atom on the carbon alpha to the double bond, the catalytic activity of the selenium slowly disappears, presumably by irreversible rearrangement of the *pi* complex to a new species (*sigma* complex) in which it is assumed that a carbon-selenium *sigma* bond is formed. In the present work, the isomerization of *cis*-stilbene was investigated not only because this is a classical substrate for *cis-trans* studies but also because the lack of an *alpha* hydrogen atom would preclude formation of the postulated sigma complex.

EXPERIMENTAL

Apparatus. The isomerization studies were performed in a short test tube fitted with a stirrer, a side-arm inlet for inert gas and a small bore, angled side arm for the insertion of a sampling tube. The test tube was placed in a salt bath heated by a mantle. Temperature control was maintained at ± 1° in the temperature range 190–210° by means of a Thermocap relay. Samples for analysis were removed by inserting an open-end, melting-point capillary tube through the side arm, allowing the liquid to fill the capillary to the desired level, and then withdrawing the tube and sample.

Materials. cis-Stilbene purchased from the Aldrich Chemical Co. was used as received since the ultraviolet spectrum showed it to be of good quality. Selenium powder, reagent grade, was purchased from the Fisher Scientific Co. and was used as received.

Analytical Procedure. The ultraviolet spectra of *cis* and *trans*-stilbene show significant differences[3] and a quantitative method based on ultraviolet absorption spectroscopy was therefore applied. After consideration of several possible methods of selecting and treating the data, the graphical absorbance ratio method[4] was employed. In this method a graph is used, which has as one coordinate, the ratio of observed absorbances at two wave lengths, one of which is an "isoabsorptive" point (the wave length at which both isomers have the same absorptivity). The other coordinate is the relative composition of the mixture and hence runs from 0 to 100% of one of the isomers. This method does not require a prior knowledge of the total concentration of the two components, a fact which is of advantage in the present work where very small liquid samples are involved. The method does however place great weight on the accurate selection of the isoabsorptive wave length. Because the graph is a straight line, the accuracy can be improved by drawing the best straight line through intermediate points of known composition as well as the intercepts. Fig. 1 shows an experimental plot of the ratio of the absorbance at the indicated wave length over the absorbance at the isoabsorptive point (λ 266 mμ) *vs.* the percent of *trans*-stilbene in the mixture. The best straight line was drawn through the points and the composition determined from these best values.

The determinations were made by removing samples from the reaction vessel by means of the capillary tube. The filled capillary was dropped into a volumetric flask without weighing and broken up by means of a glass rod. The flask was filled to the mark with spectral grade cyclohexane. Aliquots of this solution were taken for further dilution until absorbance readings were of a suitable magnitude. Readings

(1) Present address, Emery Industries Inc., Cincinnati 2, Ohio.

(2) J. D. Fitzpatrick and M. Orchin, *J. Am. Chem. Soc.*, **79**, 4765 (1957).

(3) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, New York, 1951.

(4) R. C. Hirt, F. T. King, and R. G. Schmitt, *Anal. Chem.*, **26**, 1270 (1954).

were taken on a Beckman Model DU spectrophotometer at wave lengths of 310, 300, 290, and 285 mμ. From these readings the percentage *trans*-stilbene was determined by reference to the plot in Fig. 1. The variation between these four determinations was usually 1–2% and an average value was taken.

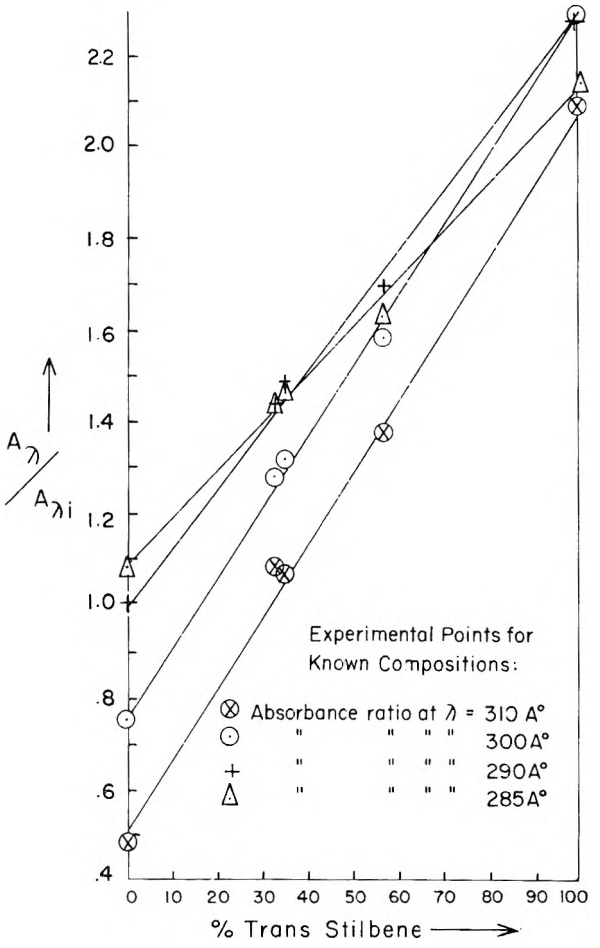

FIG. 1. ABSORBANCE RATIO *Vs.* PERCENT *trans*-STILBENE.

Isomerizations. All the isomerization experiments were carried out in essentially the same manner. A typical experiment will be described.

To the reaction vessel containing 8 g. of *cis*-stilbene at 210 ± 1° under a helium atmosphere, there was added a fragile glass boat containing 0.0240 g. of powdered selenium. The boat was dropped through the top of the apparatus after momentarily stopping the agitator while maintaining a helium atmosphere over the contents. Timing was begun at the moment the selenium sample was dropped into the reactor. The agitation was resumed as quickly as possible. Samples were removed at 10 min. intervals by inserting the melting point capillary tube.

The selenium goes into solution very rapidly. On cooling the solution, selenium precipitates again as the red modification. The solution process is reversible, continued heating and cooling do not change the behavior of the selenium.

RESULTS AND DISCUSSION

The results of rate studies at 210° with three different selenium concentrations and at 200° with one selenium concentration are shown in Table I. The effect of selenium concentration on the rate was studied at 210°, since at higher temperatures thermal isomerization becomes important and at lower temperatures the rate becomes too slow. At 210° in the absence of catalyst, 2 to 3% *trans*-stilbene was formed after 1 hr. of heating. No correction was made for this thermal conversion. At 180°C. there appears to be little solubility of selenium in *cis*-stilbene. The experiment at 200°C. was performed in order to obtain data for the calculation of the activation energy.

Since the isomerization of *cis*-stilbene to *trans*-stilbene is a reversible reaction with the equilibrium point at 93% *trans* isomer,[5] the equation applying to a simple first order reaction where the selenium concentration is constant is:

$$\log (93 - \%\ \textit{trans}\text{-stilbene}) = \frac{-k't}{2.303} + \log 93$$

This is the equation of a straight line, the slope of which gives the value of k′ the pseudo first order rate constant. When the data of Table I are plotted according to the above equation, satisfactory straight lines were obtained even though there is some spread in the data owing to the limits of the analytical procedure and the deficiencies of temperature control in all experiments. Calculations show that a 2% error in analysis would produce about a 10% change in rate constant. Accordingly, our results must be considered only semi-quantitative. Fig. 2 shows plots of these data at 210°. The values for the rate constants calculated from the slopes of these lines and the results from the 200° experiment are shown at the bottom of Table I.

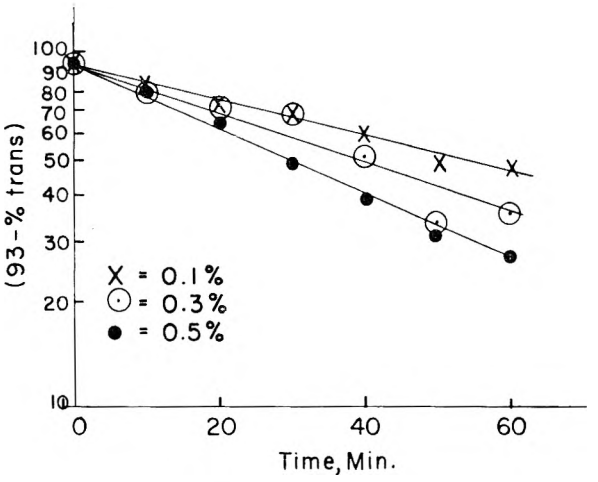

FIG. 2. SEMI-LOG PLOT FOR ISOMERIZATION OF *cis*-STILBENE AT 210° C.

For any given selenium concentration the following rate equation applies:

$$\frac{-d\ [\textit{cis}\text{-S}]}{dt} = k'_1[\textit{cis}\text{-S}] - k'_2\ [\textit{trans}\text{-S}]$$

(5) G. B. Kistiakowsky and W. R. Smith, *J. Am. Chem Soc.*, 56, 638 (1934).

TABLE I
RESULTS OF RATE STUDIES WITH *cis*-STILBENE

	Percentage *Trans*-Stilbene			
	200°C.	210°C.		
Time,		Per Cent Selenium		
Min.	0.30	0.10	0.30	0.50
10		11	15	15
20		21	23	29
30	15	26	25	44
40		35	41	54
50		45	59	61
60	31			66
90	42			
120	53			
150	57			
	Rate Constants (k′, min.$^{-1}$)			
	0.006	0.111	0.015	0.020

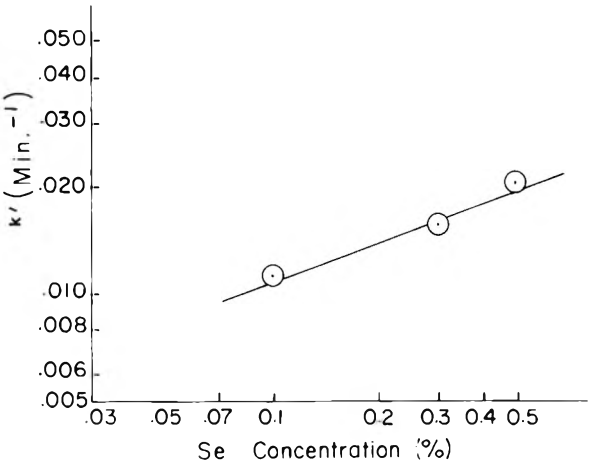

FIG. 3. LOG-LOG PLOT OF k′ AGAINST SELENIUM CONCENTRATION, 210°C.

where k_1' and k_2' include the concentration of selenium. The true rate equation is therefore:

$$\frac{-d\,[cis\text{-S}]}{dt} = k_1[cis\text{-S}][Se_x]^{1/n} - k_2\,[trans\text{-S}]\,[Se_x]^{1/n}$$

where $[Se_x]$ is the selenium concentration and n is some integer. It is apparent from these equations that

$$k_1' + k_2' = (k_1 + k_2)\,[Se_x]^{1/n} \text{ or}$$

$$k' = k\,[Se_x]^{1/n}, \text{ where } k' = k_1' + k_2' \text{ and } k = k_1 + k_2$$

Taking the log of both sides of the above equation gives

$$\log k' = \frac{1}{n}\log [Se_x] + \log k$$

from which it follows that a plot of log k′, the pseudo first order rate constants of Table I, *vs.* log $[Se_x]$ is a straight line whose slope is 1/n. Fig. 3 shows such a plot. The value of n calculated from the slope of the straight line is 2.9. It must be considered more than fortuitous that the selenium dependence previously found in isomerization experiments with oleic and elaidic acids was also close to one third. It appears quite likely that a dissociation of selenium such as $Se_6 \rightleftharpoons 3\,Se_2$ is involved. The $^1/_3$ order dependence of rate of isomerization on total selenium concentration is derived from the following argument. The equilibrium: $Se_6 \rightleftharpoons 3\,Se_2$, almost certainly favors the Se_6 species and it is assumed that $[Se_6] \gg [Se_2]$. Accordingly, $[Se_6]$ is directly related to the initial concentration of selenium, $[Se_x]$. From the above equilibrium

$$[Se_2] = [Se_6]^{1/3}K^{1/3} \text{ and}$$

$$[Se_2] = [Se_x]^{1/3}K^{1/3}$$

Appropriate substitution into the rate equation then gives the $^1/_3$ order dependence on initial selenium concentration. One may accordingly write a mechanism for the isomerization involving the following equations:

$$Se_6 \underset{}{\overset{\text{fast}}{\rightleftharpoons}} 3Se_2$$

$$cis\text{-Stilbene} + Se_2 \underset{\text{(fast)}}{\rightleftharpoons} cis\text{-Stilbene}.Se_2\ (pi)$$

$$\Big\Vert\ \text{(slow)}$$

$$trans\text{-Stilbene} + Se_2 \underset{\text{(fast)}}{\rightleftharpoons} trans\text{-Stilbene}.Se_2\ (pi)$$

The dissociation of selenium and the establishment of the equilibrium concentration of complexed selenium must be fast. The rate-determining isomerization of one *pi* complex to the other continues until complete equilibrium is established.

An Arrhenius calculation of the rate constants with 0.3 percent selenium at 200 and 210° give an activation energy of 38 Kcal.

Acknowledgment. The authors wish to thank the Emery Co., Inc. for a generous fellowship which made this study possible. The authors are grateful to Moshe Ish-Shalom for assistance with the experimental work and for valuable suggestions.

CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Optical Activity and the Direct Method of Acylation

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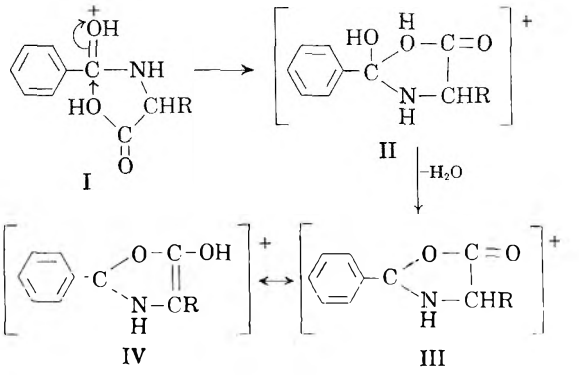
Received December 16, 1953

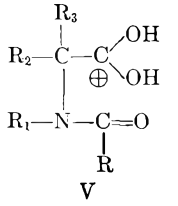
The product of the direct acylation of amino acids is optically pure in every instance except where benzoyl chloride is employed. This is not the case when the Schotten-Baumann procedure is used. Several nitrobenzoylated amino acids are characterized.

The occurrence of both partial racemization and inversion in the direct benzoylation of optically pure amino acids has been noted previously;[3] other acylating agents did not yield these effects.[3,4] Karrer and Keller[5] reported a complete racemization of the acylated leucine resulting from the Schotten-Baumann reaction between L-leucine and *p*-nitrobenzoyl chloride, which they attributed to the formation of an azlactone-alkali salt intermediate that they were able to isolate as the non-salt form (4-isobutyl-2-*p*-nitrophenyl oxazolone-5). In view of the above, it was desirable to determine whether or not direct acylation with *p*-nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride would preserve the optical purity of the amino acid moiety of the product. By comparisons of the rotation of *p*-nitrobenzoyl-L-leucine prepared by direct acylation with the optically pure product described by Karrer and Kehl,[6] and of the rotation of 3,5-dinitrobenzoyl-L-leucine prepared by direct acylation with one made by the Schotten-Baumann method, it has been established that the corresponding acylating agents do not cause racemization in direct acylation. It was noted that increased concentrations of base in the Schotten-Baumann reaction reduced the degree of racemization.

Because no prior synthesis of γ-methyl-N-benzoyl-"L"-glutamic acid ester was known, and because benzoylation by direct acylation causes racemization, no statement of the optical purity of the compound could be made. More recently attempts to synthesize the compound by the Schotten-Baumann method have met with failure. However, the degree of optical purity of the compound was determined by hydrolysis to the corresponding *N*-benzoyl-"L"-glutamic acid and comparison of the optical activity of this product with that of an authentic optically pure sample of *N*-benzoyl-L-glutamic acid that had been prepared by the Schotten-Baumann method. While the possibility exists that the γ-methyl ester was partially racemized as a consequence of the hydrolytic procedure, the data indicate that such racemization or the original racemized state of the ester was no greater than 14%. Table I contains a summary of the data on the compounds of stereochemical interest.

Since no base or metallic cation is present in the direct method, the azlactone-alkali salt intermediates suggested by Karrer and Keller[5] to explain racemization in the Schotten-Baumann medium would not be expected to form. Further, the reaction medium is somewhat on the acid side due to the HCl released in the amide formation. This suggests that the racemization which has been observed during direct benzoylation[3] might be due to the formation of an oxazolonium ion (I to IV) similar to the proposal of O'Brien and Niemann[8] to explain the cyclization of α-acylamino acids in absolute sulfuric acid or acetic anhydride. I to IV differ somewhat from the suggested intermediates of these authors, since their entity (V) would not be expected to form in the slightly acidic medium of the direct method.





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(2) Aided by a Fellowship from the National Foundation for Infantile Paralysis, Journal paper No. J-2066 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project No. 1111.

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(4) E. Ronwin, *J. Org. Chem.*, **18**, 127 (1953).

(5) P. Karrer and R. Keller, *Helv. Chim. Acta*, **26**, 50 (1943).

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(7) S. W. Fox and H. Wax, *J. Am. Chem. Soc.*, **72**, 5087 (1950).

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TABLE I
COMPOUNDS OF STEREOCHEMICAL INTEREST[a]

Compound	M.P., °C (corr.)	Lit., M.P., °C.	Synthesis,[b] Method	Specific Rotation[c]	Racemization, %
γ-Methyl *N*-Benzoyl-L-glutamic acid ester	119	107[3,d]	D	−7.0° (22°) (2% in 95% ethanol)[e]	≦14
N-Benzoyl-L-glutamic acid	136–137		O[f]	+15.7° (22°) (4% in N KOH)	≦14
N-Benzoyl-L-glutamic acid	139–140		SB[7]	+18.2° (28°) (5% in N KOH)	None
N-*p*-Nitrobenzoyl-L-leucine	228–229		D	−9.15° (28°) (2.8% in 95% ethanol)	None
N-*p*-Nitrobenzoyl-L-leucine	219–220		O[g6]	−8.87° (20°) (2.8% in alcohol)	None
N-*p*-Nitrobenzoyl-L-leucine	222–223		SB[h5]	Inactive	100
N-*p*-Nitrobenzoyl-L-leucine	228		SB[i]	−4.96° (26°) (2.9% in 95% ethanol)	46
N-3,5-Dinitrobenzoyl-L-leucine	184–185	186–187[9,j] 188[10,j]	D	−10.4[c] (28°) (2.9% in 95% ethanol)	None
N-3,5-Dinitrobenzoyl-L-leucine	188	186–187[9,j] 188[10,j]	SB	−10.5° (28°) (2.9% in 95% ethanol)	None

[a] A further description of the compounds prepared in this work can be found in Table II or under the Experimental section. [b] D = direct method of acylation; SB = Schotten-Baumann procedure; O = other method which is described by an additional footnote. Unless a reference is provided, the synthesis was performed by the author. [c] All rotations were reported at the D line of sodium. The figure in parenthesis is the temperature in degrees centigrade. [d] This discrepancy may be due to an impurity in the previous product. [e] $[\alpha]_D^{23.5}$ −7.15° (2% in 95% ethanol).[3] [f] By hydrolysis of the corresponding γ-methyl ester; see Experimental section. [g] By hydrolysis of the corresponding methyl ester.[6] [h] One equivalent of sodium hydroxide. [i] Two equivalents of sodium hydroxide. [j] Compound prepared by the Schotten-Baumann method; no rotation quoted.

Further, the presence of the *p*-nitro or the 3,5-dinitro groups on the benzene nucleus should act to suppress ring closure (I to IV) by their electron attraction which deters the oxygen atom of the amide carbonyl group from adding a proton. This notion is compatible with the experimental observations (Table I).

Saunders[9] and Town[10] raised considerable doubt concerning the identity of several of the 3,5-dinitrobenzoylated amino acids which they describe. In fact, Town labeled his norvaline and norleucine derivatives with question marks. These authors differed on melting points and, as they both employed alcohol-water mixtures for recrystallization, several of their products contained water of hydration. Also, they did not report the rotation of their optically active products.

In this work several new 3,5-dinitrobenzoylated, *p*-nitrobenzoylated, and *m*-nitrobenzoylated amino acids are characterized in addition to a number of previously reported members of each series prepared for the first time by direct acylation (Table II). As found by Town and by Saunders for the Schotten-Baumann procedure, the direct method failed to yield 3,5-dinitrobenzoylated tyrosine; similarly 3,5-dinitrobenzoyl-DL-aspartic acid could not be obtained. The difficulty which Town reported in separating the product from the 3,5-dinitrobenzoic acid was overcome by using acetone-CCl_4 or acetone-$CHCl_3$ mixtures which, additionally, avoid formation of hydrated products.

(9) B. C. Saunders, *Biochem. J.*, **28**, 580 (1934).
(10) B. W. Town, *Biochem. J.*, **35**, 578 (1941).
(11) P. Karrer and C. Christoffel, *Helv. Chim. Acta*, **27**, 622 (1944).
(12) W. S. Fones and M. Lee, *J. Biol. Chem.*, **201**, 847 (1953).

EXPERIMENTAL

Reagents. The acid chlorides were products of Eastman Kodak. Anhydrous ethyl acetate was obtained from Eastern Chem. Co. All amino acids were commercial products. γ-Methyl-L-glutamate was synthesized in 60% yield by the procedure of Hanby, Waley, and Watson,[13] m.p. 182° dec. (Lit. 182° dec.).

Direct acylation procedure. This procedure has been adequately described on two previous occasions.[3,4]

Synthesis of γ-methyl N-benzoyl-"L"-glutamic acid ester by the direct method. Three grams (0.019 mole) of the amino acid was suspended in 60 ml. of anhydrous ethyl acetate and refluxed under anhydrous conditions with 3.7 g. (0.026 mole) of benzoyl chloride. After 3 hr., the reaction mixture was filtered and the filtrate was taken to dryness with the aid of a current of air. The remaining crystalline product was washed with cyclohexane and recrystallized from acetone-hexane. This yielded 1.4 g. (28%) of material, m.p. 119° (corr.). A mixed melting point with benzoic acid gave an erratic result over a 30° range. For the optical rotation of this product see Table 1. (The product was a mixture of 93% of the L-form and 7% of the D-form.)

Anal. Calcd. for $C_{13}H_{15}NO_5$: N, 5.3. Found: N, 5.1.

Conversion of the ester to N-benzoyl-"L"-glutamic acid. One gram (0.004 mole) of γ-methyl-*N*-benzoyl-"L"-glutamic acid ester was refluxed with 7.6 ml. of 2*N* NaOH (4 equivalents) for 0.75 hr. The solution was cooled and acidified to Congo red with 4*N* HCl. No precipitate was observed. The solution was filtered and the filtrate was taken to dryness, *in vacuo*. The remaining residue was extracted with acetone. The acetone extract was filtered, reduced in volume, refiltered, and treated with hexane until turbidity. A colorless oil precipitated which upon considerable scratching crystallized. Six-tenths gram of a hard, white compound was obtained. Recrystallization from acetone-cyclohexane was hastened by scratching. This yielded 0.55 g. (58%) of a hard, white crystalline product, m.p. 136–137° (Lit. 139–140°).[7] The optical rotation of this product (Table 1) indicates that the compound is a mixture of 93% of the L-form and 7% of the D-form.

(13) W. E. Hanby, S. G. Waley, and J. Watson, *J. Chem. Soc.*, 3239 (1950).

TABLE II
NITROBENZOYLATED AMINO ACIDS

Amino Acid Moiety	M.P., °C. (Corr.)	Lit M.P., °C.	Yield, %	Reflux Time, Hr.	Description of Filtrate Residue	Solvent Used for Purification[a]	Nitrogen[b] Calcd.	Found
N-3,5-Dinitrobenzoylated Amino Acids								
L-Leucine[c]	184–185	186–187[9] 188[10]	28	3	White crys.	Acetone-CCl_4	12.9	13.0
DL-Methionine	160		39	3	White crys.	Acetone-$CHCl_3$	12.3	12.2
DL-Phenylalanine	167	161[10]	25	1.5	Col. crys.	Acetone-CCl_4	11.7	11.6
DL-Alanine	177	177[9,10]	26	1.75	White crys.	Acetone-CCl_4	14.8	14.8
DL-Valine	211–212	211.4[10]	45	2	White crys.	Acetone-$CHCl_3$	13.5	13.6
DL-Norleucine	208	163[10,d]	30	1.75	White crys.	Acetone-$CHCl_3$	12.9	12.7
DL-Isoleucine	182–183	170.4[10]	52	1.75	White crys.	Acetone-$CHCl_3$	12.9	12.8
DL-α-Amino-*n*-butyric acid	213		23	2.5	White crys.	Acetone-$CHCl_3$	14.1	14.1
DL-Norvaline	234–235	182[d,10]	33	2.5	White crys.	Ethyl acetate-$CHCl_3$	13.5	13.5
L-3-Nitro-4-hydroxyphenylalanine[e]	188–189		19	2	Yellow crys.	Acetone-CCl_4	13.3	13.2
N-*p*-Nitrobenzoylated Amino Acids								
DL-Methionine	191–192		40	2.5	White crys.	Acetone-CCl_4	9.4	9.3
L-Tyrosine[f]	236–237		8	1.5	White crys.	CCl_4	8.5	8.5
L-Leucine[c]	228–229	219–220[6]	39	1.5	White crys.	Acetone-CCl_4	10.0	10.0
DL-Phenylalanine[g]	168	168.5[11]	31	2	White crys.	Washed with ethyl ether; acetone-CCl_4	8.9	8.9
N-*m*-Nitrobenzoylated Amino Acids								
DL-Methionine	128–129		73	1	White crys.	Acetone-CCl_4	9.4	8.9
DL-Phenylglycine	169		99	3.5	White crys.	Acetone-CCl_4	9.3	8.9
DL-Alanine	163	162–164[12]	56	3.5	White crys.	Acetone-CCl_4	11.8	11.8
DL-α-Amino-*n*-butyric acid	174		69	4	White crys.	Acetone-CCl_4	11.1	10.9
DL-Aspartic Acid	133–134		42	3	White crys.	Acetone-CCl_4	9.9	9.9
DL-Norleucine	148–149		72	2	White crys.	Acetone-CCl_4	10.0	9.9
DL-Isoleucine	120		36	2	White crys.	Acetone-CCl_4	10.0	9.8
DL-Valine	151–152		83	3	White crys.	Acetone-CCl_4	10.5	10.8
DL-Phenylalanine	138–139		67	3	White crys.	Acetone-CCl_4	8.9	8.8

[a] Unless otherwise indicated the solvent was employed in recrystallization procedures. [b] Analyses were performed by the reductive Kjeldahl method using $Na_2S_2O_3$ as reducing agent. [See report of H. A. Davis, *J. Assoc. Offic. Agr. Chemists, 37*, 359 (1954)]. [c] For optical rotation see Table I. [d] Labeled by Town[10] with a question mark. [e] $[\alpha]_D^{28}$ −30.7° (2.02% in 1:1 acetone:95% ethanol). [f] $[\alpha]_D^{28}$ + 2.59° (2.09% in 95% ethanol). [g] Erroneously labeled *N*-*p*-nitrobenzoyl-DL-alanine in the paper by Karrer and Christoffel.[11]

Anal. Calcd. for $C_{12}H_{13}NO_5$: N, 5.6. Found: N, 5.4.

Synthesis of N-p-nitrobenzoyl-"L"-leucine by the Schotten-Baumann procedure. Two grams (0.015 mole) of the amino acid were dissolved in 15 ml. of 2*N* NaOH (2 equivalents) and the solution was diluted to 40 ml. Then a solution of 2.8 g. (0.015 mole) of the acid chloride in 40 ml. of ethyl ether was slowly dropped during 0.5 hr. while the reaction medium was mechanically stirred at room temperature. The aqueous layer took on a characteristic purple hue. At the end of the dropping period the solution was acidified with 25% acetic acid. An orange precipitate formed which was filtered off and air dried. Three recrystallizations from acetone-carbon tetrachloride yielded 0.9 g. (21%) of a powdery, white crystalline product, melting at 228° (corr.) to a clear slightly reddish liquid [lit. 219–220°[6], 228–229° (Table II)]. The optical rotation of this product (Table I) indicates that this compound is a mixture of 77% of the L-form and 23% of the D-form.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: N, 10.0. Found: N, 9.8.

Synthesis of N-3,5-dinitrobenzoyl-L-leucine by the Schotten-Baumann procedure. Two grams (0.015 mole) of the amino acid were dissolved in 15 ml. of 2*N* NaOH (2 equivalents) and 3.47 g. (0.015 mole) of the acid chloride were added at one time. The acid chloride immediately dissolved and the solution became purple. The solution was mechanically shaken for 0.5 hr. At the end of the reaction period, the solution was acidified with 25% acetic acid. The purple color disappeared and a pale yellow compound precipitated. It was filtered off. The filtrate yielded another crystalline crop after a night of refrigeration. Recrystallization of the combined fractions from acetone-chloroform yielded 1.4 g. (28%) of a pale yellow product, m.p. 188° (corr.) [lit. 186–187;[9] 188°:[10] 184–185° (Table II)]. The optical rotation (Table I) of this compound is in excellent agreement with that found for the product synthesized by the direct method of acylation and therefore presumed to be optically pure.

Anal. Calcd. for $C_{13}H_{15}N_3O_7$: N, 12.9. Found: N, 13.0.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DREXEL INSTITUTE OF TECHNOLOGY]

Ester Interchange Reactions of Long Chain Thiol Esters[1]

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Received March 25, 1957

Ethanethiol esters of lauric, myristic, palmitic, and stearic acids undergo ester interchange reactions with alkanethiols, arylthiols, alcohols, and phenol in the presence of sodium methoxide or β-naphthalenesulfonic acid. Eight previously unreported thiol esters were prepared by ester interchange.

This paper presents ester interchange of thiol esters with alkanethiols, arylthiols, alcohols, and phenol. The authors believe that these reactions are being reported for the first time.

$$R{-}\overset{\overset{O}{\|}}{C}{-}SC_2H_5 + R'SH \rightarrow R{-}\overset{\overset{O}{\|}}{C}{-}SR' + C_2H_5SH$$

$$R{-}\overset{\overset{O}{\|}}{C}{-}SC_2H_5 + R'OH \rightarrow R{-}\overset{\overset{O}{\|}}{C}{-}OR' + C_2H_5SH$$

The ester interchange reactions involving thiols were effected by treating ethanethiol esters of lauric, myristic, palmitic, and stearic acids with *n*-heptanethiol, *n*-octanethiol, β-naphthalenethiol and benzyl mercaptan as well as isobutyl thiostearate with β-naphthalenethiol. In each instance a less volatile thiol displaced more volatile ethanethiol or 2-propanethiol. The reactions were first attempted by heating the thiol esters with a slight excess of thiol on a steam bath in the presence of a trace of sodium ethoxide or sodium methoxide. This procedure resulted in low yields. When the reactions were repeated in pyridine, they proceeded very smoothly and were essentially complete at the end of a 1-hr. heating period. Yields of about 60% were obtained. The reaction appears to be general; the results are summarized in Table I. Altogether seventeen interchange reactions with thiols were attempted. All of these were successful. The reactions involving *n*-heptanethiol and *n*-octanethiol resulted in the formation of eight new thiol esters.

The course of the reaction is probably the same as that of alcoholysis of esters, and may be illustrated by the following equations.[2]

$$R{-}\overset{\overset{O}{\|}}{C}{-}SR' + R''SH \rightleftarrows R{-}\overset{\overset{O-}{|}}{\underset{\underset{H{-}\overset{+}{S}{-}R''}{|}}{C}}{-}SR' \rightleftarrows R{-}\overset{\overset{O}{\|}}{C}{-}SR'' + R'SH$$

Large excesses of methyl, ethyl, *n*-butyl, and *n*-octyl alcohols were caused to react with ethyl thiostearate in the presence of a trace of sodium methoxide. A slight excess of phenol in pyridine and in the presence of sodium methoxide also reacted with ethyl thiostearate. The reaction rates in this case were considerably slower than the reaction rates with thiols. Phenyl and methyl stearates were formed after about 3 hr. heating on a steam bath, ethyl stearate was formed in 24 hr., while a 48-hr. heating period was required for the formation of a *n*-butyl and *n*-octyl stearates.

Attempts to effect ester interchange between ethyl thiostearate and alcohols in the presence of an acid catalyst were unsuccessful. When 0.005 mole of ethyl thiostearate was heated with large excesses of methyl, ethyl, *n*-butyl, and *n*-octyl alcohols in the presence of 0.1 g. of β-naphthalene sulfonic acid, the only solid material isolated from the reaction mixture was unchanged ethyl thiostearate even after the reaction mixture had been heated on a steam bath for 48 hr.

Similarly, all attempts to effect an ester interchange reaction between methyl stearate and thiols were unsuccessful. Heating methyl stearate with a slight excess of benzenethiol, *p*-toluenethiol, and dodecanethiol in pyridine and in the presence of sodium methoxide on a steam bath for 48 hr. resulted in the isolation of unchanged methyl stearate. Similar results were obtained when methyl stearate was heated with large excesses of benzenethiol in the presence of sodium methoxide or β-naphthalene sulfonic acid.

In our last attempt to effect an ester interchange reaction between methyl stearate and a thiol, the former compound was heated together with dodecanethiol in the presence of sodium methoxide under nitrogen at 250° for 24 hr. Even under these "forcing" conditions, the only solid material that could be isolated from the reaction mixture was unchanged methyl stearate.

EXPERIMENTAL

Materials. Lauroyl, myristoyl, and palmitoyl chlorides, alkanethiols and benzenethiols were obtained from Distillation Products Industries. Humko's commercial stearic acid was crystallized once from methanol and once from

(1) From a thesis submitted by Paul R. Schaeffer to the Department of Chemistry of the Drexel Institute of Technology in partial fulfillment of the requirements for the degree of Master of Science.

(2) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley & Sons, Inc., New York, 1953, p. 209.

acetone and melted at 69°. All melting points are uncorrected.

Ethanethiol Esters. Ethyl thiolaurate, b.p. 116–118° at 1 mm., ethyl thiomyristate, b.p. 134–137° at 1 mm., and ethyl thiopalmitate, b.p. 173–176° at 1 mm. were prepared by the method of Ralston, *et al.*[3]

Ethyl Thiostearate. To 0.1 mole of molten stearic acid in a 125 ml. separatory funnel, protected by a calcium chloride drying tube, was added 5.5 g. of phosphorus trichloride. The mixture was heated with a steam-cone for 1 hr. and then allowed to stand overnight. The stearoyl chloride was separated from the phosphorous acid formed in the reaction and was added to 0.2 mole of ethanethiol in a 200 ml. round bottomed flask, fitted with a reflux condenser and cooled in an ice bath. The mixture was allowed to stand overnight and then was heated on a water bath for 6 hr. The resulting solid which contained some free fatty acid, was dissolved in 100 ml. of acetone and 6*N* sodium hydroxide solution in a 5% excess over that necessary to neutralize the free fatty acid was added with stirring. The insoluble sodium stearate was separated by filtration and washed with 20 ml. of acetone. The solution was cooled to 0° and the resulting solid was separated by filtration. The product was crystallized from acetone–alcohol and melted at 38°.[3] The yield was 20.3 g. or 61% of the theoretical amount.

Isobutyl Thiostearate. This compound was prepared by the method described in a previous paper.[4]

Reactions of Ethanethiol Esters and Isobutyl Thiostearate With Alkane Thiols, Benzene Thiols and Phenol. To 0.01 mole of thiol ester in a 200 ml. round bottomed flask, fitted with a reflux condenser, was added a mixture of 0.011 mole of alkane or benzenethiol, 0.05 g. of sodium methoxide, and 20 ml. of pyridine. After heating for 2 hr. on a steam bath, the pyridine was removed by distillation under diminished pressure. The product was then dissolved in 100 ml. of ether and washed with two 50 ml. portions of water. The ether solution was dried over anhydrous sodium sulfate and after removal of the solvent by distillation the products were crystallized from acetone or alcohol-acetone mixtures. The results of the interchange reactions are summarized in Table I.

Reactions of Ethyl Thiostearate With Methyl, Ethyl, n-Butyl, and n-Octyl Alcohols. To 0.01 mole of ethyl thiostearate in a 200 ml. round bottomed flask, fitted with a reflux condenser, was added a mixture of 0.05 g. of sodium methoxide and 50 ml. of the appropriate alcohol. In the case of methyl alcohol, a 3-hr. heating period on the steam bath was required. Ethyl alcohol was heated for 24 hr. and *n*-butyl and *n*-octyl alcohols required 48 hr. At the end of the heating period, the excess alcohol was removed by distillation under reduced pressure and the product was dissolved in 100 ml. of ether and washed with two 50 ml. portions of water.

TABLE I

ESTER INTERCHANGE REACTIONS OF ETHANETHIOL ESTERS

Product	Yield %	M.P. °C	Analyses Sulfur Calcd.	Found
β-Naphthyl thiolaurate	53	29.5–30	—	—
n-Heptyl thiolaurate	61	24	10.3	10.5
n-Octyl thiolaurate	63	21.5	9.8	10.0
Benzyl thiolaurate	51	35–36	—	—
β-Naphthyl thiomyristate	52	38.5–39	—	—
n-Heptyl thiomyristate	64	32	9.4	9.3
n-Octyl thiomyristate	62	31	9.0	9.0
Benzyl thiomyristate	67	45–46	—	—
β-Naphthyl thiopalmitate	60	47–47.5	—	—
n-Heptyl thiopalmitate	63	39–39.5	8.6	8.6
n-Octyl thiopalmitate	70	37.5	8.3	8.1
Benzyl thiopalmitate	55	52	—	—
β-Naphthyl thiostearate	60	56	—	—
n-Heptyl thiostearate	70	44–44.5	8.0	7.8
n-Octyl thiostearate	65	43.5–44	7.8	7.8
Benzyl thiostearate	63	59.5–60	—	—
Methyl stearate	70	39	—	—
Ethyl stearate	76	34	—	—
n-Butyl stearate	67	27.5	—	—
n-Octyl stearate	58	34	—	—
Phenyl stearate	68	52	—	—

After drying the ethereal solution over anhydrous sodium sulfate and removal of the solvent by distillation, the esters were crystallized from alcohol. The individual esters were identified by melting points and by admixture with an authentic sample of the appropriate ester. In each case there was no depression of melting point. A negative qualitative sulfur test was obtained after sodium fusion. The results of these reactions are summarized in Table I.

Attempted Reaction Between Methyl Stearate and 1-Dodecanethiol. To 9.0 g. (0.03 mole) of methyl stearate in a 100 ml. round bottomed flask was added 24 g. (0.12 mole) of 1-dodecanethiol and 0.1 g. of sodium methoxide. The reaction mixture was heated on an oil bath at 250° for 24 hr. During the entire heating period nitrogen was bubbled through the reaction mixture. The reaction mixture was cooled and dissolved in 200 ml. of ether and washed with two 50-ml. portions of water, dried over anhydrous sodium sulfate, and the ether was removed by distillation. Three crystallizations from alcohol yielded 6.0 g. of unchanged methyl stearate. The melting point and mixed melting point with an authentic sample of methyl stearate was 39°. A qualitative test for sulfur was negative.

Acknowledgment. The authors wish to thank The Trendex Division of the Humko Chemical Co. for generously supplying S-97, commercial stearic acid.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, PITTSBURGH CONSOLIDATION COAL COMPANY]

Synthesis and Properties of the Six Thioxylenol Isomers

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Received April 1, 1957

The six dimethylthiophenol isomers were synthesized and oxidized to the corresponding disulfides. The thioxylenols were also condensed with acrylic acid to form solid derivatives.

Commercial mixtures of thiophenol and its methyl homologues are available from caustic washing of gasoline. These can be separated satisfactorily by distillation into thiophenol, mixed thiocresols, and mixed thioxylenols. Analysis of the thiocresol fraction for the three individual isomers is possible by infrared spectroscopy, since pure *ortho*-, *meta*-, and *para*-thiocresols are available as standards. The determination of the isomer distribution in the thioxylenol cut has not hitherto been possible, since none of the six dimethylthiophenols is obtainable from commercial sources and only two of them have been described in the literature.

We have synthesized all six isomers from the corresponding xylidines, and have determined the boiling point and infrared spectrum of each. In addition, each compound was oxidized to the disulfide and also condensed with acrylic acid to form a solid derivative for identification.

EXPERIMENTAL

All melting points are corrected; boiling points were obtained using a calibrated Chromel-Alumel thermocouple. Distillation of the thioxylenols was carried out on a 1.2 cm. × 60 cm. column packed with Heli-Pak.

Starting materials were Eastman Kodak Co. White Label reagents except in the case of 2,3- and 3,4-dimethylanilines, which were Aldrich Chemical Co. research grade products. All were used without preliminary purification. The thioxylenols were synthesized using the method described by Leuckart[1] for the preparation of 2,4-thioxylenol *via* reaction of diazotized xylidines with potassium ethyl xanthate, followed by hydrolysis of the xylyl ethyl xanthate. The acidified hydrolysate was extracted with ether; after drying over Drierite and removal of ether at reduced pressure, the thioxylenol was immediately distilled and a center fraction retained for further work.

In the case of 3,5-thioxylenol, which appears to be especially susceptible to air oxidation, only a small amount of thiol was obtained on distillation. The residue, presumably disulfide, was reduced with hydrogen over Davison 50% MoS_2-on-alumina catalyst (20 weight % catalyst) at 160–170°C; cold hydrogen pressure 1925 p.s.i. Distillation of this reduced material produced 3,5-thioxylenol in a yield comparable to the other isomers.

Thiol titrations were carried out on each of the pure thioxylenols, using the method of Tamele and Ryland,[2] except that methanol was substituted for isopropyl alcohol as solvent.

Reported boiling points for 2,4-thioxylenol at 760 mm. are 207–208°;[3] 212–214°;[1,4] for 2,5-thioxylenol 205–206°,[3] 211–212°;[4] and 204–205°.[5] The use of 3,5-thioxylenol in synthesis is described[6] but no preparation or physical properties given.

TABLE I
PROPERTIES OF THIOXYLENOLS

	Yield, %		B.P.	Found[a]		
	%	Thiol	(50 mm.)	C	H	S
2,3-Thioxylenol	58	97.8	132.2°C	69.37	7.49	23.1
2,4-	48	99.3	127.0	69.63	7.60	22.7
2,5-	55	99.1	126.3	69.38	7.58	22.4
2,6-	47	99.2	122.0	69.37	7.40	22.6
3,4-	63	99.1	132.5	69.28	7.25	22.9
3,5-	54	99.7	127.5	69.41	7.30	22.8

[a] Calcd. for $C_8H_{10}S$: C, 69.51; H, 7.29; S, 23.20.

The *beta*-(dimethylphenylthio)propionic acids were obtained by refluxing 2.7 g. of pure thioxylenol with 1.44 g. acrylic acid (Eastman Kodak White Label) and 1.2 g. sodium hydroxide in 25 ml. of water for 1 hr. Acidification of the reaction mixtures precipitated oils, solidifying to white solids. These crude acids were purified by repeated crystallizations from hexane.

TABLE II
beta-(DIMETHYLPHENYLTHIO)PROPIONIC ACIDS

		Found[a]		
	M.P., °C	C	H	S
Beta-(2,3-dimethylphenylthio)-propionic acid	94–95	62.58	6.54	15.4
2,4-[b]	81–82	62.82	6.68	15.0
2,5-	101.5–102.5	62.96	6.89	15.3
2,6-	90–91	62.55	6.49	15.4
3,4-	70–71	62.81	6.66	15.6
3,5-	65.5–66.5	62.69	6.39	15.2

[a] Calcd. for $C_{11}H_{14}O_2S$: C, 62.82, H, 6.71; S, 15.25. [b] The reported melting point of *beta*-(2,4-dimethylphenylthio)-propionic acid is 84–85°.[7]

Bis(2,6-dimethylphenyl) disulfide was obtained by extraction of the undistillable pot residue from 2,6-thioxylenol with hot isopropyl alcohol, and purified by a series of recrystallizations from aqueous isopropyl alcohol.

The other disulfides were obtained by bubbling air through a mixture of one gram thioxylenol in 25 ml. ammonium hydroxide. The precipitated disulfide was extracted with ether, washed with 10% sodium hydroxide, and recrystallized from aqueous isopropyl alcohol. Crystals were obtained except in the case of bis(2,4-dimethylphenyl) disulfide and bis(3,5-dimethylphenyl) disulfide, which were light amber oils and not further characterized.

(1) R. Leuckart, *J. prakt. Chem.*, (2) **41**, 192 (1890).
(2) M. W. Tamele and L. B. Ryland, *Ind. Eng. Chem., Anal. Ed.*, **8**, 16 (1936).
(3) L. Gattermann, *Ber.*, **32**, 1147 (1899).
(4) S. Ruhemann, *Ber.*, **46**, 3389 (1913).
(5) F. Taboury, *Ann. Chim. (Paris)*, (8), **15**, 15 (1908).
(6) K. v. Auwers and W. Thies, *Ber.*, **53**, 2297 (1920).
(7) F. Krollpfeiffer and H. Schultze, *Ber.*, **56B**, 1819–24 (1923).

TABLE III
SYMMETRICAL BIS(DIMETHYLPHENYL) DISULFIDES

	M.P., °C	Found[a] C	H	S
Bis(2,3-dimethylphenyl)disulfide	99.0–99.5	69.86	6.46	23.4
2,4-	Oil	70.18	6.74	22.7
2,5-	46.5–48.0[b]	69.74	6.39	23.3
2,6-	102.5–104.0	70.05	6.66	23.6
3,4-	50–51	69.45	6.60	23.3
3,5-	Oil	69.80	6.84	23.1

[a] Calcd. for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.37. [b] Bis-(2,5-dimethylphenyl) disulfide is reported to melt at 46–47°.[5]

DISCUSSION

Although thiophenols are generally believed to show little intermolecular hydrogen bonding,[8] it is evident from an examination of the boiling points in Table I that this phenomenon must exist to a certain extent. The lowest-boiling compound, 2,6-thioxylenol, has a normal boiling point more than four degrees below that of any of the other isomers due to steric interference by the two ortho methyl groups with intermolecular bonding. This behavior is analogous to, although less pronounced than, that of 2,6-xylenol, which boils some 10 degrees below any of the other dimethylphenols.

Infrared spectra of the six thioxylenols were obtained and compared with the spectra of the same compounds in dilute cyclohexane solutions. No clear evidence for or against intermolecular hydrogen bonding could be secured by this method, due to the weak absorption of the SH bond.

Acknowledgment. The authors wish to thank Dr. F. V. Fair and Miss M. J. Alexander for the infrared spectra and assistance in interpreting them.

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(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, London, Methuen, 1954, p. 289.

[CONTRIBUTION FROM THE PENNSYLVANIA SALT MANUFACTURING CO.]

Some Unusual Water Solubility Properties of Alkyl Tetraalkylphosphorodiamidates

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Received March 14, 1957

A number of alkyl tetraalkylphosphorodiamidates have been prepared; some of these have been found to possess unusual water solubility characteristics. A number of other miscellaneous types of phosphorus compounds are described.

During an investigation of the physical properties of a variety of classes of organic phosphorus compounds, the unusual inverse water solubility of the alkyl tetraalkylphosphorodiamidates, $ROP(O)(NR'_2)_2$, prompted us to further investigate these compounds.

Little has appeared concerning the preparation and properties of the phosphorodiamidates, where all substituents are aliphatic,[1] since Michaelis[2] first prepared four of these compounds in 1903.

The compounds of this type which we have prepared are listed in Table I. Except where otherwise indicated in the EXPERIMENTAL, yields were 85% or better.

Most of these compounds were prepared by reacting the appropriate alcohol with phosphoryl chloride to give the alkyl phosphorodichloridate, which was then reacted with excess amine. Under the experimental conditions used, there was never any indication of diester formation. When the amine was readily available, excess amine was used as the acid acceptor. When the amine was of limited availability, triethylamine or pyridine was used. The diamidates prepared from dimethylamine were obtained in higher yield when aqueous rather than anhydrous dimethylamine was used. With all other amines, however, aqueous solutions gave lower or negligible yields. Consequently, except for the preparation of the diamidates of dimethylamine all reactions were carried out under anhydrous conditions.

Compound XVI could not be prepared by this procedure. The reaction of phosphoryl chloride with 2-ethylmercaptoethanol gave only polymeric products, so an inverse synthesis was used for this compound. Phosphoryl chloride was treated with a large excess of diethylamine, and the phosphorodiamidic chloride which was isolated was then allowed to react with the sodium salt of 2-ethylmercaptoethanol to give the desired product.

All attempts to prepare derivatives of diisopropylamine were unsuccessful.

The intermediate acid chlorides were all fuming, lachrymatory liquids; the diamidates were all liquids. The low molecular weight diamidates had pepper-like odors; the higher molecular weight diamidates generally had camphor-like odors.

(1) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, New York, 1950.

(2) A. Michaelis, *Ann.*, 326, 129 (1903).

TABLE I
PROPERTIES OF ALKYL TETRAALKYLPHOSPHORODIAMIDATES

$$ROP(NR'_2)_2$$

No.	R	R′	B.P., °C.	(mm.)	n^t_D	t., °C.	Carbon Atoms	Solubility in Water: Cold	Room Temp.	Hot
I	Methyl	Methyl	76–82	(10–15)	1.4359	27	5	+	+	+[a]
II	Methyl	Ethyl			1.4519	27	9	+	+	+[b]
III	Ethyl	Ethyl	79–80	(0.8)	1.4380	27	10	+	+	−[c]
IV	Ethyl	Butyl	150–5	(0.5)	1.4455	27	18	−	−	−[d]
V	Ethyl	n-Octyl	d.	(0.1)			34	−	−	−[e]
VI	Butyl	Methyl	123–5	(15)	1.4360	26	8	+	+	−[f]
VII	Butyl	Ethyl	111–13	(0.6)	1.4413	26	12	+	+	−[g]
VIII	Butyl	Butyl			1.4500	21	20	−	−	−[h]
IX	"Isooctyl"	Methyl			1.4440	26	12	+	+	−[i,j,k,h]
X	*n*-Octyl	Methyl	178–80	(3.5)	1.4414	27	12	+	−	−[l]
XI	*n*-Octyl	Ethyl	168–75	(0.5)	1.4450	26	16	−	−	
XII	*n*-Octyl	Butyl			1.4524	27	24	−	−	−[h]
XIII	"Iso"-tridecyl	Methyl	148–55d.	(0.3)	1.4522	23	17	+5to15	−	−[k]
XIV	"Isotridecyl"	Butyl			1.4551	27	29	−	−	−[h,k]
XV	*n*-Octadecyl	Methyl	240–55	(0.3)	1.4500	26	22	−[n]	−[n]	−[n,m,p]
XVI	2-Ethylmercapto ethyl	Ethyl			1.4720	27	12	−	−	−[h]

[a] Lit., b.p. 45–46° (1 mm.);[4] n^{20}_D 1.4385.[5] [b] Lit.[6] b.p. 94 (3 mm.). [c] Lit.[1] b.p. 140 (15 mm.); *anal.* calcd.: C 50.9; H 10.7. Found: C 50.9; H 10.6. [d] *Anal.* calcd.: C 62.0; H 11.9; Found: C 61.8; H 12.4. [e] *Anal.* calcd.: P 5.4. Found: P 6.6. [f] *Anal.* calcd.: C 46.2, H 10.2. Found: C 46.2, H 10.2. [g] *Anal.* calcd.: C 53.8, H 11.0, N 10.6, P 11.7; Found C 53.8, H 11.2, N 10.9, P 12.0. [h] Decomposes on attempted vacuum distillation. [i] Milky solution. [j] *Anal.* calcd.: C 54.4, H 11.0. Found: C 54.3, H 11.0. [k] These are made from synthetic mixed branched chain primary octyl or tridecyl alcohols obtained from Enjay Chemical Co. [l] *Anal.* calcd.: C 54.5, H 11.0; Found: C 54.5, H 11.0. [m] *Anal.* calcd.: C 65.3, H 12.2; Found: C 65.5, H 12.4. [n] Hydrate and emulsion, see discussion. [p] M.p. 18.5–20.5°.

The most interesting property of these compounds was their unusual water solubility characteristics. As can be seen by reference to Table I, these vary from being completely soluble (I and II), through materials soluble in cold water and insoluble in hot (III, VI, VII, IX) to materials that are water insoluble (others). The most unusual compound is XIII which is soluble in water over only a 3 degree range, between 5–15°, the exact 3 degrees within which it is water soluble depending on the relative proportion of water to XIII. When mixed with water at room temperature an emulsion occurs; on slow cooling, the solution suddenly becomes homogeneous and transparent; on further cooling, the solution suddenly turns milky again. Another interesting compound is XV which forms a waxy hydrate with water at room temperature and then gradually (more rapidly on warming) forms a milky emulsion.

The water solubility appears to be related to the number of carbon atoms present. An inspection of Table I shows that compounds having 8 or 9 to 12 atoms are soluble in cold but insoluble in warm water, and compounds having 12 or more atoms are insoluble. Branched chain compounds are more soluble than straight chain compounds. In compounds containing the same number of carbon atoms the one having the smaller number of carbons on the amine group is the more soluble.

The high molecular weight compounds are somewhat unstable, and on prolonged standing appear to polymerize, presumably to phosphorodiamidic anhydrides. This reaction is accelerated in many instances by heating, particularly in the presence of strong, concentrated acids, or amine salts. The low molecular weight compounds appear to be more stable.

Compound III was used for a more thorough investigation of certain physical properties. Hydrolysis experiments carried out on III showed it to be quite resistant to aqueous hydrolysis. III was recovered unchanged after an 8 hr. refluxing of a 12.5% aqueous solution. Solutions of 5% III in 0.1*N* H_2SO_4 and in 0.1*N* NaOH were refluxed 8 hr. III was recovered in 95% yield in each case.

Samples of III were heated at 100°, 150°, and 200°C. After 7 hr., the 100° sample was unchanged, the 150° material was yellow-brown in color and slightly acidic. The 200° material was dark brown and strongly basic. However, III was recovered in 93% yield on distillation. In both the 150° and 200° materials diethylamine could be detected above the samples.

III is only slightly volatile with steam. It is

TABLE II
PROPERTIES OF MISCELLANEOUS PHOSPHORUS COMPOUNDS

No.	Compound	B.P. °C.	B.P. Mm.	n'_D	t_2°C.	
XVII	$2,4\text{-}Cl_2C_6H_3OCH_2CH_2OP(O)[N(C_2H_5)_2]_2$			1.5240	27	[a]
XVIII	$2\text{-}CH_3C_6H_4OP(O)[N(C_2H_5)_2]_2$	153–5	2	1.4990	26	[b]
XIX	$CH_3CH_2OP(O)[N(CH_3)C_6H_5]_2$			1.5545	27	[a]
XX	$(CH_3CH_2O)_2P(O)N(C_2H_5)_2$	113–14	18	1.4212	27	[c,d]
XXI	$C_6H_5P(O)[N(C_2H_5)]_2$			1.5215	24	[e]
XXII	$(C_6Cl_5O)_2P(O)N(C_4H_9)_2$					[e,f]
XXIII	$C_2H_5SCH_2CH_2OP(S)[N(C_2H_5)_2]_2$			1.5130	21	[g,a]
XXIV	$(C_2H_5SCH_2CH_2O)_3PO$			1.4968	28	[a]

[a] Decomposed on attempted vacuum distillation. [b] *Anal.* Calcd. C 60.5, H 10.9; Found: C 59.9, H 9.1. [c] Lit.[1] b.p. 114–17 (25 mm.). [d] Soluble in cold water, insoluble in hot. [e] *Anal.* Calcd.: C 34.0, H 2.5, Cl 50 4; Found: C 35.3, H 2.5, Cl 49.7. [f] M.p. 144–5° C. [g] *Anal.* Calcd.: C 46.1, H 9.3; Found: C 44.7, H 9.0.

miscible with most organic solvents and readily dissolves such diverse materials as sugar, succinic acid, and Tygon, and attacks butadiene polymers. It readily extracts succinic acid from an aqueous solution. It is miscible with glycerine at room temperature, but separates into two phases on warming.

Most of the phosphorodiamidates are soluble in dilute hydrochloric acid; all are insoluble in dilute nitric acid and sodium hydroxide. Acetylene has an appreciable solubility in III only.

A variety of miscellaneous compounds were synthesized for comparison with these alkyl phosphorodiamidates. These compounds are: 2,4-dichlorophenoxyethyl tetraethylphosphorodiamidate (XVII), 2-methylphenyl tetraethylphosphorodiamidate (XVIII), ethyl *N,N'*-dimethyl-*N,N'*-diphenylphosphorodiamidate (XIX), diethyl diethylphosphoroamidate (XX), tetraethyl benzenephosphonic diamide (XXI), bis(pentachlorophenyl) dibutylphosphoroamidate (XXII), 2-ethylmercaptoethyl tetraethylphosphorodiamidothionate (XXIII), and 2-ethylmercaptoethyl phosphate (XXIV). The physical properties of these compounds are listed in Table II.

In the preparation of XVIII the conversion of *o*-cresol to the phosphorodichloridate was improved by the addition of a small amount of magnesium chloride[3] to the reaction mixture.

XXIII is the thiono analog of XVI, prepared by using thiophosphoryl chloride in place of phosphoryl chloride.

Attempts to prepare pentachlorophenyl phosphorodichloridate by reaction of phosphoryl chloride with pentachlorophenol or its sodium salt led to the diester as the major product, even when a large excess of phosphoryl chloride was used. The bispentachlorophenyl ester was converted to the amide, XXII.

XX, which is the reverse of III in having two ester groups and one amide group, was the only compound in Table II showing water solubility. It exhibited the same inverse solubility as did III, although it is more water soluble than III.

The reaction of ethyl phosphorodichloridate with *p*-phenylenediamine gave an insoluble, high melting polymer.

EXPERIMENTAL

Alkyl phosphorodichloridates. One mole of the appropriate anhydrous alcohol was added dropwise to phosphoryl chloride, the temperature being maintained below 20°. On completion of the addition, the cooling bath was removed and the solution was stirred at room temperature for 2 hr. Then the solution was placed under 100 mm. vacuum and warmed to 60° to remove unreacted phosphoryl chloride and dissolved HCl. In two instances the product was distilled; in the others, the crude phosphorodichloridate was used. In every instance the product, $ROP(O)Cl_2$, was obtained in 85–100% yield. When R = ethyl, b.p. 67–68° (18 mm.), n_D^{28} 1.4300; (lit.[7] b.p.$_{19}$ 63°); R = butyl, b.p. 80–82° (10 mm.), n_D^{28} 1.4372 (lit.[8] b.p.$_{13}$ 85°, n_D^{31} 1.4453).

Preparation of alkyl tetraalkylphosphorodiamidates by reaction of amine with alkyl phosphorodichloridates. A solution of one mole of the alkyl phosphorodichloridates in ether was gradually added to a cold ethereal solution containing 4–5 moles dialkylamine. When the dialkylamine was available in only limited quantities, the reaction was carried out using 1 mole of dialkylamine and 3–4 moles of pyridine or triethylamine. The mixture, which was viscous with precipitated amine hydrochloride, was stirred overnight and filtered. The solvent and excess amine were distilled off. When the phosphorodiamidate was thermally stable, it was distilled, usually as a colorless or pale yellow oil. Those compounds which could not be distilled were freed of solvent and amine by heating in vacuum.

During one distillation of III, decomposition occurred and a pale yellow, moderately viscous liquid distilled, b.p. 150–160° (2 mm.), n_D^{27} 1.4625 (possibly $\left[(Et_2N)_2\text{-}\overset{\overset{O}{\|}}{P}\right]_2O$, lit.[9] b.p.$_{<1\,mm}$ 95–110°, n_D^{25} 1.4668).

Preparation of tetramethylphosphorodiamidates by reaction with aqueous dimethylamine. One mole of alkyl phosphorodichloridate was added dropwise with stirring to 5 moles of

(3) S. L. Bass, U. S. Patent **2,117,283** (1938).

(4) J. D. Dickey, T. E. Stanin, H. W. Coover, U. S. Patent **2,487,859** (1948); *Chem. Abstr.*, **44**, 2456 (1950).

(5) H. Tolkmith, U. S. Patent **2,654,783** (1953); *Chem. Abstr.*, **48**, 10051 (1954).

(6) W. A. L. David and B. A. Kilby, *Nature*, **164**, 522 (1949).

(7) B. C. Saunders, G. J. Stacey, F. Wild, and I. G. E. Wilding, *J. Chem. Soc.*, 699 (1948).

(8) W. Gerrard, *J. Chem. Soc.*, 1464 (1940).

(9) A. D. F. Toy and J. R. Costello, U. S. Patent **2,717,249** (1955).

chilled 40% aqueous dimethylamine. After the addition was complete the solution was heated until the excess dimethylamine had been distilled off. The oily product was separated hot, dried, and when the product was thermally stable, distilled.

Preparation of alkyl tetraethylphosphorodiamidate by reaction of the phosphorodiamidic chloride with the sodium alcoholate. A solution of 4 moles diethylamine in chloroform was slowly added to a solution of one mole of phosphoryl chloride (or thiophosphoryl chloride) in dry chloroform at 0°. The solution was stirred 2 hr. at room temperature and then heated to distill out most of the chloroform. A large volume of petroleum ether was then added and the precipitated amine salt was filtered. The solvent was then removed and the phosphorodiamidic chloride was distilled.

The sodium alcoholate was prepared by reaction of sodium sand with the alcohol in toluene. To the dispersion of the sodium alcoholate in toluene was slowly added the phosphorodiamidic chloride. The mixture was warmed for several hours, then filtered. The organic layer was washed with water, dried, and distilled. Thermally unstable compounds were treated with a decolorizing carbon, and last traces of solvent were removed by mild heating in vacuum.

o-Cresyl tetraethylphosphorodiamidate (XVIII). *o*-Cresol (1.5 moles) was added to 3.25 moles phosphoryl chloride containing 1 g. anhydrous magnesium chloride and maintained at 90°, and then refluxed overnight. The excess chloride was distilled off and the *o*-cresyl phosphorodichloridate distilled, b.p. 110° (7 mm.), n_D^{30} 1.5170–80 (51% conversion). When the magnesium chloride was not present, the conversion dropped to 33%.

The reaction with diethylamine was carried out in a manner similar to that already described.

Bis(pentachlorophenyl) dibutylphosphoroamidate (XXII). One hundred grams (0.376 mole) pentachlorophenol in warm chlorobenzene was added to 111 g. (0.724 mole) $POCl_3$ at 70°. Refluxing for 2 hr. gave only a small quantity of evolved HCl, so the solution was cooled to 100° and 29.7 g. (0.376 mole) pyridine was added, causing formation of a heavy precipitate of amine hydrochloride. The mixture was stirred at 100° for 1 hr., cooled, and filtered. The filtrate was concentrated *in vacuo* leaving 130 g. of a brown oil which soon crystallized. This bis(pentachlorophenyl)phosphorochloridate was taken up in toluene and added to 185 g. cold dibutylamine. The solution was refluxed 3 days and cooled, and the amine salt was filtered. Volatile materials were removed in vacuum leaving a semi-crystalline brown oil which was treated with ligroin and filtered. The precipitate was recrystallized from benzene, 33 g., m.p. 144–145°, white solid, soluble in most organic solvents.

Tetraethyl benzenephosphonic diamide (XXI). Benzenephosphonic dichloride (Victor Chemical Co.) was treated with diethylamine in the same manner that was employed with the amides already described.

Diethyl diethylphosphoroamidate (XX). Diethylphosphorochloridate (Victor Chemical Co.) was reacted with 2 moles diethylamine in the manner previously described.

Polymeric material from ethyl phosphorodichloridate and p-phenylenediamine. Four grams of *p*-phenylenediamine (Eastman Technical, purple crystals) were dissolved in a solution of chloroform containing 20 cc. pyridine. Ethyl phosphorodichloridate (6.1 g.) was slowly added. The reaction was quite exothermic. No attempt was made to prevent contact with air. The thick purple precipitate was filtered and washed with petroleum ether, dried, triturated with water, then with acetone, and then dried in vacuum at 110°. The resulting hard solid was powdered, giving beautiful purple crystals (under microscope), insoluble in acetone, dimethyl formamide, and other organic solvents. On heating it turns white at 190°, starts melting at 235°, and chars at 320°. It is readily decomposed by acids and bases.

Anal. Calcd. for $C_8H_{11}N_2O_2P$: C, 48.5, H, 5.6, N, 14.1. Found, C, 45.4, H, 5.2, N, 12.5. Mol. wt. 1250 (approx.) determined cryoscopically in acetic acid.

Solubility of acetylene in various phosphoramidates. A weighed amount of phosphoramidates was saturated with acetylene and the gain in weight was determined. III absorbed 8% of its own weight, IV and XIII absorbed nothing. By comparison hexamethylphosphoramide absorbed 14% of its weight.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Pyrolysis of Esters. XII. Ketone Cleavage of Acetoacetic Esters by Pyrolysis[1,2]

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Received March 15, 1957

The pyrolysis of acetoacetic esters is shown to be an excellent procedure for the ketone cleavage. For example, in the pyrolysis of ethyl α-isopropylacetoacetate at 525° the ester portion decomposes to give ethylene and the resulting acetoacetic acid almost simultaneously loses carbon dioxide to give an 82% yield of methyl isobutyl ketone, more than double the yield obtained by conventional basic hydrolysis. In many cases the saving of time and material as well as adaptability to large quantities recommend the pyrolysis of acetoacetic ester rather than hydrolysis. The ketone cleavage by pyrolysis is particularly advantageous if the acetoacetic ester contains a branched group or if the resulting ketone has a moderately high solubility in water.

Previous work[1,4–6] in this laboratory has shown that the pyrolysis of esters is an excellent method for the preparation of strained or sensitive olefins provided that charring is eliminated. Since the products from the pyrolysis of an ester are an olefin and an acid, it seemed logical that this reaction would be useful also in the synthesis of acids and

(1) Previous paper in this series, *J. Org. Chem.*, 22, 1076 (1957).

(2) Presented in part before the Division of Organic Chemistry at the 126th National Meeting of the AMERICAN CHEMICAL SOCIETY, New York, N. Y., September 1954.

(3) Office of Naval Research Fellow, 1950–52; Union Carbide Fellow, 1952–53; Du Pont Fellow, 1953–54.

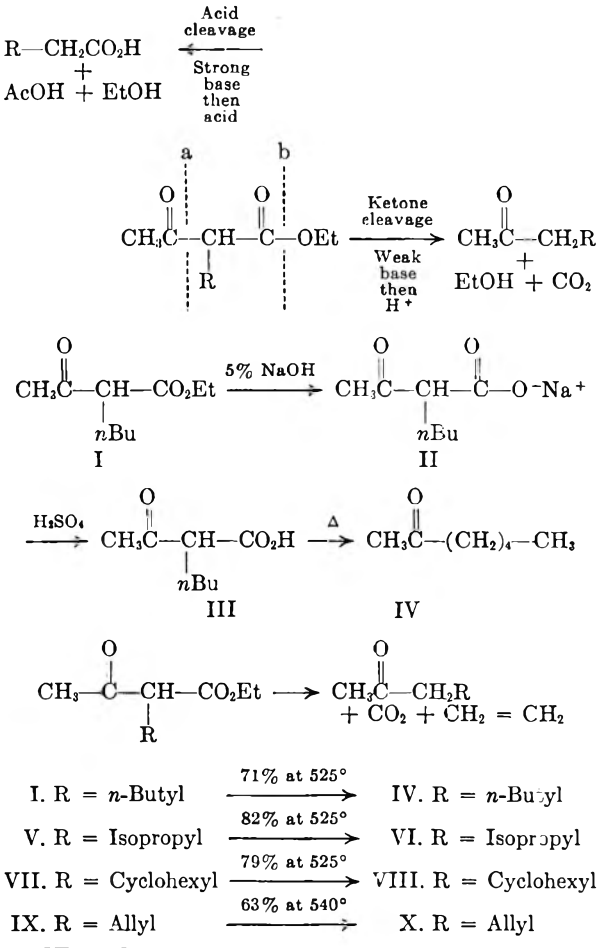
(4) W. J. Bailey and W. A. Klein, *J. Am. Chem. Soc.*, 79, 3124 (1957).

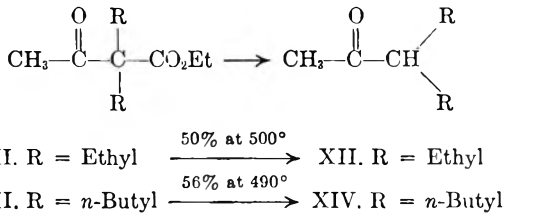
(5) W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, 77, 1133 (1955).

(6) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, 77, 73 (1955).

their derivatives. In a previous paper[7] it was shown that pyrolysis had many advantages over hydrolysis in the conversion of an ethyl ester of a fatty acid to the corresponding acid. This method was particularly useful in the preparation of water-soluble or sterically hindered acids. For example, diethyl glutarate was pyrolyzed to give a 97% yield of glutaric acid and ethyl 1,3,5-trimethylbenzoate was converted to the hindered acid in a 91% yield.

From a search for other examples of the utility of the pyrolysis reaction for the preparation of products from the acid portion it appeared that the ketone cleavage of acetoacetic esters would be an attractive field. Pyrolysis appeared to have an advantage over the basic hydrolysis of the ester group to obtain the ketone cleavage since base can cleave the acetoacetic ester in two ways. In addition to attack of the base at the ester group (cleavage point *b*) to give the ketone, attack at the ketone group (cleavage point *a*) can take place to give the acid cleavage by a reverse Claisen condensation. Strong base tends to favor acid cleavage while weak base tends to favor ketone cleavage. Steric hindrance and electronegative groups in the α-position also tend to favor acid cleavage. It seemed possible, therefore, that pyrolysis of the acetoacetic ester would promote cleavage only at the ester portion to give a high yield of the ketone cleavage product.





Several acetoacetic esters have been pyrolyzed according to the literature but none by the same procedure or conditions that are reported in this paper. Kimel and Cope[8] pyrolyzed a series of substituted allyl acetoacetates and obtained the corresponding substituted allyl acetones. In this case the allyl group migrated to the α-carbon atom by means of a cyclic mechanism similar to that of the Claisen rearrangement and the resulting acetoacetic acid immediately lost carbon dioxide. Ethyl acetoacetate has been pyrolyzed in the liquid phase but the only product isolated under these conditions was dehydroacetic acid in an 86% yield.[9]

The ester chosen for the initial pyrolysis studies was ethyl *n*-butylacetoacetate (I), since this ester gives a high yield by conventional ketone cleavage and was selected as an example for *Organic Syntheses*.[10] The reported yield of the methyl *n*-amyl ketone (IV) from acetoacetic ester was 52 to 61% or, calculated from the alkylated ester I, was 74 to 86%. It was thought that, if the pyrolysis could produce the ketone IV in any comparable yield, it would represent a large improvement since the experimental procedure for the hydrolysis method is long and tedious and cannot be conveniently adapted to the preparation of large quantities. For example, by the *Organic Syntheses* method for the preparation of 300–350 g. of IV, a 12-l. flask and 5 l. of a 5% sodium hydroxide solution are initially used. The ketone IV is isolated and purified by four separate steam distillations followed by extraction with a saturated calcium chloride solution.

For these reasons, ethyl *n*-butylacetoacetate (I) was dropped through a standard pyrolysis tube[11] packed with Pyrex helices and externally heated at 525°. Care was taken to minimize charring by the introduction of a slow stream of oxygen-free nitrogen. Under these conditions the ester portion of the molecule decomposed by a cyclic six-membered ring mechanism to produce ethylene and the acetoacetic acid III which immediately decomposed under these same conditions by another cyclic six-

(7) W. J. Bailey and W. N. Turek, *J. Am. Oil Chemist's Soc.*, **33**, 317 (1956).

(8) W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, 65, 1992 (1943).

(9) F. Arndt and P. Nachtweg, *Ber.*, **57**, 1489 (1924).

(10) J. R. Johnson and F. D. Hager, *Org. Syntheses*, **Coll. Vol. I**, 2nd ed., 351 (1941).

(11) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, 21, 543 (1956).

membered ring mechanism to produce carbon dioxide and the desired ketone IV. The pyrolysate was fractionated without further treatment to produce a 59% conversion to the methyl *n*-amyl ketone (IV) and a 17% recovery of the starting acetoacetic ester I. The yield of the ketone IV, based on unrecovered I, was 71%.

The ketone cleavage by pyrolysis of I appears to have several advantages over the conventional basic hydrolysis: (1) the procedure has been shortened from several steps to only one step; (2) the isolation of the final product has been simplified since the two by-products, ethylene and carbon dioxide, escape as a gas; (3) no additional reagents are required; and (4) the quantities can be conveniently increased to prepare large amounts of the ketone. Thus, this saving of both time and material plus the fact that the yields by these two methods are almost comparable recommend the pyrolysis method.

Of course many substituted acetoacetic esters give much poorer yields on basic ketone cleavage than does the *n*-butyl derivative I.[10,12] This is particularly true if the substituent is branched. Apparently the added strain accelerates the acid cleavage at the expense of the ketone cleavage. For example, ethyl isopropylacetoacetate (V) produces only a 36% yield of the corresponding ketone VI by conventional hydrolysis. The lower yield in this case can partly be attributed to the higher water solubility of VI. It appeared, therefore, that the cleavage of V would make an excellent test of the usefulness of the pyrolysis method of ketone cleavage.

When the isopropylacetoacetic ester V was pyrolyzed at 525° under the same conditions indicated for I, a 71% conversion to methyl isobutyl ketone (VI) was realized. Since a 13% recovery of the starting ester V also was obtained, the yield of VI, based on unrecovered material, was 82%. In this particular case, in addition to the advantages listed above, the pyrolytic procedure produces more than double the yield obtained by the conventional hydrolysis procedure.

In order to show that the ketone cleavage by pyrolysis is a general reaction, several other acetoacetic esters were studied. Ethyl α-cyclohexylacetoacetate (VII) on pyrolysis at 525° gave a 72% conversion to cyclohexylacetone (VIII) plus a 9% recovery of VII. The yield of VIII, based on unrecovered VII, was, therefore, 79%. This yield compares very favorably with the 55% yield obtained by Adams, Abramovitch, and Hauser[13] for the basic hydrolysis of VII and with the 60% yield obtained by Darzens and Rost[14] from the reaction of methylmagnesium bromide on α-cyclohexylacetyl chloride.

At 540° ethyl α-allylacetoacetate (IX) gave a 54% conversion to allylacetone (X) and at 510° a 50% conversion. At the lower temperature a 20% recovery of the starting ester was obtained so that the yield of X, based on unrecovered IX, was 63%. At either temperature it was not possible to eliminate charring completely. Although the yield of allylacetone (X) from the pyrolysis of IX is better than the 31% reported by Kimel and Cope[8] for the pyrolysis of allyl acetoacetate or the 35% obtained by conventional hydrolysis of IX,[15] it is less than the 85% reported by Schechter, Green, and La Forge[16] for a 4-day hydrolysis of IX at 0°.

It was hoped that the pyrolysis of disubstituted acetoacetic esters, which very often give poor yields of the corresponding ketones on hydrolysis, would give clean-cut results. However, a substantial amount of charring and decomposition always occurred so that the yields of ketones were lowered to approximately the same range as those from hydrolysis. Thus, pyrolysis of ethyl α,α-diethylacetoacetate (XI) at 500° gave a 33% conversion to 3-ethyl-2-pentanone (XII). Since only a 35% recovery of starting material XI was obtained, the yield of XII, based on unrecovered material, was 50%. Renfrow and Renfrow[12] reported a 45% yield of the ketone XII by basic hydrolysis.

Similarly, pyrolysis of ethyl α,α-di-*n*-butylacetoacetate (XIII) at 490° gave a 33% conversion to 3-butyl-2-heptanone (XIV) and a 41% recovery of starting material. The yield of XIV, based on unrecovered material, was, therefore, 56%. A pyrolysis at 535° increased the conversion to 45% but did not increase the yield. The reported yield for basic hydrolysis was 64%.[12]

One may conclude that, because of the saving of time and material as well as the adaptability to large quantities of material, the ketone cleavage of acetoacetic esters by pyrolysis is preferable to the conventional basic hydrolysis in many cases. It is particularly useful if the desired ketone is fairly water soluble or the starting ester contains a branched substituent.

The extension of this pyrolytic method to the production of other acids and their derivatives will be reported separately.

EXPERIMENTAL[17]

Pyrolysis of ethyl α-n-butylacetoacetate (I). Ethyl α-*n*-butylacetoacetate (I), b.p. 108–110° (14 mm.), n_D^{25} 1.4263

(12) W. B. Renfrow and A. Renfrow, *J. Am. Chem. Soc.*, 68, 1901 (1946).

(13) J. T. Adams, B. Abramovitch, and C. R. Hauser, *J. Am. Chem. Soc.*, 65, 552 (1943).

(14) G. Darzens and H. Rost, *Compt. rend.*, 153, 772 (1890).

(15) H. Hibbert and J. A. Timm, *J. Am. Chem. Soc.*, 45, 2438 (1923).

(16) M. S. Schechter, N. Green, and F. B. La Forge, *J. Am. Chem. Soc.*, 71, 3165 (1949).

(17) The authors are indebted to Dr. Mary H. Aldridge and Miss Kathryn Gerdeman for the microanalyses. All melting points are corrected.

[reported b.p. 109–112° (15 mm.),[12] n_D^{20} 1.4283[18]], was prepared in an 80% yield by the method of Renfrow and Renfrow[12] by the use of potassium *tert*-butoxide as the condensing agent and *n*-butyl bromide as the alkylating agent. At the rate of 0.6 g. per minute, 202 g. (1.075 moles) of the acetoacetic ester I was added dropwise to a Vycor combustion tube packed with 1/8-in. Pyrex helices and externally heated at 525°, as described previously.[11] Charring was minimized by the introduction of a slow stream of oxygen-free nitrogen at the top of the column. The pyrolysate was condensed in a 6-in. spiral condenser and collected in a side-arm flask cooled in a Dry-Ice bath. (In preliminary runs to determine the proper temperature for the pyrolysis the noncondensable gases were conducted through an Ascarite tube, and the extent of pyrolysis was determined from the amount of absorbed carbon dioxide.) The pyrolysate, without any further treatment, was fractionally distilled through an 8-in., helix-packed column to yield 72.1 g. (59%) of methyl *n*-amyl ketone (IV), b.p. 79° (70 mm.), n_D^{25} 1.4065 [reported[19] b.p. 151° (760 mm.), n_D^{20} 1.4086], and 33.2 g. (17% recovery) of the starting ester I. The yield of IV, based on unrecovered I, was 71%.

The methyl *n*-amyl ketone (IV) was further characterized by conversion to its semicarbazone, m.p. 125° (reported[19] m.p. 125°).

Pyrolysis of ethyl α-isopropylacetoacetate (V). Ethyl α-isopropylacetoacetate (V), b.p. 99.5–102° (26 mm.), n_D^{25} 1.4216 [reported b.p. 96–98° (20 mm.),[20] n_D^{20} 1.4240[21]], was prepared in a 70% yield by the method of Hauser[20] by the alkylation of acetoacetic ester with isopropyl alcohol, except that the time of the addition of the boron trifluoride was increased to 6 hr. and larger quantities were used. By use of the same procedure and apparatus described above, 203 g. (1.18 moles) of V was added dropwise to the pyrolysis tube heated at 525° at the rate of 0.6 g. per minute. Fractional distillation of the pyrolysate through an 8-inch, helix-packed column produced 83.4 g. (71%) of methyl isobutyl ketone (VI), b.p. 114–115°, n_D^{25} 1.3949 (reported[22] b.p. 114–120°, $n_D^{23.5}$ 1.3952[23]), and 26.4 g. (13% recovery) of the starting ester V. The yield of VI, based on unrecovered V, was, therefore, 82%.

The methyl isobutyl ketone was further characterized by conversion to its semicarbazone, m.p. 134° (reported[23] m.p. 132–133°).

Pyrolysis of ethyl α-cyclohexylacetoacetate (VII). Ethyl α-cyclohexylacetoacetate (VII), b.p. 146–148° (21 mm.), n_D^{25} 1.4570 [reported[13] b.p. 146–148° (20 mm.)], was prepared in a 32% yield by the alkylation of acetoacetic ester with cyclohexanol.[13] At the rate of 0.5 g. per minute, 98.5 g. (0.465 mole) of VII was pyrolyzed at 525° in the same pyrolysis apparatus described above. Fractional distillation of the pyrolysate through an 8-in., helix-packed column produced 46.4 g. (72%) of cyclohexylacetone (VIII), b.p. 87–88° (19 mm.), n_D^{5} 1.4499 [reported[14] b.p. 83–85° (13 mm.)], and 8.8 g. (9% recovery) of starting ester VII (slightly contaminated with a high refracting impurity). The yield of VIII, based on unrecovered VII, was 79%.

The cyclohexylacetone also was converted to its semicarbazone, m.p. 166–167° (reported[13] m.p. 166°).

Pyrolysis of ethyl α-allylacetoacetate (IX). Commercial ethyl α-allylacetoacetate (IX) (Benzol Products Co.) was fractionated to yield reasonably pure IX, b.p. 89.5–90° (9 mm.), n_D^{25} 1.4370 [reported[16] b.p. 96–97° (14 mm.), n_D^{26} 1.4365]. At 540°, 52 g. (0.306 mole) of IX was pyrolyzed over a period of 90 min., as described above. Fractionation of the pyrolysate produced 16 g. (54%) of allylacetone (X), b.p. 76–77° (125–130 mm.), n_D^{25} 1.4195 (reported[8] b.p. 127–128°, n_D^{25} 1.4174). From a second pyrolysis at 510° of 70 g. (0.41 mole) of IX in 110 min. were obtained 19.7 g. (50%) of allylacetone (X), b.p. 72° (105–110 mm.), n_D^{25} 1.4195, and 14 g. (20% recovery) of starting material. In the latter pyrolysis the yield of X, based on unrecovered IX, was 63%.

The allylacetone was further characterized by conversion to its 2,4-dinitrophenylhydrazone, m.p. 107–108° (reported[8] m.p. 107–108°).

Pyrolysis of ethyl α,α-diethylacetoacetate (XI). By a modification of the procedure of Renfrow,[22] 144 g. (0.88 mole) of ethyl acetoacetate was alkylated with ethyl bromide. If the alkylation was carried out in two steps without purification of the intermediate ethyl α-ethylacetoacetate, mixtures of products were eliminated and 90 g. (55%) of ethyl α,α-diethylacetoacetate (XI), b.p. 90–92° (9 mm.), n_D^{25} 1.4311 [reported[22] b.p. 96–99° (13–14 mm.)], was obtained. After 77 g. (0.413 mole) of XI had been pyrolyzed at 500° over a period of 2.25 hr. under the same conditions described above, the pyrolysate was fractionally distilled through an 8-in., helix-packed column to yield 15.3 g. (33%) of 3-ethyl-2-pentanone (XII), b.p. 134–139°, n_D^{25} 1.4078 (reported[22] b.p. 135–139°), and 27 g. (35% recovery) of the starting ester XI. The yield of XII, based on unrecovered XI, was, therefore, 50%.

Pyrolysis of ethyl α,α-di-n-butylacetoacetate (XIII). Ethyl α,α-di-*n*-butylacetoacetate (XIII) was prepared by the method of Renfrow and Renfrow[12] with the exception that the reaction mixture was heated at 80° for 5 hr. after the addition of the butyl bromide to insure complete reaction with the fivefold increase in the quantities of reagents. Thus, alkylation of 186 g. (1 mole) of acetoacetate with *n*-butyl bromide in the presence of potassium *tert*-butoxide gave 162 g. (67%) of ethyl α,α-di-*n*-butylacetoacetate (XIII), b.p. 146–147° (20 mm.), n_D^{25} 1.4373 [reported[12] b.p. 146–149° (18 mm.)]. Pyrolysis of 70.1 g. (0.29 mole) of XIII over a period of 1.5 hr. at 490° through the apparatus described, followed by fractionation through an 8-in., helix-packed column, gave 16 g. (33%) of 3-butyl-2-heptanone (XIV), b.p. 85–88° (8 mm.), n_D^{25} 1.4270 [reported[22] b.p. 104–107° (12 mm.)], and 28.8 g. (41% recovery) of the starting ester XIII. The yield of XIV in this case, based on unrecovered XIII, was 56%.

A second pyrolysis of 69.5 g. (0.29 mole) of XIII over a period of 1.5 hr. at 535° produced 20.3 g. (45%) of XIV, b.p. 86–89° (10 mm.), n_D^{25} 1.4269.

The 3-butyl-2-heptanone (XIV) was further characterized by conversion to its semicarbazone, m.p. 108–109° (reported[22] m.p. 109°).

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(18) V. H. Wallingford, M. A. Thorpe, and A. H. Homeyer, *J. Am. Chem. Soc.*, **64**, 581 (1942).

(19) D. M. Cowan, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, **157**, 176 (1940).

(20) J. T. Adams, R. Levine and C. R. Hauser, *Org. Syntheses*, **27**, 35 (1943).

(21) E. R. Alexander and S. Baldwin, *J. Am. Chem. Soc.*, **73**, 356 (1951).

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(23) M. C. Chiang, *J. Chinese Chem. Soc.*, **18**, 65 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Azulene. VI. Synthesis and Properties of Some 1,3-Disubstituted Azulenes[1,2]

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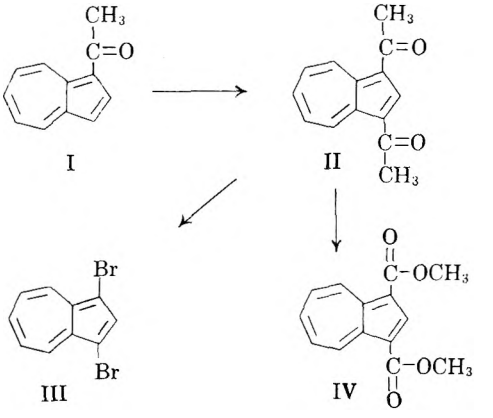
Received April 22, 1957

Improved procedures for the acetylation of azulene and for the conversion of 1-acetylazulene to a diacetylazulene have been found. Additional evidence has been obtained that the latter compound is the 1,3-derivative. An 81% yield of 1-nitroazulene has been realized by nitration with tetranitromethane. A number of new 1,3-disubstituted azulenes have been prepared and their visible absorption spectra examined with respect to the additive effect of the groups present.

In earlier papers in this series results establishing the electrophilic substitution of azulene in the 1-position and the orientation of a second substituent on to the 3-position by both *ortho*, *para*- and *meta*-directing groups were reported.[3,4]

One of the reactions investigated was Friedel-Crafts acetylation and from this were obtained 1-acetylazulene (I) and a diacetylazulene postulated to be II.[3] The 1-acetylazulene was best prepared (57%) using acetic anhydride and stannic chloride in methylene chloride. Further acetylation of I under these conditions or under those (acetic anhydride and aluminum chloride in carbon disulfide at room temperature) which gave the best (18%; 62% net) yield of diacetylazulene from azulene gave essentially none of the disubstituted product. We have now discovered that reaction of azulene with acetyl chloride and stannic chloride in carbon tetrachloride at reflux temperature gives an 83% yield of II from azulene and an 87% yield of II from I. The yields in these reactions were found to vary considerably (to as low as 5%) with changes in the relative amounts of reagents and solvent as well as in temperature and time.



Though the structure of I was firmly established,[3] there was no direct evidence for the structure of the diacetylazulene. Since all disubstituted azulenes formed by electrophilic substitution were found to be 1,3-derivatives, the structure represented by II was most probable. The displacement of the acetyl group by a positive chlorine had been noted in the formation of 1,3-dichloroazulene from 1-acetylazulene on reaction with alkaline hypochlorite.[5] Accordingly, a similar process was tried with hypobromite on the diacetylazulene and, as expected, the known 1,3-dibromoazulene (III)[3] was formed. Further evidence was provided by oxidation of II with sodium hypoiodite to the diacid which was characterized as the dimethyl ester (IV). The properties of this substance (red color and crystalline nature) corresponded to those reported[6] for diethyl azulene-1,3-dicarboxylate.

The mononitration of azulene was first accomplished in 63% yield with cupric nitrate and acetic anhydride.[3] Subsequently it was learned that Scheibli[7] had effected the reaction with tetranitromethane in comparable (59%) yield. Our further efforts to improve the former method did not succeed but conditions have now been found for the latter which give an 81% yield of 1-nitroazulene.

No dinitroazulene was produced with either of the above reagents, either from azulene directly or from 1-nitroazulene. Nitration of azulene with nitric acid and acetic anhydride, however, gave either a 43% (84% net) yield of 1-nitroazulene or a mixture of 1-nitroazulene (45%) and an orange crystalline dinitroazulene (13%) which was presumed to be the 1,3-derivative (V), depending on the conditions used. The latter product was also obtained in 35% (52% net) yield from 1-nitroazulene. The separation of the dinitroazulene from traces of 1-nitroazulene was very difficult and the dinitro compound when chromatographed on

(1) Taken in part from the Ph.D. thesis of Charles G. Fritz.

(2) Support for a part of this work by contract DA-04-200-ORD-235 with the Office of Ordnance Research, U. S. Army, and by the Agnes H. Anderson Research Fund is gratefully acknowledged.

(3) A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

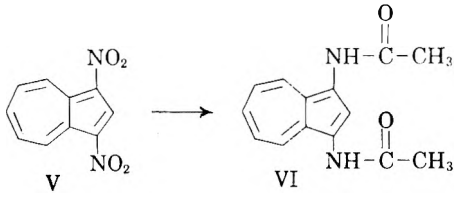
(4) A. G. Anderson, E. J. Cowles, J. J. Tazuma, and J. A. Nelson, *J. Am. Chem. Soc.*, **77**, 6321 (1955).

(5) Whether chlorination of the acetyl group occurred prior to displacement was not determined. Formation of a chloro ketone might be expected to aid the displacement reaction.

(6) T. Nozoe, S. Matsumura, and S. Seto, *Chemistry and Industry*, 1257 (1955).

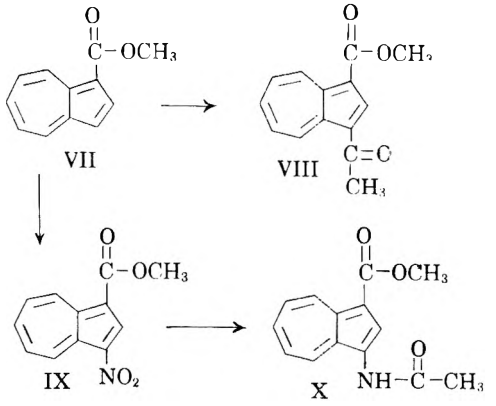
(7) K. G. Scheibli, Doctoral Thesis, Eidgenössischen Technischen Hochschule, Zurich, Switzerland, 1952, p. 30.

alumina changed completely into a yellowish green material which was strongly adsorbed and was not characterized. Purification was ultimately achieved through chromatography on specially prepared silica gel. Reductive acetylation of V gave the corresponding 1,3-diacetamidoazulene (VI).

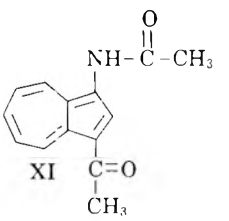


In connection with studies of the effect of substituents in the 1- and 3-positions on absorption in the visible region (see below), it was desired to prepare certain 3-substituted derivatives of methyl 1-azuloate (VII). Attempts to prepare VII directly by reaction of azulene with ethyl chlorocarbonate and stannic chloride or aluminum chloride were unsuccessful and it was prepared, therefore, as before[3] from 1-acetylazulene.

Attempts to couple VII with benzenediazonium chloride both under the conditions used for reaction with azulene[3] and by adding a large excess of the cold diazonium salt solution to a hot solution of the ester failed. The acetylation of VII, however, proceeded smoothly on addition of a slight excess of stannic chloride to a solution of the ester in acetic anhydride. The product, most probably VIII, was isolated as red crystals in 80% yield.



Treatment of VII with nitric acid in acetic anhydride in the cold gave the nitro ester (IX) in low yield and the yield was not improved by increasing the concentration of nitric acid. The recovery of most of the starting material made the net yield 38%. Nitration with cupric nitrate trihydrate in acetic anhydride as previously performed[3] gave somewhat better results (44% net yield) and when this method was repeated with a much longer reaction time the actual yield was 36% and no starting material was recovered. In a single experiment a 62% net yield of IX was obtained by nitration with tetranitromethane and pyridine in ethanol but this result could not be duplicated. Reductive acetylation[3] of IX gave X (69%). Acetylation of 1-acetamidoazulene[3] gave the 3-acetyl derivative (XI) in 78% yield and thus provided an additional compound in the series.



The additivity of the spectral shifts in the visible region caused by alkyl groups on the different positions of the azulene ring was first noted by Plattner[8] and has become known as Plattner's Rule. It has been very useful in the identification of many natural and synthetic alkylazulenes. In our work it was soon recognized that this rule could be applied, at least qualitatively, to 1- and 1,3-substituted azulenes having groups other than alkyl.

Cowles[9] has recently reported on a study of a number of these compounds and the present work affords several additional examples. Certain of the new compounds were not sufficiently soluble in the solvents previously used[9] and, therefore, all spectra were taken in alcohol. As this change in solvent caused an appreciable change in the shift caused by acetyl and nitro groups as compared to that observed in other solvents,[9] the diacetyl and dinitro compounds were also included. Although the more complex correlations using the squares of the frequencies or wave-length values determined by least squares[9] might give better agreement, it is seen (Table II) that when average shifts for either the wave lengths (mμ) or wave numbers (cm.$^{-1}$) are used the results are quite good.

TABLE I

AVERAGE SHIFTS (mμ AND CM.$^{-1}$) OF PRINCIPAL PEAK CAUSED BY GROUPS ON THE 1-(3-) POSITION[a]

Group	$\Delta\lambda_{max}$	$\Delta l/\lambda_{max}$
—C(=O)—CH3[b]	−43	+1490
—C(=O)—CCH3[b]	−36	+1180
—NO2[b]	−40	+1460
—NH—C(=O)—CH3	+41	−1330

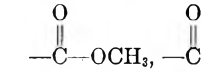
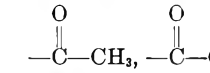
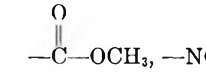
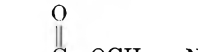
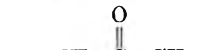
[a] Average shift values were determined by successive iterations until reasonable self-consistency was achieved. The value for 1-nitroazulene was so divergent that it was not used. [b] Groups causing a marked hypsochromic shift also remove most of the fine structure and the highest point of the band was assumed to coincide with the maximum of the principal peak.

(8) Pl. A. Plattner, *Helv. Chim. Acta*, **24**, 283E (1941); Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **30**, 1320 (1947).

(9) E. J. Cowles, *J. Am. Chem. Soc.*, **79**, 1093 (1957).

TABLE II

ABSORPTION MAXIMA (Mμ AND CM.$^{-1}$) OF 1,3-DISUBSTITUTED AZULENES[a]

Groups	λ_{max} (calcd.)	λ_{max} (obs.)	% dev.[b]	$1/\lambda_{max}$ (calcd.)	$1/\lambda_{max}$ (obs.)	% dev.[b]
	492	498	1.2	20280	20080	1.0
	506	511	1.0	19660	19570	0.9
	499	498	0.2	19970	20080	0.5
	502	503	0.2	19940	19880	0.3
	583	583	0.0	17150	17150	0.0
	576	575	0.2	17460	17390	0.4
	660	653	1.1	14640	15310	4.4
$-NO_2$, $-NO_2$	498	488	2.0	20220	20490	1.1

[a] The calculated values were obtained by addition of the appropriate values in Table I to the observed values (max, 578 mμ or 17,300 cm.$^{-1}$) for azulene. [b] % deviation = difference ÷ λ_{max} (obs.) or $1/\lambda_{max}$ (obs.) × 100 to nearest 0.1.

EXPERIMENTAL[10,11]

1,3-Diacetylazulene (II). *A. From azulene.* A solution of 7.2 mg. (0.056 mmole) of azulene, 0.1 ml. (0.06 mmole) of stannic chloride, and 5 ml. (0.07 mole) of acetyl chloride in 8 ml. of carbon tetrachloride was refluxed for 20 min. on a steam bath. It was then shaken thoroughly with 200 ml. of water, during which process the blue solution turned red, and the mixture was extracted with ether. The residue remaining after removal of the solvent from the combined extracts was chromatographed (hexane then dichloromethane) on acid-washed alumina and the red eluate fraction yielded 10 mg. (83.6%) of product, m.p. 185–188°, identical (infrared absorption spectrum) with an authentic sample.[3]

B. From 1-acetylazulene (I). To a solution of 16.5 mg. (0.097 mmole) of 1-acetylazulene in 10 ml. of carbon tetrachloride was added 0.2 ml. (0.12 mmole) of stannic chloride. An immediate orange coloration resulted. Acetyl chloride (5 ml., 0.07 mole) was then added slowly, and during this process a yellow precipitate formed. The mixture was refluxed (steam bath) for 12 min. and then worked up as described above (A) to give 17.9 mg. (86.9%) of diacetylazulene, m.p. 186–188°.

Conversion of 1,3-diacetylazulene to 1,3-dibromoazulene (III). A solution of sodium hypobromite prepared by adding 0.5 g. of bromine to 10 ml. of 10% sodium hydroxide at 0° was added to 16.6 mg. (0.078 mmole) of the diacetylazulene dissolved in 11 ml. of dioxane. After 1 hr. the blue-green solution was diluted with 200 ml. of water. Extraction with ether, removal of the solvent from the combined extracts, and chromatography (petroleum ether then 1:10 dichloromethane–petroleum ether) of the residue on alumina gave 4.8 mg. (20.8%) of blue needles, m.p. 89–91°, identical (ultraviolet, visible and infrared absorption spectra) with an authentic sample[3] of 1,3-dibromoazulene.

(10) Melting points were taken on a calibrated Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were taken in ethanol on a Cary Model 11S recording spectrophotometer unless otherwise indicated.

(11) Microanalyses were performed by B. Nist and C. H. Ludwig.

Dimethyl azulene-1,3-dicarboxylate (IV). To a cooled (0°) solution of 215 mg. (1.0 mmole) of 1,3-diacetylazulene in 50 ml. of dioxane was added 40 ml. of 12% potassium hydroxide also at 0°. To this mixture was added dropwise with stirring 25 ml. of a solution of iodine (10%) and potassium iodide (20%) in water over a period of 1 hr. Stirring was continued for 30 min., the iodoform removed by filtration and the filtrate extracted with ether. The aqueous solution was then acidified and extracted with ether (only a portion of the water-insoluble material dissolved in the ether) and the ether extracts treated with an excess of diazomethane. Slow evaporation of the ether solution left a solid residue which was chromatographed (methylene chloride) on alumina. The main fraction of red crystals, m.p. 171°, amounted to 49.1 mg. (13.1%) and showed absorption maxima (mμ, D_{max}) at 234, 0.65; 271, 0.57; 284, 0.53; 290, 0.66; 295, 0.69; 301, 0.86; 357, 0.19; 367, 0.20, and 511.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.65; H, 4.96.

1-Nitroazulene. Method A. To a solution of 64 mg. (0.5 mmole) of azulene in 2 ml. of pyridine was added 1.2 ml. of a 0.5*M* ethanolic solution (0.6 mmole) of tetranitromethane. The color of the solution changed to red after 18 min. and the mixture was treated in a separatory funnel with 100 ml. of 10% hydrochloric acid and the whole extracted with dichloromethane. Evaporation of the organic extracts left a semicrystalline residue which was chromatographed (dichloromethane) on alumina to give 70.5 mg. (81%) of product identical (m.p. and absorption spectra) with an authentic sample.[3]

Method B. To a cooled (ice bath) solution of 128 mg. (1.0 mmole) of azulene in 9.9 ml. of acetic anhydride was added dropwise and slowly 0.082 ml. (1.3 mmole) of concentrated nitric acid. After 10 min. of continued cooling and occasional shaking, the mixture was diluted with 10 ml. of water and extracted with 20 ml. of chloroform. The red-brown chloroform extract was washed with small (5–10 ml.) portions of 1*N* ammonium hydroxide until the wash solution remained strongly alkaline, then with water and, finally, with saturated salt solution. Evaporation (air stream) of the solvent and chromatography (chloroform) on alumina gave 63 mg. (49%) of recovered azulene from the first violet blue band and 74 mg. (43%, 84% net) of crystalline 1-

nitroazulene having the same infrared spectrum (Nujol mull) as the product from Method A and an authentic sample.[3]

1,3-Dinitroazulene (V). A solution of 43 mg. (0.247 mmole) of 1-nitroazulene in 5 ml. of acetic anhydride was cooled to 0° and treated with a cold solution of 3 drops (1.2 mmole) of nitric acid in 3 ml. of acetic anhydride. After 1 min. the mixture was warmed to room temperature and then, after 5 min., it was poured into cold water. The solution was extracted with dichloromethane and then with chloroform and the combined extracts dried over sodium sulfate. The residue remaining after removal (air stream) of the solvent was chromatographed on silica gel which had been previously treated with *tert*-butyl alcohol, air-dried overnight and then poured into a column filled with hexane. The sample was applied with a minimal volume of benzene and the chromatograph developed with a 1:1 mixture of 80–120° petroleum ether and carbon tetrachloride until the eluate was colorless. From this eluate was recovered 15 mg. (33%) of 1-nitroazulene. The dinitroazulene remained on the column as a sharp band which was eluted with dichloromethane. The yield of orange needles which melted with slow decomposition at *ca.* 245° was 19 mg. (35%). The material showed absorption maxima (mμ) in ethanol at 237 (log ε 4.17); 297 (4.40); 306 (4.47); 376 (4.18) and 390 (4.14) and in dichloromethane at 452 (ε 1235); 472 (1480); 480 (1490); 487 (1460); 500 (1400); 528 (785) (shoulder); 538 (616) (shoulder); and 670 (12). The principal peak in the visible region was at 488 mμ with ethanol as the solvent.

Anal. Calcd. for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77. Found: C, 54.95; H, 2.94.

1,3-Diacetamidoazulene (VI). To a solution of 20.7 mg. (0.0095) mmole) of 1,3-dinitroazulene and 1.5 g. of sodium acetate in 15 ml. of acetic anhydride and 2 ml. of glacial acetic acid heated to 100° was added 0.5 g. of powdered zinc. Heating was continued for 5 min. and the mixture then poured into 300 ml. of water. Extraction with chloroform (all of the blue color was not extracted from the aqueous layer) and removal (air stream) of the solvent from the extracts left a residue which was chromatographed on alumina. A greenish brown and a small blue fraction (1-N-acetylaminoazulene) were removed with chloroform. Elution with ethyl acetate then gave a yellow-green fraction and, finally, acetone was used to obtain a red and a larger blue-green fraction. The latter afforded 8 mg. (34.8%) of product as green needles, m.p. 251–253°. The substance showed absorption maxima (mμ, D_{max}) at 245, 0.79; 298, 1.46; 379, 0.25 and a single broad peak at 653 mμ.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.36; H, 5.83. Found: C, 69.20; H, 5.78.

Methyl 3-acetylazuloate (VIII). Stannic chloride (0.05 ml., 0.03 mmole) was added to a solution of 5.0 mg. (0.027 mmole) of methyl 1-azuloate in 1 ml. of acetic anhydride. After 20 min. the mixture was hydrolyzed with 150 ml. of water and the solution extracted with ether. The residue obtained by evaporation of the extract solution was chromatographed (alumina) with benzene as the eluent. Red, yellow, and blue zones developed. The red zone afforded 4.9 mg. (79.7%) of red crystals, m.p. 118–119°. Ultraviolet absorption maxima (mμ, D_{max}) were observed at 238, 1.6; 281, 2.1; 306, 1.75; 368, 0.51, and 378, 0.52. The visible spectrum had a single maximum at 498 mμ.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.74; H, 5.55.

Methyl 3-nitroazuloate (IX). A solution of 6.5 mg. (0.035 mmole) of methyl 1-azuloate in 1 ml. of acetic acid was treated with a suspension of 34 mg. (0.14 mmole) of cupric nitrate trihydrate in 1 ml. of acetic anhydride for 2 min. The reaction was quenched by hydrolysis with 200 ml. of water and the aqueous solution extracted with ether. Evaporation of the solvent and chromatography of the residue on Florisil with petroleum ether (70–120°), to remove unreacted ester, and then dichloromethane gave 2.9 mg. (35.8%) of product as red needles, m.p. 146°. The substance showed absorption maxima in the ultraviolet (mμ, D_{max}) at 220, 1.25; 286, 1.08; 374, 0.32; 390, 0.23, and a single peak in the visible at 503 mμ.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.29; H, 3.94. Found: C, 62.06; H, 3.91.

Methyl 3-acetamidoazuloate (X). A solution of 8.0 mg. (0.028 mmole) of the above nitro ester (IX) and 1 g. of sodium acetate in 2 ml. of acetic anhydride and 0.1 ml. of glacial acetic acid was treated with 0.5 g. of zinc dust for 10 min. The mixture was then diluted with 200 ml. of water and extracted four times with ether. The residue obtained by evaporation of the ether was chromatographed on alumina. Benzene eluted a yellow fraction and a green band was removed with benzene–dichloromethane. Chloroform eluted first a brown and then a violet fraction. The latter yielded 5.81 mg. (69%) of product as blue needles, m.p. 206°. Absorption maxima (mμ, D_{max}) in the ultraviolet were observed at 243, 0.97; 300, 1.45; 311, 1.29 and 380, 0.32. The visible spectrum had a single maximum at 583 mμ.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.11; H, 5.76. Found: C, 69.27; H, 5.51.

1-Acetamido-3-acetylazulene (XI). A solution of 0.08 ml. (0.4 mmole) of stannic chloride and 0.1 ml. (0.3 mmole) of acetyl chloride in 1 ml. of dichloromethane was added to a solution of 37.9 mg. (0.2 mmole) of 1-acetamidoazulene in 5 ml. of dichloromethane. The resulting suspension was shaken for 20 min., then hydrolyzed with 200 ml. of water and the hydrolyzate extracted with ether. Evaporation of the solvent from the combined extracts left a residue which was chromatographed on alumina. Elution with dichloromethane removed a small amount of starting material and the product was then removed with chloroform. The yield of green needles, m.p. 202° (dec.) was 36.4 mg. (78%). The substance exhibited absorption maxima in the ultraviolet (mμ, D_{max}) at 247, 0.75; 285, 0.85; 309, 0.90 and 398, 0.26. The visible spectrum had a single maximum at 575 mμ.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 73.96; H, 5.78. Found: C, 73.74; H, 6.03.

SEATTLE, WASH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Studies Related to Pyracene. An Improved Synthesis[1,2]

ARTHUR G. ANDERSON, JR., AND ROBERT G. ANDERSON

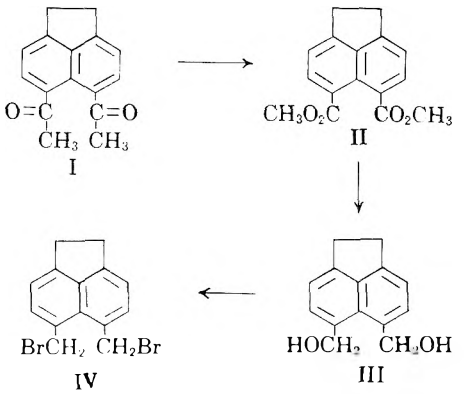
Received April 10, 1957

Formation of a second carbocyclic five-membered *peri*-ring on naphthalene has been attempted by several reactions not involving direct substitution on the naphthalene nucleus. The results are consistent with the concept that there is a definite increase in the distance between the 5- and 6-carbon atoms in acenaphthene as compared to the 1- and 8-carbons in naphthalene. An improved synthesis of pyracene has been achieved which is considerably shorter than the previous one.

In the previous paper[3] describing the first synthesis of pyracene (IX) it was noted that acenaphthenone could be prepared by the usual Friedel-Crafts ring closure but the corresponding cyclization of 5-acenaphtheneacetic acid (or derivatives) could not be realized. From considerations of the reported bond lengths and bond angles of the *peri*-ring in acenaphthene[4] it was thought that the strain in the molecule could cause an increase in the distance between the 5- and 6-positions and thus account for the observed results.

Further consideration of the problem led to the theorization that a particular distance between the 5- and 6-positions which would not permit direct electrophilic substitution would still allow ring closure by a reaction involving only the aliphatic carbons. The success of such a scheme would provide a most convenient route to pyracene not involving a dehydrogenation step. Bergmann and Szmuszkovicz[5] had found that acenaphthene could be prepared in high yield from 1,8-bis(bromomethyl)naphthalene and this method seemed well suited to the authors' purpose.

A necessary intermediate, 5,6-diacetylacenaphthene (I), had been prepared by Dziewouski and Spirer[6] by a Friedel-Crafts reaction of acenaphthene and acetic anhydride but no yields were reported. In this laboratory their procedure gave a small amount of diketone and a large amount of carbonaceous material. An alternate procedure[7] specifying acetyl chloride was modified (a large excess of the acyl halide was used) and a 59% yield of product was obtained. Oxidation of the diketone with potassium hypochlorite gave 5,6-acenaphthenedicarboxylic acid in good yield. This acid was difficult to purify and was also insoluble in the solvents usually employed for lithium aluminum hydride reductions. Accordingly, the impure acid was treated with diazomethane and the resulting diester (II) reduced to 5,6-bis(hydroxymethyl)acenaphthene (III). The desired dibromo derivative (IV) was readily obtained by treatment of the diol with phosphorus tribromide in the presence of pyridine.



Two methods for the cyclization of the dibromide were investigated. Treatment with phenyllithium according to the procedure of Bergmann and Szmuszkovicz[5] gave only yellow polymeric material. Similar results were obtained when an ethanolic solution of the dibromide was added to a suspension of zinc dust in the same solvent. These observations may be an indication that the activation energy for the cyclization of 5,6-bis(bromomethyl)acenaphthene is higher than that of 1,8-bis(bromomethyl)naphthalene due to the increased distance between the atoms concerned. No definite conclusion on this point is possible since it is not known whether the process is kinetically or thermodynamically controlled and, also, the reactions leading to polymerization may not be the same for both cases.

A final attempt to achieve the pyracene structure through this series was made on the diester (II). Subjecting this compound to conditions for the acyloin condensation as described by Le Clercq[8] resulted in a 92% recovery of starting

(1) From the Ph.D. thesis of Robert G. Anderson.

(2) Support for a part of this work by contract DA-04-200-ORD-235 with the Office of the Ordnance Research, U. S. Army, is gratefully acknowledged.

(3) A. G. Anderson, Jr. and R. H. Wade, *J. Am. Chem. Soc.*, **74**, 2274 (1952).

(4) The values for the aliphatic carbon-carbon bond distance and aliphatic bond angle have subsequently been reduced from 1.8 Å. to 1.64 ± 0.04 Å. and from 114° to 101°, respectively [A. I. Kitaigordoskii, *J. Phys. Chem. (U.S.S.R.)*, **23**, 1036 (1949)]. The departure from normal values is still such as to indicate the presence of considerable strain.

(5) E. D. Bergmann and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **75**, 2760 (1953).

(6) K. Dziewouski and J. Spirer, *Bull. Intern. Acad. polon. sci.*, **1931A**, 231.

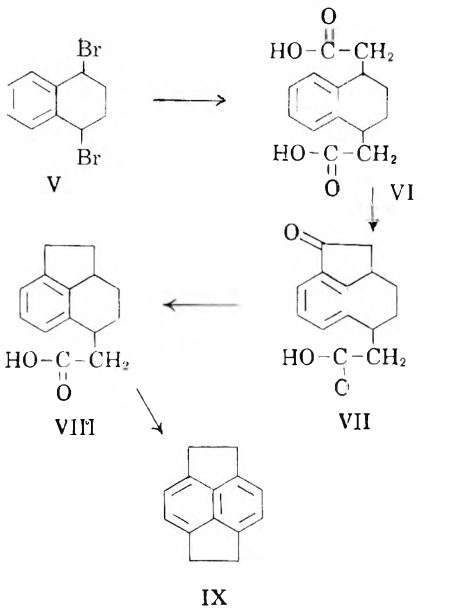
(7) K. Fleischer and P. Wolff, *Ber.*, **53**, 925 (1920).

(8) G. M. Le Clercq, Ph.D. thesis, University of Washington, 1956.

material and a small amount of a high-melting substance which could not be identified.

As the original synthesis of pyracene[3] was quite long and included some steps which were not adaptable to relatively large amounts, a new route was desirable. Of necessity the formation of the fourth ring had to involve a structure with only a benzene ring unsaturated and, since success had been had with 2a,3,4,5-tetrahydro-5-acenaphtheneacetic acid (VIII), an improved means of preparing this intermediate was sought and achieved.

Bromination of tetralin with *N*-bromosuccinimide gave 1,4-dibromotetralin (V) in 54% yield. In agreement with Orazi and Salellas,[9] who prepared it by a similar procedure, we found that this compound eliminated hydrogen bromide and formed naphthalene when warmed either in the solid state or in a polar solvent. This prevented the use of the usual polar solvents in the next reaction and, therefore, a mixture of diethyl sodiomalonate and xylene was added to a solution of pure 1,4-dibromotetralin in zylene. Hydrolysis and decarboxylation of the tetraester product gave a 71% yield of 1,2,3,4-tetrahydro-1,4-naphthalenediacetic acid (VI). If the mode of addition was reversed (dibromide added to diethyl sodiomalonate) in the displacement reaction, very impure diacid (VI) was obtained and the yield was considerably lower (47%). The diacid melted over a range of several degrees even when analytically pure and this was attributed to the presence of more than one stereoisomer. The same property was noted for the subsequent compounds made from the diacid.



Cylization of VI to 1-keto-2a,3,4,5-tetrahydro-5-acenaphtheneacetic acid (VII) was readily accomplished (71%) with polyphosphoric acid or *via* the acid chloride by a Friedel-Crafts reaction (61%) with aluminum chloride. The infrared spectrum of the keto acid surprisingly showed only one carbonyl band. Presumably both carbonyl groups in this compound absorb at the same wave length (5.85μ). All attempts to effect the cyclization of the keto acid with concentrated sulfuric acid or polyphosphoric acid at 150° or to prepare the ethylene ketal were unsuccessful.

Reduction of VII by a modified Wolff-Kishner reaction afforded 90% of the desired acid (VIII). For the conversion of VIII to pyracene, ring closure of the acid was effected (80%) with polyphosphoric acid, rather than as originally[3] with aluminum chloride on the acid chloride, and, after Wolff-Kishner reduction of the keto group in the product, the tetrahydropyracene was dehydrogenated (81%) with a rhodium-on-alumina catalyst and benzene in place of the earlier method[3] with palladium-on-charcoal. Both of these changes resulted in cleaner products and higher yields than were obtained previously.

The total number of isolation steps in the synthesis of pyracene has been reduced from the 15 in the original procedure to seven and the over-all yield raised from 12% (from cinnamic acid)[3] to 15% (from tetralin).

EXPERIMENTAL[10,11,12]

5,6-Diacetylacenaphthene (I). The procedure of Fleischer and Wolff[7] was modified such that 308 g. (2.34 moles) of aluminum chloride was added in 10-g. portions with stirring over a period of 2 hr. to a warm (42°) solution of 154 g. (1 mole) of acenaphthene and 234 g. (3 moles) of acetyl chloride in 850 ml. of carbon disulfide. After approximately 6 hr. (at 42°) the evolution of hydrogen chloride had ceased and the complex in the cooled (0°) mixture was decomposed with ice and 10% hydrochloric acid. The collected black precipitate was continuously extracted with ethanol (24 hr.) and the extract treated several times with decolorizing carbon, dried over magnesium sulfate, and concentrated to dryness under reduced pressure. The yield of crude (m.p. 147–149°) product was 140 g. (59%). A portion recrystallized twice from ethanol melted sharply at 149°.[7] The infrared spectrum (Nujol mull) showed a strong band at 5.98 μ. The dioxime, recrystallized from toluene, melted at 196–197°.[7]

5,6-Acenaphthenedicarboxylic acid. To a warm (55°) aqueous solution of potassium hypochlorite, prepared from 24.15 g. (0.17 mole) of calcium hypochlorite,[13] was added dropwise with stirring a solution of 11.5 g. (0.05 mole) of 5,6-diacetylacenaphthene in 50 ml. of dioxane. After the exothermic reaction began the temperature was maintained at 60–70° by cooling. When the addition was complete (45 min.), a solution of potassium hypochlorite, prepared from

(9) O. O. Orazi and J. F. Salellas, *Anales asoc. quim. argentina*, 38, 12 (1950).

(10) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(11) Qualitative ultraviolet absorption spectra were taken in ethanol on a Cary Model 11S recording spectrophotometer. Quantitative ultraviolet spectra were determined with a Beckmann Model DU spectrophotometer. Infrared spectra were measured by a Perkin Elmer Model 21 recording spectrophotometer with sodium chloride cells.

(12) Microanalyses were performed by B. Nist and C. H. Ludwig.

(13) M. S. Newman and H. L. Holmes, *Org. Syntheses*, Coll. Vol. II, 428 (1943).

12.07 g. (0.09 mole) of calcium hypochlorite, was added and the mixture warmed (60–70°) for 6 hr. After the mixture was cooled and a small amount of gray solid separated, a solution of 10 g. of sodium bisulfite in 40 ml. of water was added and the resulting solution acidified with concentrated hydrochloric acid. The glutinous acid formed was separated, washed with water, and dried (vacuum oven at 80°) to yield 9.7 g. (81%) of product sufficiently pure for conversion to the diester. Treatment (several times) of an aqueous basic solution of the crude acid with Norite gave, on acidification and drying, tan crystalline material, m.p. 290–296°, which had a neutral equivalent of 122 (calcd. 121). The reported melting point is 293–294°.[14]

Dimethyl 5,6-acenaphthenedicarboxylate (II). A dichloromethane solution (200 ml.) of diazomethane from the reaction of 10 g. (0.013 mole) of *N*-nitroso-*N*-methylurea, 110 g. of potassium hydroxide, and 100 ml. of water, was dried over potassium hydroxide pellets and then added in portions to a cold (0°) suspension of 3.1 g. (0.0128 mole) of 5,6-acenaphthenedicarboxylic acid in 60 ml. of dichloromethane. The mixture was allowed to stand for 8 hr. in an ice bath and then 12 hr. at room temperature. The solvent was then removed (air stream) and a solution of the tan residue in benzene washed with 5% sodium bicarbonate and then water. Removal of the solvent from the dried (magnesium sulfate) solution gave 2.1 g. (59%) of crude diester, m.p. 138–141°. A portion sublimed *in vacuo* and recrystallized twice from methanol melted at 140–141°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.88; H, 5.23.

5,6-Bis(hydroxymethyl)acenaphthene (III). To a cold (0°) mixture of 0.13 g. (0.0022 mole) of lithium aluminum hydride and 15 ml. of dry tetrahydrofuran was added dropwise with stirring a solution of 0.6 g. (0.0022 mole) of dimethyl 5,6-acenaphthenedicarboxylate in 15 ml. of dry tetrahydrofuran. The reaction mixture was allowed to warm to room temperature, heated under reflux for 1 hr., and cooled to 0°. After destroying excess hydride by adding 25 ml. of ethyl acetate and removing the solvent (reduced pressure), the gray solid complex was decomposed with 75 ml. of a 20% Rochelle salt solution and the resulting suspension washed with several portions of ether. Removal of the solvent from the dried (magnesium sulfate) ether solution yielded 0.34 g. (72%) of the diol, m.p. 130–135°. A portion recrystallized from ethyl acetate and sublimed *in vacuo* melted at 141–142°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.49; H, 6.27.

5,6-Bis(bromomethyl)acenaphthene (IV). A mixture of 0.5 g. (0.0023 mole) of the above diol (III), a few drops of pyridine, and 75 ml. of benzene was heated under reflux until most of the diol had dissolved. Phosphorus tribromide (2.48 g., 0.0092 mole) was then added dropwise with stirring to the cooled (0°) solution. After maintaining the resulting white suspension at 55° for 2 hr., then cooling it to 0°, 30 ml. of water was added and the separated organic layer washed with 5% sodium bicarbonate and water. The solvent was removed under reduced pressure from the dried (magnesium sulfate) solution and the residue of product, m.p. 154–160°, found to be 0.63 g. (80%). A portion recrystallized twice from hexane melted at 160–162°.

Anal. Calcd. for $C_{14}H_{12}Br_2$: C, 49.44; H, 3.56; Br, 47.00. Found: C, 49.44; H, 4.00; Br, 46.82.

1,4-Dibromotetralin (V). The procedure used was a modification of those described by Orazi[9] and by Barnes.[15] A mixture of 132 g. (1.0 mole) of tetralin, 356 g. (2.0 moles) of *N*-bromosuccinimide, 2 liters of anhydrous carbon tetrachloride, and a few grains of benzoyl peroxide was brought to reflux in a 5-l. flask equipped with two Allihn condensers. After the vigorous reaction which ensued, and which was moderated by cooling with tap water, had subsided, the straw-colored mixture was refluxed for an additional 30 min., the succinimide then separated from the cooled contents of the flask, and the red filtrate concentrated to dryness (reduced pressure) under an inert atmosphere. The yield of crude dibromide, m.p. 89–93°, was 174 g. (60%). Two recrystallizations from sodium-dried hexane yielded 157 g. (54%) of pure product, m.p. 94–95°.[9] The dibromide slowly decomposed with the evolution of hydrogen bromide on standing at room temperature. This process was slowed by storage in the dark at 0° under a nitrogen atmosphere. The dibromide could be converted to naphthalene by refluxing in 95% ethanol for 30 min.

Anal. Calcd. for $C_{10}H_{10}Br_2$: C, 41.39; H, 3.47. Found: C, 41.54; H, 3.61.

1,2,3,4-Tetrahydro-1,4-naphthalenediacetic acid (VI). Under anhydrous conditions 480 g. (3.0 moles) of redistilled diethylmalonate was added slowly to a stirred mixture of 23 g. (1 mole) of molten sodium and 1300 ml. of dry xylene. The solution which was formed was added dropwise with stirring over a period of 1 hr. to a refluxing solution of 104 g. (0.36 mole) of 1,4-dibromotetralin in 650 ml. of dry xylene. The reaction mixture was heated under reflux for an additional hour and then washed with water until the washings were colorless. The organic portion was dried (magnesium sulfate) and the xylene and excess diethyl malonate then removed by distillation under reduced pressure. No attempt was made to purify the red oil (130 g.) which remained and which was presumed to be mostly tetraethyl 1,2,3,4-tetrahydro-1,4-naphthalenedimalonate.

The crude tetraester was refluxed with 303 g. (5.4 moles) of potassium hydroxide, 303 ml. of water, and 330 ml. of ethanol for 5 hr., and then most of the ethanol was removed by distillation. After the addition of 300 ml. of water and extraction with three 200-ml. portions of ether, the aqueous solution was acidified and the small amount of brown viscous material which formed separated by filtration. The aqueous solution was then extracted with an equal volume of ether for 24 hr. in a liquid-liquid extractor, the ether extract dried (magnesium sulfate), and the solvent removed. All attempts to purify the tan oil (93 g.), assumed to be crude 1,2,3,4-tetrahydro-1,4-naphthalenedimalonic acid, which remained were unsuccessful.

Heating the acidic oil at 140° for 30 min. and then at 180° until the evolution of carbon dioxide had ceased (20 min.) gave a brown oil which was taken up in 400 ml. of the 10% aqueous potassium hydroxide. The solution was washed with several portions of ether, treated with Norite, and then acidified by the dropwise addition of 100 ml. of concentrated hydrochloric acid without stirring. After being swirled gently, the milky solution was allowed to stand overnight. The tan crystalline diacid which formed amounted to 63 g. (71%) after being dried at 50° in a vacuum oven and melted at 156–163°. This material was used in the next step. Recrystallization of a portion three times from toluene and then sublimation at 180° (0.5 mm.) gave material which melted at 166–69°, and thus apparently was predominantly one isomer, and had a neutral equivalent of 240 (calcd. 248).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.73; H, 6.58.

1-Keto-2a,3,4,5-tetrahydro-5-acenaphtheneacetic acid (VII). *Method A.* A mixture of 50 g. (0.2 mole) of finely powdered tetrahydro-1,4-naphthalenediacetic acid as isolated above and 500 g. of polyphosphoric acid[16] was warmed at 70–80° for 40 min.[17] with stirring under anhydrous conditions. The deep red solution was poured into 2 l. of cold water and, after 10–12 hr., the brown precipitate which formed was

(14) M. Freund and K. Fleischer, *Ann.*, **399**, 182 (1913).

(15) R. A. Barnes, *J. Am. Chem. Soc.*, **70**, 145 (1948).

(16) Kindly provided by the Victor Chemical Works, Chicago, Ill.

(17) If the temperature was above 80°, or at 70–80° for longer than the optimum 40 min., predominantly tars were formed. If the temperature was maintained at 60° or below, mostly starting material was isolated.

separated and dissolved in ether. The ethereal solution was extracted with 10% aqueous potassium hydroxide until a portion of the extracts gave no precipitate when acidified.[18] Treatment of the basic extract with Norite and then acidification with 10% hydrochloric acid gave a tan oil which solidified on standing. The isolated solid material was dried in a vacuum oven at 50° and then weighed 33 g. (72%) and melted at 132–155°.

Method B. A mixture of 9 g. (0.036 mole) of the tetrahydro-1,4-naphthalenediacetic acid and 52 ml. of thionyl chloride was warmed carefully until the evolution of sulfur dioxide had ceased (15 min.). After removal of the excess thionyl chloride *in vacuo*, a solution of the residual acid chloride in 100 ml. of redistilled nitrobenzene was added with stirring over a period of 2 hr. to a cold (0°) solution of 19 g. (0.145 mole) of anhydrous aluminum chloride in 300 ml. of nitrobenzene. After standing for 10–12 hr. in a refrigerator, the dark red complex was hydrolyzed with ice and 10% hydrochloric acid. The organic layer was washed with several portions of 15% hydrochloric acid and then with 5% potassium hydroxide until a portion of the aqueous extract gave no precipitate when acidified. The basic solution was worked up as described in Method A to yield 5.1 g. (61%) of the crude keto acid, m.p. 132–156°. Treatment of the solution of a portion in 10% aqueous alkali several times with Norite followed by isolation as before and recrystallization from ethanol yielded colorless crystals, m.p. 140–156°. The wide range of melting point was attributed to the presence of more than one stereoisomer.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.50. Found: C, 72.75; H, 6.58.

2a,3,4,5-Tetrahydro-5-acenaphtheneacetic acid (VIII). A modified Wolff-Kishner reduction of 7.1 g. (0.03 mole) of the keto acid with 35 ml. of 99% hydrazine hydrate, 28 ml. of ethanol, 35 ml. of diethylene glycol, and 3.3 g. of potassium hydroxide was carried out according to the procedure previously described[3] except that the crude product was not chromatographed. The oil obtained solidified on standing to yield 6 g. (90%) of material which melted at 89–96°. Recrystallization of a portion twice from petroleum ether afforded a product which melted at 99–101°[3] and apparently was predominantly the less soluble isomer. The ultraviolet and infrared absorption spectra of the recrystallized material were identical to those of a known sample.

2a,3,4,4a-Tetrahydro-1-pyracenone. Cyclization of 5.5 g. (0.025 mole) of the above tetrahydroacenaphtheneacetic acid by treatment with 50 g. of polyphosphoric acid[16] was effected as described above for the preparation of 1-keto-2a,3,4,5-tetrahydro-5-acenaphtheneacetic acid (VII). The reddish brown solution obtained was poured into cold water and the mixture stirred for 2 hr. at room temperature. The separated precipitate was dissolved in ether and the ether solution washed with 5% sodium bicarbonate, water, and saturated sodium chloride solution and then dried over magnesium sulfate. Removal of the solvent under reduced pressure left 3.9 g. (80%) of crude product. After one recrystallization from 70–90° ligroin followed by sublimation *in vacuo*, 3.0 g. (61%) of the ketone was obtained as colorless needles, m.p. 96–100°,[3] having ultraviolet and infrared absorption spectra identical to those of a known sample. A small amount of starting material was recovered from the bicarbonate washes.

Pyracene (IX). The above tetrahydro-1-pyracenone was converted to 2a,3,4,4a-tetrahydropyracene as previously described.[3] A mixture of 0.24 g. (0.0013 mole) of the tetrahydropyracene, 15 ml. of anhydrous benzene, and 0.1 g. of 5% rhodium-on-alumina catalyst[19] was heated in a sealed tube at 290 ± 10° for 18 hr. in a rocker-type autoclave packed with glass wool and charged with 90 ml. of benzene. Separation of the catalyst and concentration of the filtrate yielded 0.19 g. (81%) of pyracene, m.p. 210–215°. A portion recrystallized from benzene melted at 215–216°[3] and gave no depression of melting point when mixed with a known sample.

SEATTLE 5, WASH.

(18) A small amount of yellow, base insoluble material from the ether solution was isolated. It gave a positive reaction with 2,4-dinitrophenylhydrazine but could not be identified as the diketone resulting from cyclization of both carboxyl side chains.

(19) Baker and Company, Inc., Newark 5, N. J.

[CONTRIBUTION FROM THE RAILWAY RESEARCH LABORATORY OF THE METAL & THERMIT CORP.]

Preparation of Some Vinylsilanes with Vinylmagnesium Chloride[1]

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Received May 31, 1957

Tetravinylsilane, trivinylmethylsilane, trivinylphenylsilane, trivinylsilane, dibutyldivinylsilane, dimethyldivinylsilane, diphenyldivinylsilane, trimethylvinylsilane, and triphenylvinylsilane have been prepared by the reaction of vinylmagnesium chloride with appropriate silicon chlorides.

The development of the new intermediate, vinylmagnesium chloride, in this laboratory[2] has made possible the direct synthesis of organosilanes containing more than one vinyl group. In order to ascertain the utility of vinylmagnesium chloride, a group of nine organosilanes was prepared.

The development of the synthesis of tetravinylsilane involved the preparation of this compound in several solvent systems. The basic reaction of vinylmagnesium chloride in tetrahydrofuran with silicon tetrachloride in a solvent was used in all preparations. The solvents used were tetrahydrofuran, heptane, and benzene. The yields of tetravinylsilane ranged from 40% to 60%. Finally, as more was learned about the physical properties of tetravinylsilane, pentane was used as it was

(1) This paper was presented before the 130th meeting of the AMERICAN CHEMICAL SOCIETY at Atlantic City, N. J., Sept. 1956.

(2) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, unpublished results. S. D. Rosenberg, A. J. Gibbons, Jr., and H. E. Ramsden, *J. Am. Chem. Soc.*, 79, 2137 (1957).

TABLE I

PHYSICAL PROPERTIES OF SOME VINYLSILANES

Compound	B.P. or M.P.	n_D^{25}	d_4^{25}	Yield,[a] %	Analyses, % Si	
					Calcd.	Found
$(CH_3)_4Si$[4]	26.5°	1.3591[b]	0.6480[c]			
$(CH_3)_3SiCH{=}CH_2$	55°	1.3898	0.6917	64.0	28.00	27.50
$(CH_3)_2Si(CH{=}CH_2)_2$	80°	1.4182	0.7408	67.1	25.01	24.86
$CH_3Si(CH{=}CH_2)_3$	107.6°	1.4411	0.7692	72.0	22.59	22.29
$(CH_2{=}CH)_4Si$	130.6°	1.4611	0.7926	87.5	20.60	20.42
$C_6H_5Si(CH{=}CH_2)_3$	39–41° 0.05 mm.	1.4932	0.9159	81.4	15.06	14.76
$(C_6H_5)_2Si(CH{=}CH_2)_2$	130–131° 0.05 mm.	1.5350	1.0092	80.0	11.87	12.01
$(C_6H_5)_3SiCH{=}CH_2$	m. 57.5–59.5°			86.1	9.80	9.63
$(C_6H_5)_4Si$[5]	m. 228°					
$(CH_2{=}CH)_3SiH$	92.5°	1.4498	0.7725	54.7	25.46	25.21
$(n\text{-}C_4H_9)_2Si(CH{=}CH_2)_2$	59–61° 2.0 mm.	1.4528	0.7916	81.0	14.29	14.41

[a] Based on the mole of silicon chloride used. [b] n_D^{20}. [c] d_4^{20}.

thought that this low-boiling solvent would exert a moderating influence upon the reaction. This solvent proved to be beneficial: an 87% yield of tetravinylsilane was obtained.

$$CH_2{=}CHMgCl + SiCl_4 \xrightarrow[\text{at reflux}]{\text{Pentane}} (CH_2{=}CH)_4Si$$

Similarly, it was possible to prepare trivinylmethylsilane, trivinylsilane, dimethyldivinylsilane, and trimethylvinylsilane from vinylmagnesium chloride in tetrahydrofuran and the appropriate organochlorosilane in pentane.

The problem of separation of the product from tetrahydrofuran becomes more difficult with each succeeding silane because of the proximity of boiling points (Table I). The problem is further complicated by the fact that these silanes, particularly trivinylsilane, polymerize when held at their boiling points for prolonged periods. This problem was partially solved by using columns with sufficient efficiency and throughput to achieve the separation of the tetrahydrofuran from the product with a minimum of reflux return. Once the tetrahydrofuran was separated, the columns were by-passed and the product distilled rapidly through a simple still-head. In the case of trimethylvinylsilane,[3] the product distills first and careful fractionation on a 75-theoretical plate column was used.

The preparation of the last four compounds of the series was straight forward. Triphenylvinylsilane is a low-melting solid which was crystallized from ethanol-benzene.

Diphenyldivinylsilane, trivinylphenylsilane, and dibutyldivinylsilane are liquids which were purified by distillation under reduced pressure. Because of the danger of heat-induced polymerization, very low pressures should be maintained when distilling these materials.

Although pentane was used as the solvent in the work reported, exploratory work showed that heptane was a satisfactory solvent in the preparation of diphenyldivinylsilane and trivinylphenylsilane. These results indicate that heptane should be useful in the preparation of these high boiling silanes, eliminating the hazards of pentane.

In the reactions reported here tetrahydrofuran as delivered by the Du Pont Co., purified new tetrahydrofuran and purified recovered tetrahydrofuran were used as solvents in the preparation of vinylmagnesium chloride. No difference was noted in the behavior of the reactions in comparative duplicate runs provided the solvents were maintained anhydrous. In our hands tetrahydrofuran exhibited no unusual behavior or hazard provided standard safety precautions were observed.

EXPERIMENTAL

Vinylmagnesium chloride. In a 12.0-l. flask equipped with a stainless steel anchor stirrer, a dropping funnel, and a Dry Ice–acetone cold condenser, was placed 414 g. (17.0 g.-atom) of magnesium turnings. To this was added 100 ml. of a solution of 1274 g. (20.4 mole) of vinyl chloride in 3680 g. (51.0 mole) of tetrahydrofuran. The temperature of the mix was raised to 40° by warming with an electric mantle and 5.0 ml. of ethyl bromide was added to initiate the reaction. When the temperature of the mix reached 50°, the mantle was removed and the remainder of the solution was added at a rate to maintain a reaction temperature of 45–55°. The addition time was 6.0 hr. The reaction mix was then stirred for 3.0 hr. while the reaction temperature was gradually raised to 60° using the heating mantle. The vinylmagnesium chloride was now ready for use. The yield, as ascertained by back-titration with standard acid and base, was 15.6 mole (91.8%).

Tetravinylsilane. In a 22.0-l. flask equipped with a stainless steel anchor stirrer, a dropping funnel, and a water condenser, was placed 15.6 mole of vinylmagnesium chloride in 3680 g. of tetrahydrofuran. To this was added, at a rate to maintain reflux, 595 g. (3.5 mole) of silicon tetrachloride in 8.0 l. of pentane. The addition took 3.0 hr. On

(3) L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. S. Evans and F. C. Whitmore, *J. Am. Chem. Soc.*, **76**, 1613 (1954).

(4) H. H. Anderson, *J. Am. Chem. Soc.*, **69**, 3049 (1947).

(5) A. Polis, *Ber.*, **18**, 1542 (1885).

completion of the addition, the mix was refluxed for 5.0 hr. The mix was then partially hydrolyzed by the cautious addition of 2.3 l. of 5% aqueous hydrochloric acid. At this point $MgCl_2 \cdot 6H_2O$ dropped out of suspension and the clear organic layer was separated. The salt was then dissolved by the addition of 2.0 l. of water. The very small organic layer that resulted was separated and combined with the major fraction.

The solution was fractionally distilled through a column of 8 theoretical plates to yield (*1*) 6800 ml. (85%) of pentane, b.p. 35–40° and (*2*) 3128 g. (85%) of tetrahydrofuran, b.p. 63–68°.

When the temperature of the distillate at the head of the column reached 129°, the column was by-passed and the product was distilled through a simple distillation head to yield (*3*) 417.5 g. (87.5%) of tetravinylsilane, b.p. 129–132°.

Dimethyldivinylsilane. In a 22.0-l. flask was placed 13.5 mole of vinylmagnesium chloride in 3100 g. of tetrahydrofuran. To this was added 725 g. (6.0 mole) of dimethyldichlorosilane in 8.0 l. of pentane; addition time 5.0 hr., reflux time 5.0 hr. The reaction mixture was then hydrolyzed and the organic layer separated.

The solution was fractionally distilled through a column of 8 theoretical plates to remove 7 0 l. (87.5%) of pentane, b.p. 36–40°. The residue was then fractionally distilled through a column of 75 theoretical plates to remove 2985 g. (96.4%) of tetrahydrofuran, b.p. 60–68°. When the temperature of the distillate at the head of the column reached 79°, the column was by-passed and the product was distilled through a simple distillation head to yield 396.7 g. (66.1%) of dimethyldivinylsilane, b.p. 79–82°.

Diphenyldivinylsilane. In a 22.0-l. flask was placed 9.2 mole of vinylmagnesium chloride in 2160 g. of tetrahydrofuran. To this was added 1042 g. (4.12 mole) of diphenyldichlorosilane in 8.0 l. of pentane at a rate to maintain reflux; addition time 3.0 hr., reflux time 8.0 hr. The reaction mixture was then hydrolyzed and the organic layer separated.

The solvents were then stripped using steam as the heat source and the residue was distilled under reduced pressure to yield 778.9 g. (80%) of diphenyldivinylsilane distilling at 130–131°/0.05 mm.

Triphenylvinylsilane. In a 22.0-l. flask was placed 10.8 mole of vinylmagnesium chloride in 2600 g. of tetrahydrofuran. To this was added 2659 g. (9.0 mole) of triphenylchlorosilane in 5.0 l. of tetrahydrofuran plus 3.0 l. of pentane; addition time 1.5 hr., reflux time 8.0 hr. The reaction mixture was then hydrolyzed and the organic layer separated. The solvents were then removed by distillation with the last traces distilling under reduced pressure (25 mm.). The residual oil was transferred to a crock and was solidified by cooling the crock in an ice bath. The solid was ground up, transferred to a 12.0 l. flask, and crystallized by dissolving in 3.0 l. of 90% ethanol plus 1.0 l. of benzene at reflux and cooling slowly to 15° with stirring. The solid was filtered by suction and thoroughly air-dried to give 1900 g. (73.5%) of triphenylvinylsilane melting at 57.5–59.5°. Concentration of the mother liquid led to the isolation of 350 g. (13.6%) of triphenylvinylsilane melting at 53–58°.

Acknowledgment: The authors would like to thank Dr. Marie Farnsworth and her coworkers in the Physical and Analytical Section of this laboratory for their assistance throughout this work.

RAHWAY, N. J.

[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL & THERMIT CORP.]

Arylmagnesium Chlorides. Preparations and Characterizations[1]

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Received May 10, 1957

Substitution of tetrahydrofuran for ethyl ether allows conversion of aryl chlorides to arylmagnesium chlorides.

Although phenylmagnesium chloride has been known for a number of years, no general procedure has been forthcoming for the preparation of other arylmagnesium chlorides. The preparations of phenylmagnesium chloride in chlorobenzene in the absence of solvent under pressure,[2] using freshly prepared magnesium,[3] catalytic quantities of metal salts,[4] a special magnesium-copper alloy and ethyl ether and allowing an initiating period of 4–11 days[5] or using the diethyl ether of ethylene glycol[6] do not seem to be general enough for preparing other arylmagnesium chlorides. Usually for these compounds it is necessary to use molar quantities of ethyl bromide as an entrainment carrier for the aryl chloride.[7] Compounds made in this way include phenylmagnesium chloride and *p*-chlorophenylmagnesium chloride. Pentamethylphenyl-

(1) Parts of this paper were presented at the 130th National Meeting of the AMERICAN CHEMICAL SOCIETY, Atlantic City, Sept., 1956.

(2) H. Gilman and R. Brown, *J. Am. Chem. Soc.*, 52, 3330–2 (1930); P. Shornigin, *et al.*, *Ber.*, 64B, 2584 (1931); E. Britton and Slagh, U. S. Patents 1,996,746 [*Chem. Abstr.*, 29, 3352 (1935)] and 2,056,822 [*Chem. Abstr.*, 30, 8246 (1936)].

(3) R. Manske and A. Ledingham, *Can. J. Research*, 27B, 158 (1949); A. Weissenborn, Ger. Patent 697,420 (1940) [*Chem. Abstr.*, 35, 6600[4] (1941)]; and U. S. Patent 2,058,373 [*Chem. Abstr.*, 31, 1182 (1937)].

(4) A. Weissenborn, Ger. Patent 660,075 (1938) [*Chem. Abstr.*, 32, 5857[1] (1938)].

(5) H. Gilman and N. St. John, *Rec. trav. chim.*, 49, 717 (1930).

(6) J. Hill, U. S. Patent 2,552,676 (1951) [*Chem. Abstr.*, 45, 9079f (1951)].

(7) W. V. Evans and E. M. Diepenhorst, *J. Am. Chem. Soc.*, 48, 715 (1926); R. T. Dufford, S. Calvert, and D. Nightingale, *J. Am. Chem. Soc.*, 45, 2068 (1923); T. Jezierski, *Roczniki Chem.*, 20, 47 (1946) [*Chem. Abstr.*, 42, 1910 (1948)].

TABLE I

PREPARATION OF GRIGNARD REAGENTS

Aryl Chloride	Heating	Addition, Time/Hr.	Time to Complete,[a] Hr.	Yield[b]	Remarks
Chlorobenzene	None	1.0	2.0	95	
o-Chlorotoluene	Throughout	1.5	2.25	98.5	
p-Chlorotoluene	Throughout	1.0	1.3	93	
m-Chlorotoluene	Throughout	1.0	2.5	96	The *m*-chlorotoluene must be freshly distilled
2-Chloro-*p*-xylene	Throughout	3.5	0.5	92.5	Difficult initiation
p-Ethylchlorobenzene	Throughout	1.5	6.0	97	Magnesium used, 96.7%
p-Chloroanisole	To initiate[c]	3.0	5.0 at 45° C.	77	
o-Chlorophenetole	Throughout	1.75	2.5	98.5	
p-Dichlorobenzene	None	1.0	2.0	96	[d]
o-Dichlorobenzene[e]	Throughout	8.75	22.5	19	
Hexachlorobenzene[f]	Throughout	7.0	0.5	77.5	
p-Chlorodiethylaniline	Throughout	1.25	10.0	95.5	Magnesium used, 91.7%
p-Chlorodimethylaniline				88	
2,4-Dichlorotoluene	To initiate			83	
2,4-Dichlorophenetole	To initiate			90	Magnesium used, 92.1%
o-Trifluoromethylchlorobenzene	Throughout			62	
m-Trifluoromethylchlorobenzene[g]	Throughout			5.7	
p-Trifluoromethylchlorobenzene[g]	Throughout			9.1	
Ethylpentachlorobenzene	None			49	Strongly exothermic
m-Fluorochlorobenzene	Throughout		3	50	Magnesium used, 89.2%
Monochlorobiphenyl[h]	Throughout	14.3	8.0	22.6	
α-Chloronaphthalene	Throughout	2.0	6.0	40	

[a] After addition. [b] Titration.[20] [c] At 79° C. a rapid exothermic reaction began. [d] On hydrolysis, no benzene was found. In further work, some benzene has been obtained, as well as higher boiling residues. [e] Illustration of the *ortho* chlorine effect. Some 65–70% of the magnesium was consumed. [f] Hexachlorobenzene required a cyclic process and 7.0 moles of tetrahydrofuran. A second run adding solid hexachlorobenzene was exothermic after initiation.[18] [g] The *m*- and *p*-trifluoromethylchlorobenzenes reacted vigorously at first, but coated the magnesium badly. [h] Arochlor 1221, an impure monochlorobiphenyl.

magnesium chloride has been prepared, but no details of its preparation are available.[8]

Normant recently reported the successful preparation of phenylmagnesium chloride and *p*-chlorophenylmagnesium chloride using tetrahydrofuran as solvent.[9] Although he gives no details of procedure, these preparations are easily carried out. In an extensive study of the preparation of arylmagnesium chlorides carried out in this laboratory and independently of Normant,[10] it has been determined that every aryl chloride or heterocyclic chloride[11] tried reacts with magnesium in tetrahydrofuran. With most aryl chlorides results have been excellent in forming Grignard reagents, except where ortho chlorine atoms are present or more than two chlorine atoms are on the same aromatic ring, in which case considerable coupling occurs. Hexachlorobenzene is an exception and does not display this behavior. Yields as summarized in Table I, show, this reaction to be very much more general than Normant states.

In a further study of the scope of this reaction, ethers other than tetrahydrofuran were investigated as suitable solvents. No simple ethers of the open chain type R-O-R′ were found to be effective for aryl chlorides other than chlorobenzene. However, with the cyclic ethers a limitation was found. Tetrahydropyran[12a] 2-methyltetrahydrofuran, tet-

(8) H. Clement and J. Savard, *Compt. rend.*, 204, 1724 (1937).

(9) H. Normant, *Compt. rend.*, 239, 1510 (1954).

(10) Our work was carried out within a few months of that by Normant (as determined by private communications with Prof. Normant, of the Sorbonne, Paris, France, during 1955).

(11) H. E. Ramsden and A. E. Balint, unpublished results.

(12a) As contrasted to the discouraging results obtained by H. Hepworth, *J. Chem. Soc.*, 119, 1249–52 (1921). (b) In further reactions where excess acidic reagents are present these two solvents are unstable.

rahydrofurfuryl ethyl ether, 2-ethoxytetrahydropyran,[12b] and dihydropyran[12b] were all found to be good solvents for the preparation. *N*-Methylmorpholine has shown some use as a solvent in this reaction. Pentamethylene sulfide, tetramethylene sulfide, and furan do not seem to be suitable solvents, although 4-thiapentamethylene oxide does function to some extent. Reaction does not occur in 2,5-dimethyltetrahydrofuran or 2,2,5,5-tetramethyltetrahydrofuran as solvent; not even chlorobenzene could be induced to react in these two solvents.

These facts may suggest that a possible mechanism is tied in with the availability of the oxygen *p* electrons. The configuration of the ring is such as to make these electrons more available for coordination than is true with ethyl ether or any of the R-O-R types and the coordination may serve to drive the reaction to completion, either by the simple matter of dissolving reagent off the surface of the magnesium, by free energy relationships, or by an ill-defined solvation of the aryl chloride. Anything which renders the electrons less available, such as the resonance in furan or the steric influence which seems to operate in 2,5-dimethyltetrahydrofuran or 2,2,5,5-tetramethyltetrahydrofuran also stops the reaction.

Because of the known complex character of the Grignard reagent[13] and its preparation,[14] any attempt at posing a well-defined mechanism for this process requires more data.

More evidence of the solubility effect is given by sodium *p*-chlorophenoxide, a compound fairly soluble in tetrahydrofuran. On addition of a tetrahydrofuran solution of sodium *p*-chlorophenoxide to activated magnesium, we obtained evidence of an extremely vigorous reaction. However it was short-lived and a gelatinous precipitate appeared on the magnesium. Apparently, as expected, the effect of the charge on the oxygen atom was transmitted through the ring and a very much activated carbon to chlorine bond resulted. However the reagent, *p*-sodio oxyphenylmagnesium chloride, was not soluble in the tetrahydrofuran. This resulted in an impenetrable coating on the magnesium, thus ending attack on the magnesium. A similar type of inhibition by rapid initial attack and insolubility of product is shown by Mihailescu and Caragea in the case of diiodobenzene[15] where use of a different solvent allowed the reaction to go to completion. The greater energy of formation of alkylmagnesium chloride complexes with tetrahydrofuran over that of the corresponding complexes with ethyl ether[9] (and of boron trifluoride etherates[16]) is inherently shown by Normant in his quantitative replacement of the ethyl ether of these complexes.

Concentration seems to have little effect in this reaction, at least in the preparation of phenylmagnesium chloride. In studies of the ratio of moles of tetrahydrofuran to moles of chlorobenzene needed for optimum reaction, the ratio has been varied from as low as 0.5 to as high as 4.0. At the lower ratios, however the resulting solution has been found to be too viscous for efficient stirring and a ratio of 2:1 was found to be about the lowest for ease of handling. At this ratio, if the solution is allowed to cool and stand overnight, the complex crystallizes and the solution solidifies into a mass of fine long white needles of relatively low melting point. Little success has been obtained in attempts to free these crystals of mother liquor as they appear to be pressure sensitive. However, there is actually very little mother liquor present.

With solid aryl chlorides the amount of tetrahydrofuran necessary is governed by the solubility of the aryl chloride. The Grignard reagents themselves are very soluble and, by a cyclic process of distilling a portion of the tetrahydrofuran off, dissolving more aryl chloride in this solvent, and adding the resulting solution to the reaction mass, the amount necessary can be kept to a minimum.

In their reactions, the reagents are similar to the more common Grignard reagents. The reactivity of the simpler less substituted types is at least as great as that of phenylmagnesium bromide. Many of these reagents were characterized by further reactions with aldehydes, ketones, and esters, metal and metalloid halides (such as those of tin,[17] phosphorus, silicon,[18] and antimony), and other reactive compounds. They react with carbon dioxide as expected and also give Gilman and Schultz' Color Test I[19] with the exception of some of those containing *ortho* or two or more chlorine atoms on the ring. Pentachlorophenylmagnesium chloride did not carbonate nor did it give a strongly positive Color Test, although it reacted with silicon tetrachloride.[18] Addition of the tetrahydrofuran solutions to Dry Ice (or bubbling dry carbon dioxide into the Grignard at 10°) and a subsequent recovery of the acids served to help in structure determination. One preparation of phenylmagnesium chloride was intentionally carried out in an atmosphere of dry carbon dioxide to ascertain if this would hinder the reaction. No inhibition of reaction was noted.

Conversion of the arylmagnesium chlorides to arylethanols by use of ethylene oxide has been

(13) See, in particular, M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, pp. 99–115.

(14) See, in particular, M. S. Kharasch and A. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, pp. 44–45.

(15) M. A. Mihailescu and St. P. Caragea, *Bull. Soc. Sci., Acad. Roumaine*, **12**, No. 4/5, 7–18 (1929) [*Chem. Abstr.*, **24**, 2116 (1930)]; also A. Bourgom, *Bull. soc. chim. Belg.*, **33**, 101 (1924) for another analogy.

(16) H. Normant, *Bull. soc. chim. France*, 739 (1950).

(17) S. D. Rosenberg and H. E. Ramsden, unpublished results.

(18) S. D. Rosenberg, J. J. Walburn, and H. E. Ramsden, unpublished results.

(19) H. Gilman and F. Schultz, *J. Am. Chem. Soc.*, **47**, 2022 (1925).

TABLE IV

Arylethanol	Boiling Point	Yield[a]	n_D^{25}	Lit.
β-*o*-Tolylethanol	95° at 6 mm.	91	1.5324	1.5347[b]
β-*m*-Tolylethanol	96° at 6 mm.	77	1.5254	1.5231[b]
β-*p*-Tolylethanol	94° at 6 mm.	74.5	1.5253	1.5271[b]
β-*p*-Anisylethanol	124° at 7 mm.[c]	75.6	1.5351	
β-*p*-Phenethylethanol	123° at 3 mm.[d]	69.5	1.5213	
β-2-*p*-Xylylethanol	98° at 4 mm.	70.8	1.5290	

[a] Based on ethylene oxide. [b] K. K. Ling, *Anzeuger Akad. Wiss. Krakau*, 632 (1908), [*Chem. Z.*, 1863 (1908II)]. [c] M.p. 20–22°. Grignard, *Compt. rend.*, **141**, 45 (1905) gives 22–24°. [d] M.p. 39°.

found an excellent device for a rough check on yields and products. Contrasted to Manske *et al.*,[3] who found that phenylmagnesium chloride in excess chlorobenzene gave moderate yields of phenylethanol, we have consistently obtained good yields (based on Grignard reagent) in tetrahydrofuran. This is true when ethylene oxide equivalent to the reagent is added. If excess ethylene oxide is added, the yield of arylethanol is lowered proportionately to the excess. A higher-boiling residue, presumably made up of arylethoxyethanols, is formed.

EXPERIMENTAL

All of the preparations were carried out under dry nitrogen (commercial low-oxygen grade) and were stirred by means of an anchor stirrer (which swept the bottom fairly closely) at 100–200 r.p.m.

The trifluoromethylchlorobenzenes were supplied by the Hooker Electrochemical Co. Arochlor 1221 was supplied by the Monsanto Chemical Co.

Tetrahydrofuran as supplied by the Du Pont Company was found to be quite suitable for use. Its content of water was below 0.1% (frequently below 0.05%) and peroxide content was so low that analysis showed none present. This material is stabilized by 0.1% hydroquinone and remained free of peroxides for some months. If the material were colored it was distilled with the usual precautions to prevent possible build-up of peroxides. Purified tetrahydrofuran and purified recovered tetrahydrofuran were found suitable but of no advantage over the commercial material. If stored over sodium, the tetrahydrofuran should be distilled before use, as the sodium seems to cause some decomposition after a few weeks.

Magnesium turnings as supplied by the Dow Chemical Co. were used.

Grignard preparations. In general, the aryl chlorides (1 mole) were dissolved in three moles of tetrahydrofuran. Initiation was made by adding 2–4 ml. of ethyl bromide to one g.-atom of magnesium turnings and 15 to 20 ml. of the aryl chloride–tetrahydrofuran solution, and the stirrer was started. Initiation frequently was immediate, although occasionally it was necessary to heat the reaction mass to reflux in order to get the initiation reaction going well. Once the reaction was going, the solution was added at a rapid dropwise rate and the reaction allowed to proceed at reflux. (Sometimes no external heating was necessary after initiation.) After completion of addition, the reaction was heated at reflux for 0.5 to 2.0 hr., until the magnesium was nearly consumed.

In determining yields by titration, the solution was diluted with tetrahydrofuran to 1000 ml. in a volumetric flask, 20 ml. aliquots were pipetted into 50 ml. of 0.5*N* sulfuric acid and 50 ml. of water, heated on a steam bath for 30 min., and back-titrated with 0.2*N* sodium hydroxide (with phenolphthalein or bromcresol purple as indicator).[20]

Carbonation of phenylmagnesium chloride during preparation. Two g.-atoms (48.6 g.) of magnesium turnings were activated by 2 ml. of ethyl bromide, a small iodine crystal, and 20 ml. of a solution of 225.2 g. (2 moles) of chlorobenzene, and 433 g. (6 moles) of tetrahydrofuran. An atmosphere of carbon dioxide was maintained during this entire preparation. As soon as the initiation reaction began, the solution of chlorobenzene–tetrahydrofuran was added dropwise to the mixture, heated to reflux. The addition required 8.5 hr. Heating under carbon dioxide was continued for an additional 2 hr., the mixture was cooled, hydrolyzed by the addition of 330 ml. of concentrated hydrochloric acid, diluted to 2000 ml. with water. The two layers were separated, the aqueous layer was extracted with two 200-ml. portions of ether and discarded. The extracts and the organic layer were combined and extracted with one liter of 10% sodium hydroxide. This extraction on acidification yielded solid acid, which, recrystallized from 95% ethanol, yielded a small amount of benzoic acid, m.p. 120–121°, and 14.0 g. of triphenylacetic acid, m.p. 263–267° (lit.[21] 267°); neut. equiv. 286.8 (calcd. 288.3).

The *amide*, m.p. 244° (sublimes) (lit.[21] 246–247°) and the *anilide*, m.p. 166–168° (lit.[21] 167–168°, 173.5–174.5°) were prepared.

The organic layer was evaporated to yield 90 g. of residue which was fractionated to yield 23 g. benzophenone, b.p. 142–189° at 28 mm., and 19 g. triphenylcarbinol, b.p. 176–180° at 0.3 mm.

Carbonation of phenylmagnesium chloride. Phenylmagnesium chloride (from 1.0 g.-atom of magnesium and 1.0 mole of chlorobenzene) was carbonated by bubbling dry carbon dioxide gas in at 10–20°. Crude benzoic acid, 82.0 g. (67.2%) m.p. 117–118° was obtained. Recrystallization from water yielded material, m.p. 122° (corrected).

Carbonation of p-tolylmagnesium chloride. p-Tolylmagnesium chloride [from 126 g. (1 mole) *p*-chlorotoluene, 24.3 g. (1 g.-atom) magnesium turnings and 216 g. (3 moles) tetrahydrofuran] was added to an ethyl ether slurry of Dry Ice and allowed to stand overnight. The dark supernatant liquid was decanted; the remaining solid was dissolved in 300 ml. of water; a second organic liquid layer was decanted, the water solution was acidified with concentrated hydrochloric acid to yield (after chilling and standing) 102.3 g. (76%) of crude *p*-toluic acid melting at 164–165.5°.

β-Phenylethanol. General procedure. A solution of 2.0 moles (88 g.) of ethylene oxide in 2 moles (144 g.) of tetrahydrofuran was added slowly to a solution of phenylmagnesium chloride (from 225 g. chlorobenzene, 48.6 g. magnesium turnings, and 432 g. tetrahydrofuran) cooled by means of an ice bath to keep the temperature below 50°. As soon

(20) H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

(21) I. Heilbron, *Dictionary of Organic Compounds*, Vol. IV, Oxford University Press, New York, 1953, p. 628.

as the addition was completed, the mixture was heated to reflux until the clear solution became a grey slurry[22] (about 1 hr.). The mixture was hydrolyzed by addition of 186 ml. of 37% hydrochloric acid in 500 ml. of water and the two layers were separated. The aqueous layer was extracted with two 50-ml. portions of toluene. The organic layer and the extracts were combined and distilled through a 4-inch Vigreux head at atmospheric pressure to remove tetrahydrofuran and toluene, and finally at 3–5 mm. where phenylethanol boiling at 84–86° came over. Yield, 215.5 g., 88.4% (based on original Mg and ethylene oxide). n_D^{19} 1.5332 (Beilstein: n_D^{20} 1.5337).

(22) If heating is stopped just before this point, the reaction mass sets up to a hard gel, which may be dispersed on addition of more tetrahydrofuran.

Acknowledgments. The authors would like to thank Dr. S. D. Rosenberg for his helpful and critical advice in the later phases of this work. We are also indebted to Dr. C. K. Banks for his constant encouragement, throughout. We also thank the management of the Metal & Thermit Corp. for permission to publish as well as for its continuous support during the work.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Formation of Dieckmann Reaction Products under Acyloin Conditions. Competition of the Two Reactions

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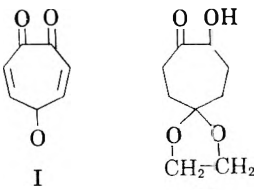
Received May 6, 1957

The acyloin reaction, under conditions which effected the condensation of ethyl sebacate satisfactorily, has been shown to give Dieckmann products from the lactone of ethyl γ-hydroxypimelate (IX) and ethyl γ,γ-ethylenedioxypimelate (III). It is suggested that the anomaly resulted from an intramolecular interaction of functions producing an enhanced polarization of the carbonyl group(s). The preparation of pimeloin has been re-examined and found to be as reported. When stabilized dispersion is used, however, products derived from the Dieckmann reaction were also obtained. Interesting derivatives of compounds in this series were obtained, two of which appear to have resulted from oxidation by phenylhydrazine.

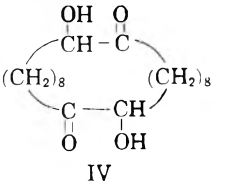
The experimental conditions required for the cyclic acyloin reaction are in many respects similar to those used in the Dieckmann reaction. Major differences between the two are (*a*) particle size of the sodium, the acyloin reaction requiring colloidal dispersions,[1,2] and (*b*) concentration, acyloin (intramolecular) conditions being most satisfactory when the ester is added at high dilution.[3]

The work herein described resulted from an attempt to synthesize tropoquinone (I). The proposed synthesis required the formation of 2-hydroxy-5,5-ethylenedioxycycloheptanone (II) (or the corresponding dione) by the acyloin condensation of ethyl γ,γ-ethylenedioxypimelate (III).[4] The approach appeared to be sound in that pimeloin itself has been prepared in this manner[5,6] and substances possessing the dioxolane linkage have been shown to cyclize normally without destruction of the ketal linkage.[7]



I

II



IV

To avoid the use of high-speed stirring, a prepared (stabilized with 1% of sodium oleate) dispersion of sodium in xylene[8] was employed in early experiments. It was found to be quite satisfactory for the well-known cyclization of sebacic ester[2] from which there was obtained sebacoin and a by-product, tentatively formulated as cyclododecane-2,12-diol-1,11-dione or the isomeric 2,11-diol-1,12-dione (IV). No Dieckmann products were detected. When III was submitted to reaction under the same conditions, however, the only products isolated were the Dieckmann product, 2-carbethoxy-4,4-ethylenedioxycyclohexanone (V) and its decarbethoxylation product 4,4-ethylenedioxycyclohexanone (VI). The appearance of the latter substance in later fractions from the distillation of the reaction mixture, and the occurrence of gas evolution during the entire operation, suggested that VI formed thermally from the corresponding β-keto acid. That any of the β-keto ester (V) survived the reaction conditions is somewhat surprising since

(1) V. L. Hansley, U. S. Patent 2,228,268; *Chem. Abstr.*, **35**, 2534 (1941).

(2) N. L. Allinger, *Org. Syntheses*, **36**, 79 (1956).

(3) Compare, for example, ref. (2) with M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).

(4) During the preparation of this manuscript, a paper appeared containing mention of an attempted acyloin reaction with this substance. N. J. Leonard, L. A. Miller, and J. W. Berry, *J. Am. Chem. Soc.*, **79**, 1482 (1957).

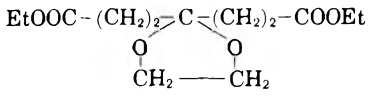
(5) J. D. Knight and D. J. Cram, *J. Am. Chem. Soc.*, **73**, 4136 (1951).

(6) N. J. Leonard and G. C. Robinson, *J. Am. Chem. Soc.*, **75**, 2143 (1953).

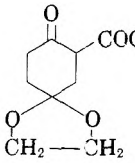
(7) M. Stoll, J. Hulstkamp, and A. Rouve, *Helv. Chim. Acta*, **31**, 543 (1948).

(8) We are grateful to E. I. du Pont de Nemours and Co., Inc., for a most generous gift of this dispersion.

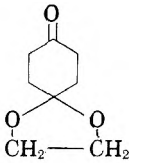
the ester function is quite unstable in the acyloin medium. The major by-product from most cyclic acyloin formations is, in fact, the corresponding dicarboxylic acid, and none of the starting diester is recovered. No acyloin could be isolated from this reaction mixture. The use of freshly dispersed sodium (*ca.* 12,000 r.p.m.) gave virtually the same results; no acyloin could be isolated.



III

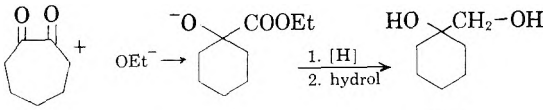


V



VI

These findings prompted a re-examination of the reported preparation of pimeloin under the usual conditions and under conditions incorporating stabilized dispersion. When the latter dispersion was employed there was formed a mixture of cyclohexanone, pimeloin, and 1,2-cycloheptanedione but no 2-carbethoxycyclohexanone could be isolated. When the reaction was repeated, however, using sodium freshly dispersed at *ca.* 12,000 r.p.m., it proceeded as described.[5] In addition to the acyloindione mixture, there was obtained a very small quantity of the known 1-hydroxymethylcyclohexanol, formed presumably *via* a benzilic acid-type rearrangement of the dione followed by reduction of the ester function (VII → VIII).



VII VIII

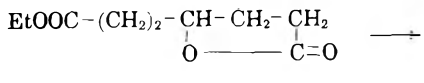
A final attempt was made to prepare II by use of the sodium-ammonia medium.[9] From this reaction there was isolated a small amount of V and a quantity of an acyloin insufficient to permit characterization.

The lactone of ethyl γ-hydroxypimelate (IX) was prepared from ethyl γ-ketopimelate by reduction with sodium borohydride and submitted to reaction under acyloin conditions. The relative proximity of carbonyl groups in this substance would appear, from a construction on models, to be approximately equivalent to that in glutaric ester. The latter has been shown to yield the corresponding acyloin, glutaroin.[10] The product, 2-carbethoxy-4-hydroxycyclohexanone(X), was as in the other reactions, that of a Dieckmann reaction.

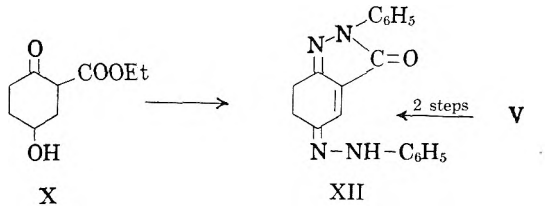
(9) See for example. J. C. Sheehan, R. A. Coderre, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **75**, 6231 (1953).

(10) J. C. Sheehan, R. C. O'Neill, and M. A. White, *J. Am. Chem. Soc.*, **72**, 3376 (1950).

This substance was also prepared from the lactone under more conventional Dieckmann conditions.

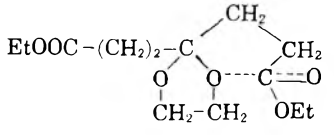


IX



X XII

An explanation of the anomalous behavior of III and IX under the conditions of the acyloin reaction is not immediately obvious. A construction of III with models reveals no bond deformation about the acetal carbon atom and the carbethoxy groups appear to be no differently situated in any of the various possible conformations than in ethyl pimelate. It would appear very reasonable, however, for an interaction to occur between the carbonyl of a carbethoxy group and an oxygen atom of the dioxolane ring (XI, one or both carbethoxy functions being involved).[11] This enhanced polarization of the carbonyl is such as to retard *both* the Dieckmann reaction (ionic) and the acyloin reaction (radical).[12] It is apparent from many studies, however, that the acyloin condensation is greatly dependent upon molecular environment and very sensitive to changes in reaction conditions. On the other hand, the vast number and types of diester which have reacted successfully under Dieckmann conditions suggests that this reaction is relatively insensitive to subtle environmental changes.



XI

Some rather interesting derivatives resulted from this series of compounds. The reaction of the dione ester, obtained by hydrolysis of V, with phenyl hydrazone afforded a dark red derivative incorporating two molecules of the hydrazine but having lost two hydrogen atoms. No examples could be found in the literature of dehydrogenation by phenylhydrazine to form the olefinic linkage, but an alternate hypothesis is not apparent. The deriva-

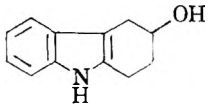
(11) This structure approximates, to some extent, the probable transition state attained in the conversion of γ-ethoxybutyryl chloride to ethyl γ-chlorobutyrate [V. Prelog and S. Heimbach-Juhaz, *Ber.*, **74B**, 1702 (1941)]. Other such proximity effects between N and C are known from the work of Leonard and his students, *J. Am. Chem. Soc.*, **76**, 630 (1954).

(12) E. Van Heyningen, *J. Am. Chem. Soc.*, **77**, 4016 (1955).

tive is tentatively formulated as XII, a structure satisfying analytical data and most of the spectral data. The intense color of the substance (due to absorption at 450 mμ, ε 49,800) would suggest a longer chromophore system than that in XII.

Even more extensive oxidation occurred when 2-carbethoxy-4-hydroxycyclohexanone (X) was allowed to react with excess phenylhydrazine. The normal pyrazolone was formed along with the red derivative (XII), the yield of the latter increasing as the reaction time was lengthened. Compound X exhibited a strong tendency to polymerize, rather than lactonize, when heated. Moreover, an attempt to prepare a 3,5-dinitrobenzoate derivative gave only ethyl 3,5-dinitrobenzoate and polymeric material.

To determine if this unusual oxidation demanded the presence of a carbethoxy group, a sample of 4,4-ethylenedioxycyclohexanone was reduced with sodium borohydride and then hydrolyzed to 4-hydroxycyclohexanone. The reaction of this substance under moderate conditions gave the normal phenylhydrazone derivative and, under more drastic conditions, the corresponding carbazole derivative, 4-hydroxy-2,3,4,5-tetrahydrocarbazole (XIII). No product resulting from oxidation was isolated. Treatment of 1,4-cyclohexanedione under similar conditions afforded only the bisphenylhydrazone.



XIII

EXPERIMENTAL[13]

Acyloin reaction apparatus. The equipment used incorporated features described by others. These include a stirring motor rated at 20,000 r.p.m., a high-dilution mixing chamber arranged for magnetic stirring, a Hershberg dropping funnel and a train for nitrogen purification. Most of the dispersions used were prepared and used in reactions at speeds of about 12,000 r.p.m. When previously prepared (stabilized) dispersions were used, a speed of about 1500 r.p.m. was employed.

Sebacoin. This preparation employed sodium dispersion containing stabilizer (92.0 g. of 50% dispersion, 2.0 atoms of sodium) in 700 ml. of purified xylene. Ethyl sebacate (129.0 g., 0.500 mole) was submitted to reaction and the product isolated as described for other cases.[2] Distillation of the crude product afforded 40.0 g. (47.8%) of sebacoin, b.p. 140–145° (19 mm.). This material crystallized upon cooling and was recrystallized from ether-petroleum ether (60–68°) to give 34.9 g. (41%) of white needles, m.p. 36–38° (lit.[14] 38–39°). The remainder of the distillate boiled over a large range with decomposition. Some of these fractions partially solidified, however, and recrystallization from ethyl acetate gave 0.10 g. of colorless needles, m.p. 125–126.5°. This substance reacted with Fehling's reagent and gave no coloration with alcoholic ferric chloride solution. It is tentatively formulated as *cyclododecane-2,12-diol-1,11-dione* or the isomeric *2,11-diol-1,12-dione* (IV).

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.56; H, 10.66; mol. wt., 340. Found: C, 70.64; H, 10.50; mol. wt., 286 (Camphor).

Lactone of ethyl γ-hydroxypimelate. The following procedure was found to be more convenient than that reported. To a solution of 145.0 g. (0.630 mole) of ethyl γ-ketopimelate in 200 ml. of ethanol there was added at 0° a solution of 15.2 g. (0.40 mole) of sodium borohydride in 500 ml. of ethanol during a 45 min. period. Reaction was allowed to proceed with stirring for 5 hr. The cool solution was treated with excess 10% hydrochloric acid, 500 ml. of ether, and 100 ml. of saturated sodium chloride solution. Separation and processing of both phases in the usual manner, including washing with sodium hydrogen carbonate solution and evaporation of solvent, gave the crude product. Distillation afforded 76.3 g. (65.2%) of the lactone (VI), b.p. 120–125° (0.10 mm.) in a short-path system, n_D^{25} 1.4539. A sample was hydrolyzed to the lactone acid (m.p. 81.5°) which was then purified by several recrystallizations and reesterified, n_D^{25} 1.4511. Infrared spectra of these two samples were identical with that of the lactone ester prepared by the hydrogenation of ethyl γ-ketopimelate.[15]

The *2,4-dinitrophenylhydrazone* was crystallized from ethanol to give yellow needles, m.p. 166–167°.

Anal. Calcd. for $C_{13}H_{14}N_4O_7$: C, 46.17; H, 4.17; N, 16.6. Found: C, 46.30; H, 4.19; N, 16.7.

Pimeloin (a) using stabilized dispersion. Using the acyloin apparatus described above, 139.2 g. (0.644 mole) of ethyl pimelate[16] was allowed to react with 180 g. (3.13 atoms) of 40% sodium dispersion in xylene diluted with an additional liter of xylene (75 hr. addition time). Processing of the reaction mixture in the usual manner afforded a liquid mixture which was distilled through a 45 × 0.5 cm. wire-helix column. Gas evolution occurred during distillation and there resulted 8.2 g. (13%) of colorless liquid, b.p. 56–59° (24 mm.), identified as cyclohexanone by conversion to the 2,4-dinitrophenylhydrazone derivative. Following this, a second fraction of 11.8 g. (14.5%) was obtained as a light yellow liquid, b.p. 96–99° (24 mm.). The latter fraction, a mixture of pimeloin and 1,2-cycloheptanedione, gave a deep purple color with alcoholic ferric chloride and a positive Fehling's reaction. Analysis gave data consistent with the mixture hypothesis.[5] The phenylosazone crystallized in almost quantitative yield as a yellow solid, m.p. 136–137° (lit.[5] 136–137.5°).

(b) Using freshly prepared dispersion. Use of the ratios of materials and conditions described by Knight and Cram[5] afforded 23% of pimeloin-cycloheptanedione mixture, b.p. 70–79° (6.0 mm.). The five fractions collected all gave nearly quantitative yields of the osazone derivative. Two attempts to prepare semicarbazone derivatives, one from the former preparation and one from that described here, gave anomalous products.

(a) M.p., 187–189°. *Anal.* Found: C, 59.29; H, 6.67; N, 24.6.

(b) M.p., 189.5–190.5° [depressed with (a) above]. *Anal.* Found: C, 49.84; H, 8.11; N, 22.8.

Knight and Cram obtained a derivative, m.p. 173.0–173.5° which gave a satisfactory analysis.

A small fraction, b.p. 100–110° (6.0 mm.), was next collected which solidified in the receiver. Crystallization from ether-petroleum ether (60–68°) and sublimation at 0.1 mm. gave 0.2 g. of colorless solid, m.p. 76.0–76.5°. This material did not produce a coloration with alcoholic ferric chloride nor did it react with Fehling's solution. Its infrared spectrum exhibited strong absorption at 3.0–3.2 μ (hydroxyl) but showed no absorption in the 5–6 μ region.

(13) Melting points are corrected.

(14) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 1822 (1947).

(15) A. E. Tchitchibabine, *Bull. soc. chim. France*, **8**, 670 (1941).

(16) P. D. Gardner, L. Rand, and G. R. Haynes, *J. Am. Chem. Soc.*, **78**, 3425 (1956).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84; Mol. Wt., 130. Found: C, 64.58; H, 10.85; Mol. Wt., 170.

This substance was shown to be 1-hydroxymethylcyclohexanol by comparison with an authentic sample.[17]

Further distillation gave several fractions of yellow to colorless liquid boiling over the range 125–185° (0.25 mm.) totaling 27.5 g. All of these gave positive Fehling's reactions and red-violet colorations with alcoholic ferric chloride. These are being further investigated.

Reaction of ethyl γ,γ-ethylenedioxypimelate (III) *under acyloin conditions.* (*a*) *Using stabilized dispersion.* This reaction was conducted as in (*a*) of the pimeloin procedure described above. Ethyl γ,γ-ethylenedioxypimelate[16] (III) (140.0 g., 0.511 mole) was added to 184 g. (3.2 atoms) of a 40% sodium dispersion, which had been diluted with 1 l. of xylene, during a 75-hr. period. The mixture was refluxed for an additional hr., cooled to 0° and treated with 210 g. (3.5 moles) of acetic acid in 300 ml. of ether during 1 hr. After dilution with water, processing was completed in the usual manner. Distillation of the residue through an 18-in. Vigreux column gave a fraction, 38.7 g., b.p. 119–125° (0.75 mm.). Near the end of the distillation considerable gas evolution occurred and a white solid (2.0 g.) was collected, b.p. 120–125° (1.5 mm.). Crystallization from petroleum ether (60–68°) and sublimation afforded colorless needles, m.p. 73–74°. This substance gave negative ferric chloride and Fehling tests.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.51; H, 7.74. Found: C, 61.78; H, 7.74.

The infrared spectrum exhibited an absorption at 5.85 μ (carbonyl).

The 2,4-dinitrophenylhydrazone formed as a *bis* derivative in acidic medium and crystallized from pyridine as yellow needles, m.p. 240.0–240.5° (reported for the *bis* derivative of 1,4-cyclohexanedione,[18] 240°). Thus the material having m.p. 73–74° is *4,4-ethylenedioxycyclohexanone* (VI).[19] Dilute acid hydrolysis followed by sublimation gave 1,4-cyclohexanedione, m.p. 78–79° (lit.[20] 78°). An additional quantity (*ca.* 1 g.) of this substance was obtained as a forerun during a redistillation of the 119–125° (0.75 mm.) fraction described above, apparently existing as a contaminant in this fraction as a result of co-distillation as the pyrolysis of 2-carboxy-4,4-ethylenedioxycyclohexanone proceeded. The remainder of the material (37.0 g., 32%) crystallized upon cooling and was recrystallized from petroleum ether (60–68°) to give colorless needles, m.p. 52–53°. This substance gave a deep purple color with alcoholic ferric chloride and a negative Fehling's reaction and was identified by mixed melting point as 2-carbethoxy-4,4-ethylenedioxycyclohexanone (V).[21] A sample of V was hydrolyzed by warming a 6*N* hydrochloric acid solution (containing some methanol) of the substance on a steam bath for 5 min. The product, 2-carbethoxy-1,4-cyclohexanedione, was isolated by dilution with water and extraction with ether. The liquid obtained upon evaporation of solvent was not purified but was treated directly with an excess of phenylhydrazine in alcohol solution. A dark red solid formed after 30 min. on the steam bath. Recrystallization from *n*-propyl alcohol or, better, from butyrolactone gave dark red needles, m.p. 243.0–243.5°.

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.15; H, 5.10; N, 17.7. Found: C, 72.21; H, 5.26; N, 17.7.

The infrared absorption spectrum exhibited bands at 2.90 and 3.06 μ characteristic of N—H stretching and one at 6.02 μ (carbonyl). The latter is identical in position with that observed in the spectrum of the pyrazolone of 2-carbethoxycyclohexanone. The ultraviolet spectrum (alcohol) showed λ_{max} 253 mμ, ε 21,900 and λ_{max} 450 mμ, ε 49,800. A sample of this substance (0.28 g.) was hydrolyzed by refluxing for 14 hr. in 12 ml. of constant-boiling hydrochloric acid. A mixture of products resulted which, although not yet resolved, gave a strong positive ferric chloride color reaction. The red derivative is tentatively formulated as XII.

(*b*) *Using freshly dispersed sodium.* The procedure and quantities of reagents used were identical with those described in the above reaction except that the sodium was freshly dispersed at *ca.* 12,000 r.p.m. The product was isolated in the same manner but in this case gas evolution was more vigorous and continued throughout the distillation. There was obtained 9.4 g. (11.8%) of VI and 17.6 g. (15.1%) of V. A substantial non-distillable pot residue remained. The small accumulated residue from recrystallizations resulting in the isolation of V and VI gave a positive Fehling's reaction, suggesting that at least trace quantities of an acyloin were formed in the reaction. However, no other pure substance could be isolated.

(c) *Using sodium-ammonia.* To a solution of 13.5 g. (0.590 atom) of sodium in 1 l. of liquid ammonia (purified nitrogen) was added a solution of 32.4 g. (0.118 mole) of III in 200 ml. of anhydrous ether during 7 hr. The reaction mixture was stirred and maintained under a slight positive pressure of nitrogen during the entire operation. Ammonia was allowed to evaporate and the residue was treated with 40 g. of acetic acid in 200 ml. of ether. The mixture was then filtered, the filtrate washed with water and processed in the usual manner. Distillation of the small residue remaining upon evaporation of ether afforded two fractions, (*a*) 1.2 g., b.p. 101–118° (0.3 mm.) and (*b*) 0.4 g., b.p. 130–165° (0.3–0.5 mm.). The non-distillable residue weighed 0.8 g. Fraction (*a*) crystallized upon seeding with VI and was shown to be identical with it by mixed melting point. Fraction (*b*) crystallized upon trituration with petroleum ether and was recrystallized from ethyl acetate cyclohexane, m.p. 117–118°. This substance gave no color with alcoholic ferric chloride but reacted with Fehling's reagent. Its quantity was insufficient to permit a structure proof.

Anal. Found: C, 54.58; H, 7.55.

Reaction of the lactone of ethyl γ-hydroxypimelate (IX) *under acyloin conditions.* Following procedures described above, 98.0 g. (0.527 mole) of IX was added to 180 g. (3.13 atoms) of a 40% sodium-xylene dispersion (diluted with 1 l. of xylene) over a 65-hr. period. Processing in the usual manner, followed by distillation of the product through a short path system, gave 8.0 g. (7%) of colorless *2-carbethoxy-4-hydroxycyclohexanone* (X), b.p. 113–118° (0.15 mm.) in a short path system, n_D^{25} 1.4920. The distillation of this material was invariably accompanied by some decomposition leaving a colorless non-distillable residue. An experiment using freshly dispersed sodium gave essentially the same results.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C 57.74; H, 7.31.

This substance developed a deep purple color in alcoholic ferric chloride solution. The infrared spectrum possessed a strong band at 2.9 μ (hydroxyl) and two at 5.6–5.9 μ and 6.0–6.2 μ characteristic of β-dicarbonyl compounds capable of enolization.[22]

An alternative preparation of X under more conventional Dieckmann reaction conditions proceeded as follows. Sodium *t*-butylate was prepared by the addition of *t*-butyl

(17) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, 61, 1057 (1939).

(18) W. Borsche, M. Wagner-Roemich, and J. Barthenheier, *Ann.*, 550, 160 (1942).

(19) The isolation of this structure from the attempted acyloin condensation of III has recently been effected.[4] We are grateful to Professor Leonard for informing us of this prior to publication.

(20) F. Feist, *Ber.*, 28, 738 (1895).

(21) This substance was previously reported as a liquid.[16] It crystallized upon standing and was found to be identical with the product described here.

(22) N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Peterson, *J. Am. Chem. Soc.*, 74, 4070 (1952).

alcohol to a xylene (1 l.) dispersion containing 19.6 g. (0.85 atom) of sodium. A solution of 68.0 g. (0.370 mole) of IX in 200 ml. of xylene was added (30 hr.) to the dispersion by use of the high-dilution assembly described above. The entire operation was conducted in an atmosphere of nitrogen. The reflux temperature was maintained at 125–135° by continuous distillation of lower boiling materials. Reflux was continued for 1 hr. after addition was complete and the mixture was then processed as were the acyloin mixtures described above. Distillation of the product was accompanied by gas evolution and all material distilling below 225° (0.2 mm.) was collected. Redistillation through a short path system afforded 9.00 g. (13.2%) of 2-carbethoxy-4-hydroxycyclohexanone (VII), b.p. 115–120° (0.2 mm.). A certain degree of superheating was unavoidable due to the nature of the system and, as described above, the use of more conventional systems permitting liquid-vapor equilibration resulted in prohibitive polymerization. The infrared spectrum of this material was identical with that described above.

The reaction of X with excess phenylhydrazine in alcohol solution gave a red derivative identical with that (XII) formed from 2-carbethoxy-1,4-cyclohexanedione, m.p. and mixed m.p., 243.0–243.5°. The mother liquors were cooled to 0° whereupon a second derivative crystallized. Recrystallization from water gave colorless needles, m.p. 216–217° (after apparently losing solvent at 70–75°). A sample dried at 100° (0.2 mm.) lost 50% of its weight during drying.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.2. Found: C, 67.90; H, 6.36; N, 12.3.

That this derivative is the pyrazolone rather than the phenylhydrazone-lactone was established by examination of its infrared spectrum. It exhibited, in addition to absorption at 2.9 μ attributable to hydroxyl, a band in the 6.05–6.30 μ region, characteristic of pyrazolone derivatives and due to carbonyl absorption. An attempted preparation of the 3,5-dinitrobenzoate of X yielded only ethyl 3,5-dinitrobenzoate, identified by mixed melting point and white solid which was extremely slightly soluble in common solvents and considered to be polymeric.

Reaction of 1,4-cyclohexanedione with phenylhydrazine. 1,4-Cyclohexanedione (1.1 g.) was prepared by the acid hydrolysis of 2.0 g. of 4,4-ethylenedioxycyclohexanone (VI). The crude product was used without purification. It gave a 91% yield of the bisphenylhydrazone, m.p. 148–149° (lit.[23] 150°), during a reaction time of 1 hr. in an alcoholic solution containing excess phenylhydrazine. Longer reaction times did not afford any other product.

Reaction of 4-hydroxycyclohexanone with phenylhydrazine. 4-Hydroxycyclohexanone was prepared from VI. A solution of 3.00 g. of VI in 15 ml. of methanol was reduced by the portion-wise addition of 0.38 g. of sodium borohydride. Acidification followed by isolation by ether extraction gave 1.01 g. of crude product. A solution comprised of 0.60 g. of this material and 1.62 g. of phenylhydrazone in 10 ml. of acetic acid was warmed on the steam bath. Solid began to crystallize almost immediately (presumably the normal derivative) and an additional 15 ml. of acetic acid and 5 ml. of ethanol were added. After 3 hr. under reflux, the dark red solution was concentrated under reduced pressure to *ca.* 6 ml. and diluted with sufficient water to produce clouding. Cooling and scratching induced crystallization. The mixture was filtered and the semi-solid washed with cold ether. Crystallization from methanol-water gave 0.31 g. of tan solid, m.p. 144–146°. Further crystallization from ethyl acetate-petroleum ether (60–68°) gave pure 4-hydroxy-2,3,4,5-tetrahydrocarbazole (XIII), m.p. 148.5–149.5°.

Anal. Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.09; N, 7.51.

A mixed melting point of this substance with the bisphenylhydrazone of 1,4-cyclohexanedione (m.p. 150°) was depressed to 120°. The infrared spectrum exhibited strong absorption at 3.0 μ (NH, OH). The ultraviolet absorption spectrum showed λ_{max} 227 mμ, ϵ 40,200, λ_{max} 282 mμ, ϵ 6,740, and λ_{max} 290 mμ, ϵ 6,270. These values are very close to those recorded for 3-indoleacetic acid.[24]

Acknowledgment. We are grateful to Research Corporation for the financial support of this work.

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(24) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc. New York, N. Y., 1951, curve 193.

[CONTRIBUTION FROM THE CHEMICALS AND PLASTICS DIVISION, QUARTERMASTER RESEARCH AND DEVELOPMENT CENTER]

DDT Synergists. The Synthesis and Properties of Some 2,2-Difluoro-1,1-diarylethanols and 2-Fluoro-1,1-diarylethenes

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Received April 29, 1957

A number of 2,2-difluoro-1,1-diarylethanols have been prepared by treatment of ethyl difluoroacetate with aryl Grignard reagents. These alcohols were reduced to the corresponding ethanes, which, in turn, were dehydrofluorinated to yield a series of 2-fluoro-1,1-diarylethenes. Some preliminary results of a study of the insecticidal power and of the synergistic activity of these compounds with DDT are reported.

In connection with studies on synergism of DDT, we undertook the preparation of a number of diarylethanols containing fluorine in the ethane moiety. While this program was in progress, Kaluszyner and coworkers[2,3] reported the preparation of a number of 2,2,2-trifluoro-1,1-diarylethanols from the reaction of aryl Grignard reagents with ethyl trifluoroacetate. This paper summarizes the results obtained in this laboratory from the treat-

(1) Inquiries should be addressed to this author at Department of Chemistry, Boston College, Chestnut Hill, Mass.

(2) A. Kaluszyner, S. Reuter, and E. D. Bergmann, *J. Am. Chem. Soc.*, 77, 4164 (1955).

(3) R. Mechoulam, S. Cohen, and A. Kaluszyner, *J. Org. Chem.*, 21, 801 (1956).

TABLE I

2,2-DIFLUORO-1,1-DIARYLETHANOLS $Ar_2C(OH)CHF_2$

Ar	B.P., °C.	Mm.	Yield, %	Formula	Color with Concd. H_2SO_4	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl[a]	110–111	0.15	64	$C_{14}H_{12}F_2O$	Orange	71.78	72.1	5.17	5.1
p-Fluorophenyl[b]	99–100	0.05	43	$C_{14}H_{10}F_4O$	Red-orange	62.23	62.5	3.73	3.7
p-Chlorophenyl[c]	130–136	0.20	53	$C_{14}H_{10}Cl_2F_2O$	Cherry-red	55.47	55.63	3.33	3.47[d]
p-Bromophenyl[e]	153–164	0.17	40[f]	$C_{14}H_{10}Br_2F_2O$	Red	42.88	42.9	2.57	2.4[g]

[a] n_D^{25} 1.5593. [b] n_D^{24} 1.5276. [c] n_D^{20} 1.5780. [d] Calcd.: Cl, 23.40. Found: Cl, 23.94. [e] $n_D^{26.5}$ 1.6039. The compound crystallized in the form of thick prisms after standing six months, m.p. 54.5–56.0°. [f] A large amount of tarry residue was obtained on distillation of the crude material. [g] Calcd.: Br, 40.77. Found: Br, 40.5.

TABLE II

2,2-DIFLUORO-1,1-DIARYLETHYL ACETATES $Ar_2C(OCOCH_3)CHF_2$

Ar	M.P., °C.	Recryst. Solvent	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	51.0–52.0	Methanol	80	$C_{16}H_{14}F_2O_2$	69.55	69.6	5.11	5.1
p-Fluorophenyl[a]	...	...	89	$C_{16}H_{12}F_4O_2$	61.53	61.8	3.87	3.9
p-Chlorophenyl	86.0–86.8	Pet. ether	82	$C_{16}H_{12}Cl_2F_2O_2$	55.67	55.8	3.50	3.3
p-Bromophenyl	80.0–80.5	Methanol-water	86	$C_{16}H_{12}Br_2F_2O_2$	44.25	44.3	2.79	2.9[b]

[a] Resisted all attempts to induce crystallization; isolated as very viscous oil by molecular distillation at 80° and 0.1 mm., n_D^{25} 1.5158. [b] Calcd.: Br, 36.80. Found: Br, 36.8.

ment of ethyl difluoroacetate with various arylmagnesium bromides.

Phenylmagnesium bromide and its derivatives carrying either chlorine, bromine, or fluorine in the *p*-position reacted readily at 0° with ethyl difluoroacetate to yield the expected 2,2-difluoro-1,1-diarylethanols, $Ar_2C(OH)CHF_2$. As Table I shows, the yields of the ethanols varied from 40 to 64%, depending upon the substituent in the aromatic ring. The yields were lowered when the reaction was carried out at room temperature or above. All of the tertiary alcohols were isolated as colorless or faintly straw-colored, high-boiling, viscous oils; only the *p*-bromo compound crystallized. The ethanols gave characteristic colors with concentrated sulfuric acid and displayed the typical O-H stretching band at 3590 cm.$^{-1}$ in the infrared (carbon tetrachloride solution). The alcohols were further characterized by conversion to the acetates (Table II).

The ethanols were reduced to the corresponding ethanes in good yield (Table III) by heating under reflux for ten days with phosphorus and iodine in aqueous acetic acid.[4] It was interesting to note that the ethanes, unlike the ethanols, were rather mobile oils and all of them, except for 2,2-difluoro-1,1-bis-(*p*-fluorophenyl)ethane, crystallized readily. The ethanes, as expected, gave no coloration with concentrated sulfuric acid and their infrared spectra showed complete absence of hydroxyl.

The ethanes were converted smoothly to the corresponding 2-fluoro-1,1-diarylethenes (Table IV) when refluxed with 2% ethanolic potassium hydroxide. The clean-cut nature of this dehydrofluorination is interesting in view of the report[3] that treatment of 2,2,2-trifluoro-1,1-diarylethanes with ethanolic potassium hydroxide or sodium ethoxide results in alcoholysis of the trifluoromethyl group. All of the ethenes displayed very intense absorption in the infrared at 1630 cm.$^{-1}$ (carbon tetrachloride solution), indicative of the presence of $>C=C<$ conjugated with an aromatic ring.[5] Furthermore, these compounds gave positive tests with bromine in carbon tetrachloride and with potassium permanganate in water-acetone solution, whereas the ethane progenitors were completely unreactive toward these diagnostic reagents.

Dimroth and Bockemüller had previously described[6] the preparation of 2-fluoro-1,1-diphenylethene and claimed this compound was a solid melting at 93.5°. Our preparation, in contrast, is a mobile oil at room temperature and, moreover, as Table IV reveals, all of the *p*-halo substituted derivatives melt below 93.5°. These investigators prepared their sample of this ethene by dehydrofluorinating with ethanolic potassium hydroxide 1,2-difluoro-1,1-diphenylethane, which was claimed to have been formed by treating 1,1-diphenylethene with a mixture of lead tetraacetate and hydrogen fluoride in chloroform. The isolation of desoxybenzoin as a by-product from the latter reaction suggests that possibly the structure believed by Dimroth and Bockemüller to be 2-fluoro-1,1-di-

(4) F. A. Gunther and R. C. Blinn, *J. Am. Chem. Soc.*, 72, 4282 (1950).

(5) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 36.

(6) O. Dimroth and W. Bockemüller, *Ber.*, 64, 516 (1931).

TABLE III

2,2-DIFLUORO-1,1-DIARYLETHANES Ar_2CHCHF_2

Ar	M.P., °C.	Recryst. Solvent	Yield, %	B.P., °C.	Mm.	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	38.5–39.5	Ethanol	91	85	0.15	$C_{14}H_{12}F_2$	77.05	76.8	5.54	5.5
p-Fluorophenyl[a]	...	...	90	79–80	1.5[b]	$C_{14}H_{10}F_4$	66.14	66.6	3.97	4.0
p-Chlorophenyl	37.5–38.5	Methanol-water	90	110–118	0.08	$C_{14}H_{10}Cl_2F_2$	58.56	58.8	3.51	3.5[c]
p-Bromophenyl	42.0–42.8	Methanol	89	...	...	$C_{14}H_{10}Br_2F_2$	44.70	44.80	2.68	2.8[d]

[a] Could not be obtained crystalline. [b] n_D^{24} 1.5179. [c] Calcd.: Cl, 24.69. Found: Cl, 24.8. [d] Calcd.: Br, 42.48. Found: Br, 42.5.

TABLE IV

2-FLUORO-1,1-DIARYLETHENES $Ar_2C{=}CHF$

Ar	M.P., °C.	B.P., °C.	Mm.	Recryst. Solvent	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl[a]	...	77	0.05	...	91	$C_{14}H_{11}F$	84.82	85.1	5.59	5.7
p-Fluorophenyl	32–33	81–82	1.0[b]	Methanol	93	$C_{14}H_9F_3$	71.79	71.9	3.87	4.0
p-Chlorophenyl	78.0–79.5	...	...	Methanol	85	$C_{14}H_9Cl_2F$	62.91	62.9	3.39	3.4[c]
p-Bromophenyl	84.2–85.2	...	...	Methanol	85	$C_{14}H_9Br_2F$	47.20	47.0	2.55	2.4[d]

[a] Crystallizes in refrigerator, n_D^{25} 1.5872. [b] $n_D^{24.5}$ 1.5481. [c] Calcd.: Cl, 26.53. Found: Cl, 26.4. Calcd.: F, 7.11. Found: F, 6.96. [d] Calcd.: Br, 44.86. Found: Br, 44.7.

phenylethene is actually an isomer prepared by the dehydrofluorination of an unexpected rearranged product. Further support of the validity of our structure, in addition to the evidence cited above, was obtained by oxidizing the compound by chromic anhydride in acetic acid to benzophenone, isolated, in excellent yield, as the 2,4-dinitrophenylhydrazone.

EXPERIMENTAL[7]

The preparation of *2,2-difluoro-1,1-diphenylethanol* illustrates the general procedure used in obtaining the substituted ethanols. Freshly purified ethyl difluoroacetate (20.0 g., 0.16 mole), diluted with an equal volume of ether, was added with stirring in the course of 1 hr. to the ice-cold Grignard reagent prepared from 10.7 g. (0.44 g.-atom) of magnesium turnings and 69.0 g. (0.44 mole) of bromobenzene in 100 ml. of ether. Stirring and cooling in the ice-bath were maintained for 2 hr. after completion of the addition of the ester. The reaction mixture, after standing at room temperature overnight, was treated, while stirring and cooling, with saturated ammonium chloride, prepared by shaking 40 g. of the salt with 100 ml. of water. The yellow suspension was filtered with suction through a sintered-glass funnel, the filter cake was washed with ether, and the combined ethereal extract washed twice with water before being dried over sodium sulfate. Evaporation of the ether yielded a dark orange oil which was diluted with an equal volume of methanol and refrigerated at −35° for 2 days in order to allow the traces of biphenyl to crystallize. Filtration of the mixture followed by steam distillation of the filtrate (2 l. of distillate was collected and discarded) gave a product which was essentially free of starting material and derived products. The oily residue was dissolved in ether and dried over sodium sulfate. Removal of the solvent and distillation of the residue afforded 24.0 g. (64%) of the product, b.p. 110–111° at 0.15 mm., as a colorless oil.

The *2,2-difluoro-1,1-diarylethyl acetates* were prepared either by heating the alcohol with acetic anhydride in the presence of catalytic amounts of concentrated sulfuric acid[8] or by allowing the alcohol to stand at room temperature for several hours with a mixture of acetic acid-trifluoroacetic anhydride.[9] The products, isolated in the usual way, showed the characteristic carbonyl absorption band at 1750 cm.$^{-1}$ in carbon tetrachloride solution.

Reduction to *2,2-difluoro-1,1-diarylethanes* was effected by heating 8.0–10.0 g. of the appropriate alcohol under reflux for 10 days with a mixture of 3.5 g. of red phosphorus, 1.27 g. of iodine, 50 ml. of glacial acetic acid, and 1.0 ml. of water. The cooled reaction mixture was filtered with suction directly into a separatory funnel containing 300 ml. of 2.5% sodium bisulfite. The oily suspension was neutralized by adding portions of solid sodium bicarbonate with intermittent shaking and was then extracted with ether. The ether extract was dried over sodium sulfate after being washed with water. Removal of the ether and distillation of the residue *in vacuo* yielded a colorless, mobile oil, which spontaneously crystallized, except in the case of the *p*-fluoro compound.

General procedure for the preparation of 2-fluoro-1,1-diarylethenes. The substituted ethane (2.2 g.) was heated under reflux for 2.5 hr. with 60 ml. of 2% ethanolic potassium hydroxide. The solvent was removed under reduced pressure and the residue extracted with several portions of ether. The combined ethereal extract was washed with water and dried over magnesium sulfate. Removal of the ether afforded a colorless oil which was distilled at diminished pressure. Of this series, only 2-fluoro-1,1-diphenylethene could not be obtained crystalline at room temperature.

Oxidation of 2-fluoro-1,1-diphenylethene. A 281-mg. quantity of this compound was heated under reflux for 3 hr. with a mixture of 550 mg. of chromium trioxide, 15 ml. of glacial acetic acid, and 3 drops of water. The green solution was

(7) Melting points are corrected and boiling points are uncorrected. Infrared measurements were made using a Baird double beam recording spectrophotometer equipped with a sodium chloride prism. The majority of the elemental analyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass.

(8) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd. ed., D. C. Heath and Company, Boston, 1941, p. 397.

(9) J. M. Tedder, *Chem. Revs.*, **55**, 787 (1955).

poured onto cracked ice, 30 ml. of water was added, and the mixture was extracted twice with 50-ml. portions of ether. The combined extract was washed successively with water, 10% potassium carbonate (20 ml.), and water. After drying over sodium sulfate and evaporation of the ether the residue was dissolved in 8 ml. of ethanol and treated with 2,4-dinitrophenylhydrazine. Recrystallization of the precipitate from glacial acetic acid gave orange needles, m.p. 239–240° (recorded[10] m.p. 238–239°). A mixed melting point with an authentic specimen of benzophenone 2,4-dinitrophenylhydrazone showed no depression. The infrared spectra of the two samples (chloroform solution) were totally superimposable.

Biological results. In tests with house flies, the ethanes carrying *p*-chloro- and *p*-bromo-substituents were the most active insecticides of the entire series of compounds; the corresponding ethanols were somewhat less active. None of the acetates and ethenes displayed significant insecticidal activity.

On the other hand, the *p*-chloro- and *p*-bromo-substituted ethanes, ethanols, and acetates proved to be excellent synergists for DDT in tests with DDT-resistant house flies. The synergistic activity of these compounds surpassed that of 1,1-bis(*p*-chlorophenyl)ethanol (DMC), one of the most effective DDT synergists.[11] The ethenes were less effective. A detailed report of this study will be published elsewhere.

NATICK, MASS.

(10) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, Order I, John Wiley and Sons, Inc., New York, 1941, p. 363.

(11) R. L. Metcalf, *Organic Insecticides, Their Chemistry and Mode of Action*, Interscience Publishers, Inc., New York, 1955, p. 368.

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL COMPANY]

Cupric Acetate Catalyzed Monocyanoethylation of Aromatic Amines

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Received April 11, 1957

Cupric acetate monohydrate has been shown to be a highly effective new catalyst for the monocyanoethylation of a variety of aromatic amines. Unlike other cyanoethylation catalysts, its action is not appreciably inhibited by the presence of *ortho*- or *N*-substituents on the amines to be cyanoethylated. Also, its use leads to improved yields and shorter reaction times than obtained with conventional catalysts.

Cyanoethylation of 17 aromatic amines with cupric acetate catalyst is reported, and some observations are made on the relative influence of steric and electronic effects of the substituent groups upon the mechanism of the reaction, the reaction conditions required, and yields and nature of the products obtained.

The reaction of acrylonitrile with compounds containing active hydrogen atoms has been widely investigated.[1,2] While primary and secondary aliphatic amines react readily with acrylonitrile in the absence of catalysts to give high yields of 3-aminopropionitriles, some heterocyclic amines (carbazole, indole, pyrrole) react only in the presence of basic catalysts.[1] Aniline, however, does not react with acrylonitrile in the absence of catalysts,[3] and early investigators reported that aniline does not undergo cyanoethylation even in the presence of basic catalysts.[3,4] The cyanoethylation of a variety of aromatic amines is reported, however, to proceed readily with acid catalysts, particularly acetic acid.[4,5,6] It has also been shown that copper salts, particularly cuprous chloride, have a beneficial effect when employed in conjunction with acetic acid.[6,7,8] Also reported is cyanoethylation of aromatic amines in the presence of acetic anhydride,[9] aniline salts,[10] and by the exchange reaction of an aromatic amine hydrochloride with 3-diethylaminopropionitrile.[11]

This last reaction has been considered to occur *via* an S_N2 reaction involving attack of the arylamino nitrogen upon the β-carbon of the cyanoethyl group rather than an S_N1 elimination-addition reaction.[11c]

Pietra[12] has recently disclosed that good yields

(1) H. A. Bruson, *Org. Reactions*, **V**, 79 (1949).

(2) American Cyanamid Company, *The Chemistry of Acrylonitrile*, Beacon Press, Inc., New York, 1951.

(3) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

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(7) (a) P. A. S. Smith and T. Y. Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952). (b) W. S. Johnson and W. DeAcetis, *J. Am. Chem. Soc.*, **75**, 2766 (1953).

(8) (a) British Patent **404,744**, to I. G. Farbenindustrie, (1933). (b) British Patent **457,621**, to I. G. Farbenindustrie, (1936).

(9) A. P. Terentev, A. N. Kost, and V. M. Potapov, *J. Gen. Chem.* (*USSR*), **18**, 82 (1948).

(10) A. F. Bekhli and A. G. Serebrennikov, *J. Gen. Chem.* (*USSR*), **19**, 1553 (1949).

(11) (a) L. Bauer, J. Cymerman, and W. J. Sheldon, *J. Chem. Soc.*, 3312 (1951). (b) R. J. Bates and J. Cymerman-Craig, *J. Chem. Soc.*, 1153 (1954). (c) J. Cymerman-Craig, M. Moyle, J. C. Nicholson, and R. L. Werner, *J. Chem. Soc.*, 3658 (1955). (d) R. J. Bates, J. Cymerman-Craig, M. Moyle, and R. J. Young, *J. Chem. Soc.*, 388 (1956). (e) J. Cymerman-Craig and M. Moyle, *Org. Syntheses*, **36**, 6 (1956).

(12) S. Pietra, *Gazz. chim. ital.*, **86**, 70 (1956).

of arylaminopropionitriles can be obtained by the base(choline)-catalyzed reaction of acrylonitrile and certain substituted aromatic amines. This is the first report of a base-catalyzed cyanoethylation of an aromatic amine, and is particularly interesting in light of the amines employed, the majority of which are substituted with electronegative groups (NO_2, Cl) and have not been reported to undergo acid-catalyzed cyanoethylations.

During preparation of a series of arylaminopropionitriles in these laboratories, most of the previously mentioned acidic catalysts were ineffective in producing consistently good yields of monocyanoethylated aromatic amines. Two major problems were observed. First, the acetic acid catalyst was not sufficiently active to produce acceptable yields of cyanoethylated derivatives from sterically hindered (*ortho*-substituted) or deactivated (negatively-substituted) aromatic amines even when employed in large excess and at high temperatures for long periods of time.[6a] This difficulty is shared by the Cymerman-Craig exchange reaction between an aniline hydrochloride and diethylaminopropionitrile.[11d] Second, while the addition of cuprous chloride to acetic acid considerably enhanced its catalytic activity, it frequently produced undesired mixtures of mono- and dicyanoethylated derivatives, even when the acrylonitrile was not employed in excess. Thus, the need for a catalyst capable of giving consistently good yields of monocyanoethylated product from all types of substituted aromatic amines remained.

It was observed in these laboratories that addition of sodium acetate to the acetic acid-cuprous chloride mixture caused an improvement in yield over that obtained by either acetic acid or the acetic acid-cuprous chloride catalyst. This was particularly apparent in the case of the less reactive aromatic amines and may be illustrated by two experiments with *o*-chloroaniline in a bomb at 150° for 12 hr.: With acetic acid (7.1%) plus cuprous chloride (0.4%) catalyst, a 14% yield of 3-(*o*-chloroanilino)propionitrile resulted, while with a catalyst containing acetic acid (7.1%), cuprous chloride (0.4%), and sodium acetate (2.0%) the yield of propionitrile was 39%.

It was also found that replacement of the acetic acid/cuprous chloride/sodium acetate system by cupric acetate monohydrate provided still further improvements, and that this salt was, in fact, a highly effective catalyst of general utility for monocyanoethylation of a wide variety of aromatic amines. The cupric acetate employed throughout this work was in the form of the monohydrate, a readily available commercial product. It was demonstrated, however, that anhydrous cupric acetate was identical with the monohydrate in catalytic activity. As the utility of copper salts in the cyanoethylation of aromatic amines had previously been mentioned,[1,6,7,8] it was of interest to determine whether other copper salts would serve as cyanoethylation catalysts in the absence of acetic acid.[13] The catalytic activity of several salts in the cyanoethylation of aniline (at 100° for 1.5 hr.) was compared, using 0.025 mole of catalyst per mole of aniline. Cupric acetate monohydrate gave a 73% yield of 3-anilinopropionitrile, cuprous chloride gave 52%, while cupric sulfate, copper powder, cupric oxalate, cupric borate, and acetic acid alone were completely ineffective at this concentration. Sodium acetate, effective in improving yields when added to acetic acid-cuprous chloride mixtures, had no catalytic activity when used alone, nor did polyphosphoric acid or stannic chloride. It is thus apparent that cupric acetate possesses a high order of catalytic activity, shared only by cuprous chloride among the copper salts tested, and then to a lesser degree. A combination of 0.025 mole each of cuprous chloride and acetic acid gave a slightly improved (61%) yield of the monopropionitrile.

Summarized in Table I are the results obtained from cyanoethylation of 17 anilines of various structures with from 2 to 5% (by weight of the amine) of cupric acetate as catalyst.

Several major advantages are obtained from the use of cupric acetate as a cyanoethylation catalyst for aromatic amines. Foremost is the observed activity of the catalyst with both sterically hindered and certain negatively-substituted anilines. Thus *ortho* substituents on the aromatic nucleus do not reduce the activity of this catalyst as they do with other methods of carrying out the cyanoethylation of aromatic amines. This is shown by the results obtained with three isomeric chloroanilines and *ortho* and *meta*-toluidine (Table I). Steric interference by a bulky substituent attached to the amino nitrogen appears to be of only minor importance since *N*-*n*-butylaniline gave a 68% yield of the cyanoethylated derivative with cupric acetate catalyst. Ready cyanoethylation of the chloroanilines, *p*-bromoaniline and *m*-nitroaniline in good yields with cupric acetate demonstrates the ability of the catalyst to promote cyanoethylation of even some negatively-substituted anilines, although the *ortho* and *para*-nitroanilines failed to react to any appreciable extent.

A further advantage of this new catalyst is its ability to promote monocyanoethylation as the primary and in most instances, exclusive reaction. It was shown, however, that under vigorous conditions (excess acrylonitrile, 10% cupric acetate and 12 hr. at reflux) dicyanoethylation of aniline did occur to the extent of 32%. Thus, while cupric acetate is not a selective catalyst for monocyanoethylation, under ordinary reaction conditions employing equimolar quantities of acrylonitrile and

(13) The reported value of copper salts in promoting cyanoethylation of aromatic amines has, with the possible exception of cuprous chloride, always been in conjunction with acetic acid.[1,6,7,8] Their mode of action was originally ascribed to functioning as polymerization inhibitors,[1,8] a claim not supported by our work.

TABLE I

CYANOETHYLATION OF AROMATIC AMINES WITH CUPRIC ACETATE CATALYST

Amine	Catalyst, %	Time, hr.	Yield,[a] %	B.P., °C./mm.	n_D^{25}	M.P.,[b] °C.
Aniline	2.0	1.0	73	114–116/0.3	1.5632	52–53[c]
o-Chloroaniline	3.9	3.0	62	139–141/0.3[d]	1.5734	—
m-Chloroaniline	5.0	2.0	65	146–149/0.3	1.5785	48–49[e]
p-Chloroaniline	5.0	1.25	78	168–169/1.0	—	73.5–75[f]
p-Bromoaniline	5.0	1.0	96	—	—	96.5–97.5[g]
o-Toluidine	4.9	1.5	62	139–140/1.0[h]	1.5590	—
m-Toluidine	4.7	0.33	71	143–146/0.5	—	49.5–50.5[i]
Amylaniline[j]	3.1	3.0	66	172–180/0.8	1.5332	—
Dodecylaniline[k]	3.4	3.0	64	197–202/0.3	1.5167	—
o-Nitroaniline	7.2	12.0	—	—	—	—
m-Nitroaniline	5.0	12.0	81	—	—	95–96[l]
p-Nitroaniline	5.0	6.0	—	—	—	—
	10.0	12.0	<10	—	—	121–123[m]
N-*n*-Butylaniline	3.4	5.0	68	145–148/0.7[n]	1.5360	—
α-Naphthylamine	3.5	5.5	89	180–210/0.5	—	69–70[o]
Benzidine	5.0	4.0	93[p]	—	—	—
4,4′-Methylenedianiline	5.0	3.0	96	—	—	115–117[q]
o-Phenylenediamine	4.6	14.0	63	—	—	115–118[r]
m-Phenylenediamine	5.0	0.67	95[s]	—	—	—

[a] Runs at 100° or reflux. Yield of monocyanoethyl derivative based on distilled liquids or crude, nondistillable products. [b] Uncorrected. [c] Reported m.p. 51.5°.[4] [d] Calcd. for $C_9H_9ClN_2$: C, 59.9; H, 5.0; N, 15.5. Found: C, 60.1; H, 4.9; N, 15.5. [e] Reported m.p. 48°.[10] [f] Reported m.p. 74.5–75.5°.[6b] [g] Calcd. for $C_9H_9BrN_2$: C, 48.0; H, 4.0; N, 12.5. Found: C, 48.1; H, 4.2; N, 12.3. [h] Reported b.p. 120–121°/0.7 mm., n_D^{26} 1.5530.[11d] [i] Reported m.p. 47.5–48.5°.[6a] [j] Commercial alkylaniline, average C_5. [k] Commercial alkylaniline, average C_{12}. [l] Reported m.p. 97.5°[6c], also reported m.p. 135.5°.[12] [m] Crude. Reported m.p. 128–130°.[6b] [n] Calcd. for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0; N, 13.9. Found: C, 77.4; H, 9.0; N, 13.5. [o] Reported m.p. 70–71°.[6b] [p] Crude. Reported m.p. 245–245.5°.[6b] [q] Calcd. for $C_{19}H_{20}N_4$: C, 75.0; H, 6.6; N, 18.4. Found: C, 74.6 H, 6.8 N, 18.4. [r] Reported m.p. 118.5–119°.[6b] [s] Crude product. Calcd. for $C_{12}H_{14}N_4$: C, 67.3; H, 6.6; N, 26.1. Found: C, 66.7; H, 6.5; N, 25.2.

the amine, dicyanoethyl derivatives are not formed. This contrasts with the action of cuprous chloride which appears to favor dicyanoethylation in the majority of cases.[6b,7]

Finally, cupric acetate promotes rapid reactions, frequently observed to be exothermic, and in most cases produces higher yields of the monocyanoethylated products than have been previously reported. Formation of by-product acetanilide, sometimes reported to occur with acetic acid or acetic acid-cuprous chloride catalysts,[6a,6b] has not been observed.

In addition to the cupric acetate catalyzed cyanoethylations of aromatic amines in Table I, a number of additional cyanoethylations using catalytic amounts of acetic acid as catalyst have been carried out and are summarized in Table II. In these cases, good yields were usually obtained by refluxing the reactants for from 12 to 24 hr. Included in this table are three isomeric hydroxyanilines whose reaction with acrylonitrile has not previously been reported. That cyanoethylation of the amino group occurs in preference to the hydroxy group in the presence of acidic catalysts was shown by spectroscopic examination of the propionitriles obtained. All showed marked cyano absorption at 2220–2230 cm.$^{-1}$ and phenolic hydroxyl at 1240–1280 cm.$^{-1}$ Confirming the phenolic hydroxyl, the ultraviolet spectrum of the product from cyanoethylation of *o*-hydroxyaniline (0.01% in ethanol) showed a characteristic maximum at 292 mμ. Addition of sodium hydroxide to the solution caused a shift in this maximum to 305 mμ, as expected if phenolic hydroxyl were present.

From our work and a review of the literature on the cyanoethylation of aromatic amines, certain conclusions may be drawn. Cyanoethylation of activated anilines (*e.g.* with electron-donating substituents) is readily accomplished with acid catalysts such as acetic acid. Sterically hindered anilines (those with *ortho* or *N*-substituents) react less readily and require catalysis with cuprous chloride-acetic acid mixtures, or, preferably, cupric acetate. Negatively substituted anilines, on the other hand, may require either acidic or basic catalysts, depending upon the location of the substituent groups. *meta*-Nitroaniline cyanoethylates readily with cupric acetate or other acidic catalysts,[6b,6c] whereas *ortho* and *para*-nitroanilines react with acrylonitrile to a limited extent or not at all in the presence of acids. By the choline-catalyzed method of Pietra, this order of reactivity is reversed,[14] suggesting that the basic strength of the aniline is the major factor determining whether acidic or basic

(14) A discrepancy in melting points for 3-(*m*-nitroanilino)propionitrile exists: Braunholtz and Mann report the melting point of the acid-catalyzed addition product as 97.5°,[6c] while Pietra reports 135.5° for the product from the base-catalyzed reaction.[12] Use of cupric acetate gave a product, m.p. 95–96° (Table I), whose infrared spectrum showed CN absorption at 2240 cm.$^{-1}$ and an NH band at 3260 cm.$^{-1}$

TABLE II

CYANOETHYLATION OF AROMATIC AMINES WITH ACETIC ACID CATALYST[a]

Amine	Catalyst, %	Time, hr.	Yield,[b] %	B.P., °C./mm.	n_D^{25}	M.P.,[c] °C.
p-Toluidine[d]	7.0	12	56	148–155/1.0	—	103.5–105[e]
o-Ethylaniline	8.2	12	53	125–132/0.3[f]	1.5529	—
N-Methylaniline	12.5	22	84	170–171/19[g]	1.5590	—
N-Ethylaniline	9.1	19	52	172–176/19[h]	1.5511	—
o-Anisidine	8.1	18	33	140–141/1.0[i]	1.5599	—
p-Anisidine	20.3	15	84[j]	154–155/0.8[k]	—	59–61[l]
o-Phenetidine	7.3	22	45	141–143/0.7[m]	1.5476	—
p-Phenetidine	8.5	22	90	165–166/0.7	—	73–75[n]
o-Hydroxyaniline	12.0	24	78	—	—	110–111[o]
m-Hydroxyaniline	9.2	24	69[p]	—	1.573	—
p-Hydroxyaniline	12.2	24	22	—	—	86–88[q]
o-Aminobiphenyl	10.0	12	56	180–185/1.0	1.6021	85–86.5[r]

[a] Reactions run at reflux unless specified otherwise. [b] Yields of monocyanoethyl derivative based on distilled products. [c] Uncorrected. [d] 0.7% CuCl and 2.1% sodium acetate used as additional catalysts at 150°. 36% dipropionitrile, m.p. 61–62°, also obtained. Reported m.p. 62°.[6a] [e] Reported m.p. 103–104°.[6a] [f] Run at 150°. Calcd. for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.4; H, 8.0; N, 15.7. [g] Reported b.p. 175–177°/20 mm.[3] [h] Reported b.p. 126–127°/0.5 mm. n_D^{24} 1.5505.[11d] [i] Reported b.p. 165–167°/0.6 mm., n_D^{24} 1.5600.[11d] [j] Also obtained 14% of dipropionitrile, b.p. 210–212°/0.7 mm., m.p. 100–101°. Reported m.p. 100–101°.[6a] [k] Reported b.p. 247°/0.7 mm.[5] This boiling point reported by Elderfield for the monopropionitrile is considerably higher than that found for the authentic dipropionitrile (see *j* above). [l] Reported m.p. 62–64°.[11c] [m] Calcd. for $C_{11}H_{14}N_2O$: C, 69.4; H, 7.4; N, 14.7. Found: C, 69.8; H, 7.5; N, 14.4. [n] Reported m.p. 75–76°.[11d] [o] Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.8; H, 6.3; N, 16.5. [p] Crude, noncrystalline product. [q] Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.7; H, 6.7; N, 16.9. Low yield was due to high losses in crystallization. [r] Run at 150°. Reported m.p. 86°.[6b]

catalysis is required. Basic catalysts undoubtedly function by removal of a proton from the aniline and subsequent attack of the anion upon the β-carbon atom of acrylonitrile. Acid catalysts, on the other hand, probably operate through the cyano group or the acrylonitrile and promote the development of an electron deficiency upon the β-carbon atom.

While the actual role the copper catalysts play in the cyanoethylation of aromatic amines has not been experimentally established, it is undoubtedly associated with the well-known activity of cupric and cuprous ions in complex formation, since both the amino group of the aniline and the cyano group of acrylonitrile are capable of forming complexes with these ions. The relative efficiency of the acetate compared with other salts of copper is probably due mainly to its greater solubility in the reaction mixture. Use of other known complexing agents as catalysts for cyanoethylation reactions is being investigated, as is use of cupric acetate in other reactions known to be catalyzed by copper salts.

EXPERIMENTAL

The catalyst employed in Table I was commercially available cupric acetate monohydrate, used without further treatment. The acrylonitrile was a commercially available grade containing 35 p.p.m. hydroquinone monomethyl ether as inhibitor, and was ordinarily employed in from equimolar quantities with the amine to a 2 to 1 excess with relatively little influence upon the yields observed. In most runs, 0.5 to 2% of hydroquinone was added as additional inhibitor. The cyanoethylated products were isolated by direct vacuum distillation of the reaction mixtures, and subsequent recrystallization of solid products from 95% ethanol or ethanol–water mixtures. In all cases virtually quantitative recovery of the unreacted aromatic amine as lower boiling fraction was obtained. No evidence of acetanilide formation was observed. With anilines melting above 75°, dioxane was used as solvent and the products were isolated by pouring the reaction mixtures into water and recrystallizing the resulting solids. The reactions were usually carried out at the reflux temperature of the mixture or at 100–110°, whichever was lower. The addition of the catalyst initially or at the reflux temperature was observed to have no influence upon yields obtained. The cyanoethylation of aniline with cupric acetate monohydrate catalyst is exemplary of the general procedure employed.

3-Anilinopropionitrile. A 500-ml. three-necked flask equipped with a stirrer, reflux condenser, and thermometer was charged with 186 g. (2.0 moles) of aniline, 106 g. (2.0 moles) of acrylonitrile and 3.72 g. (2.0% by weight of aniline) of cupric acetate monohydrate. The contents were then heated to 95° when rapid refluxing of the acrylonitrile began. Heating was discontinued, and the exothermic reaction carried the temperature to 105° in 30 min. before refluxing ceased and the temperature began to drop. The mixture was then heated at 100° for an additional 30 min. Unchanged acrylonitrile and aniline were stripped off under reduced pressure and the 3-anilinopropionitrile distilled as a slightly yellow liquid, solidifying in the receiver. The distillate, 214 g. (73%), b.p. 114–116°/0.3 mm., gave large, colorless prisms, m.p. 52–53° from 95% ethanol. Reported m.p. 51.5°.

Cyanoethylations with acetic acid catalyst were carried out at reflux or occasionally in a stainless steel bomb at 150° as noted in Table II. An excess of 1.5 or 2 moles of acrylonitrile per mole of amine was usually employed, with recovery of the excess upon distillation. An example of this method is the cyanoethylation of *o*-phenetidine.

3-(o-Phenetidino)propionitrile. A mixture of 412 g. (3.0 moles) of *o*-phenetidine, 265 g. (5.0 moles) of acrylonitrile and 30 ml. of glacial acetic acid was refluxed for 22 hr. The unreacted acrylonitrile was removed under reduced pressure and the residue vacuum-distilled, collecting 220 g. of unchanged *o*-phenetidine, b.p. 84–90°/1.5 mm., and 256 g.

(45%) of colorless 3-(*o*-phenetidino)propionitrile, b.p. 141–143°/0.7 mm., n_D^{25} 1.5476. The analytical values are reported in Table II.

Acknowledgment. The author expresses appreciation for the analytical values obtained by E. M. Hubbard and his coworkers of these laboratories and for interpretation of the spectral data by D. R. Beasecker.

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[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH COLLEGE OF MEDICINE]

Convenient Synthesis for β-(3-Indolyl)-DL-Lactic Acids[1]

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Received March 25, 1957

A convenient synthesis o β-(3-indolyl)-, β-[3-(5-methoxyindolyl)]-, and β-[3-(5-benzyloxyindolyl)]-DL-lactic acids is described.

Many of the procedures used to synthesize α-hydroxy acids cannot be used with compounds containing an indole group because of the chemical reactivity of this nucleus toward acidic and oxidizing conditions. Thus, the usual methods which involve halogenation of β-substituted-α-carboxypropionic acids followed by decarboxylation and hydrolysis of the α-halo acids in the manner used for the preparation of β-phenyllactic acid,[2] or known conversions of α-amino acids to the α-hydroxy acids *via* the diazonium salt by treatment with nitrous acid,[3] nitrosyl bromide,[4] or silver nitrite[5] do not seem applicable as convenient preparative routes to indolelactic acids. Syntheses from the appropriately substituted aldehydes *via* the cyanohydrin as an intermediate[6] are precluded because of the difficulty of preparation and the instability of some indole-substituted acetaldehydes.[7]

β-(3-Indolyl)lactic acid, itself, appears to be the only indolelactic acid which has been prepared. This compound was first made by the biological conversion of L-tryptophan to β-(3-indolyl)-D-lactic acid by the mold *Oidium lactis*;[8] the racemic compound has been prepared from this product by racemization with alkali.[9,10] The completely synthetic approaches to indolelactic acid all have involved the use of indolepyruvic acid as an intermediate; it is readily converted to indolelactic acid by reduction with sodium amalgam.[9] The chemical instability of indolepyruvic acid itself[11,12] indicated that the use of substituted indolepyruvic acids as intermediates would be impractical unless they could be prepared readily and in good yield from available precursors. Consequently, a more direct route to indolelactic acid and substituted indolelactic acids was sought.

Tryptophan and some of its derivatives have been prepared conveniently by the condensation of gramine and substituted gramines with various aminomalonate derivatives using alkaline catalysis.[13,14] By analogy with this reaction, the condensation of gramine (I) with diethyl acetoxymalonate (II) was investigated and was found to proceed smoothly. Hydrolysis of the product (III) yielded β-(3-indolyl)-α-carboxy-α-hydroxypropionic acid (IV), which was decarboxylated to give indolelactic acid (V), in a yield of 52%, based on I.

With a similar sequence of reactions, 5-methoxyindolelactic acid (VI) was prepared from 5-methoxygramine (VII), and 5-benzyloxyindolelactic acid (VIII) from 5-benzyloxygramine (IX). 5-Hydroxyindolelactic acid (X), which is of interest as a possible metabolite of 5-hydroxytryptophan, was prepared by catalytic hydrogenation of VIII. It was not possible to obtain X crystalline, but paper chromatography showed the compound to be homogeneous and to have the expected properties.

The generality of this procedure for the preparation of other substituted lactic acids was

(1) Supported by research grants from the National Institutes of Health, U. S. Public Health Service.

(2) E. Fischer, *Ber.*, **37**, 3062 (1904); E. Fischer and G. Zemplén, *Ber.*, **42**, 4891 (1909).

(3) P. R. Shildneck, U. S. Patent 2,461,701 (Feb. 15, 1949); *Chem. Abstr.*, **43**, 3841 (1949).

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(6) P. Karrer, *Organic Chemistry*, 3rd ed., Elsevier Publishing Co., Inc., New York, N. Y., 1947, p. 152.

(7) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

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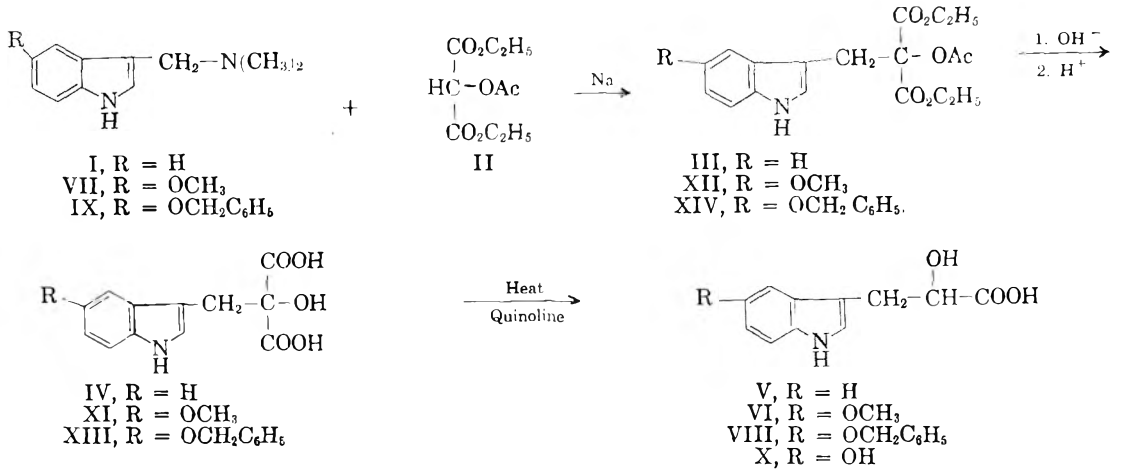

tested in an attempted synthesis of β-phenyllactic acid. The condensation of II with *N*,*N*-dimethylbenzylamine[15] (sodium as the condensing agent) followed by saponification of the crude product and decarboxylation (in quinoline) of the crude dicarboxylic acid afforded only a very small amount of phenyllactic acid. By using benzyl chloride[16] in place of the amine (sodium ethoxide as the condensing agent) some improvement in the yield of phenyllactic acid was observed, but it appears that the method, as it presently exists, is not satisfactory for the preparation of phenyllactic acid. An extensive study of the preparation of other lactic acids with this procedure was not conducted since most of them can be prepared more readily by other methods.

EXPERIMENTAL[17]

Diethyl acetoxymalonate (II).[18] A solution of 80 g. (0.5 mole) of diethyl malonate in 200 ml. of glacial acetic acid was placed in a 1-l. three-necked flask fitted with a stirrer, condenser, and an Erlenmeyer flask attached with a rubber sleeve, and was heated to 100° in an oil bath. To the hot solution was added, with stirring, 217.3 g. (0.49 mole) of lead tetraacetate in small portions (by means of the attached Erlenmeyer flask) at such a rate that a gentle reflux was maintained (20 min.). After the addition was completed, the mixture was maintained at 100–105° for 1.5 hr. The acetic acid was then removed by distillation *in vacuo*. To the resulting white pasty mass was added 300 ml. of water, and the mixture was extracted with ether (4 × 100 ml.). The combined ether extracts were washed successively with saturated sodium bicarbonate solution (4 × 100 ml.) and a 25% solution of sodium sulfate and dried over anhydrous sodium sulfate. The ether was removed and the residual yellow oil was distilled *in vacuo*. The yield of pure II was 69.2 g. (65% based on lead tetraacetate), b.p. 137–138°/17 mm., n_D^{30} 1.4200.

β-(3-Indolyl)-α-hydroxy-α-carboxypropionic acid (IV). A mixture of 17.42 g. (0.10 mole) of I, 32.73 g. (0.15 mole) of II, 0.07 g. (0.003 g.-atom) of sodium, and 150 ml. of toluene was heated at reflux temperature while a slow stream of nitrogen was bubbled through the solution. Completion of reaction, as indicated by the cessation of the evolution of dimethylamine (moist *p*H paper), required about 20 hr. The mixture was cooled, the unreacted sodium was removed, and the solution was poured into 300 ml. of water containing 15 ml. of concentrated hydrochloric acid. The mixture was extracted with ether (4 × 100 ml.), and the combined ether extracts were washed successively with a saturated solution of sodium bicarbonate and a 25% solution of sodium sulfate. The ether solution was dried over anhydrous sodium sulfate, and the solvent was removed by distillation; the residual amber-colored oil (47.2 g.) consisted of a mixture of II and III. Because extensive attempts to crystallize II were unsuccessful, the crude mixture was saponified in the following manner to yield IV. To the crude mixture of II and III was added a solution of 40 g. (1.0 mole) of sodium hydroxide in 200 ml. of water and 50 ml. of ethanol, and the mixture was heated at reflux temperature for 6.5 hr. The condenser was then set for distillation and 75 ml. of distillate was collected and discarded. The residual alkaline solution was cooled, extracted with ether (2 × 200 ml.) and acidified to *p*H 1 by the dropwise addition of cold dilute hydrochloric acid to the rapidly stirred ice-cold solution. The turbid solution was extracted with ethyl acetate (4 × 100 ml.), the combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* (bath temp. below 40°). The residual brown oil (28.4 g.) was mixed with 100 ml. of ethylene dichloride and crystallization was induced by scratching. The resulting slurry was cooled to room temperature and finally to −5° for several hours. The product was collected, washed with 50 ml. of cold ethylene dichloride and dried. The pink, rectangular prisms of IV amounted to 17.4 g. (70% based on I), m.p. 163–165° (dec.). The combined filtrate and ethylene dichloride washings from the first crop were concentrated to dryness *in vacuo*, but only 0.7 g. more of crude IV was obtained.

The 17.4 g. of IV was recrystallized from a mixture of 60 ml. of ethylene dichloride and 47 ml. of glacial acetic acid to yield pure IV; 11.3 g. (45% based on I), m.p. 163° (dec.). The mother liquor was reworked to yield an additional 2.0 g., m.p. 158° (dec.).

A sample recrystallized for analysis melted at 165° (dec.).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.08; H, 4.24; N, 5.45.

β-(3-Indolyl)-DL-lactic acid (V). A mixture of 2.49 g. (0.01 mole) of IV, 12.9 g. (0.10 mole) of quinoline (redistilled)[19] and 0.1 g. of copper powder was heated at 125° for 45 min. under a slow stream of nitrogen; the temperature was then raised to 145° and maintained for an additional hour. The resulting straw-colored solution was cooled,

(15) Compare with H. R. Snyder, E. L. Eliel, and R. E. Carnahan, *J. Am. Chem. Soc.*, **72**, 2958 (1950).

(16) Similar procedure used for preparation of diethyl benzylmalonate; *Org. Syntheses*, **Coll. Vol. III**, 705 (1955).

(17) All melting and boiling points are uncorrected.

(18) O. Dimroth and R. Schweizer, *Ber.*, **56**, 1380 (1923).

(19) Much lower yields are obtained if unpurified quinoline is used.

poured into 60 ml. of cold 2*N* hydrochloric acid, and the resulting solution was saturated with sodium sulfate and extracted with ethyl acetate (5 × 100 ml.). The combined ethyl acetate extracts were extracted with 5% sodium bicarbonate solution (6 × 25 ml.). The combined bicarbonate extracts were cooled in ice and acidified to *p*H 1.5 by the dropwise addition of cold 4*N* hydrochloric acid. The slurry that resulted was saturated with sodium sulfate and extracted with ethyl acetate (4 × 100 ml.). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to yield 1.82 g. (89%) of V, m.p. 140–144°. The crude product was recrystallized from 175 ml. of ethylene dichloride (Norite) to yield 1.54 g. (75% based on IV) of white, glistening plates, m.p. 146–147°, undepressed on admixture with authentic DL-indolelactic acid.[9]

β-[3-(5-Methoxyindolyl)]-α-hydroxy-α-carboxypropionic acid (XI). A mixture of 1.27 g. (0.006 mole) of VII[20] (m.p. 124–125°), 2.18 g. (0.01 mole) of II, a 1 mm.[3] piece of sodium and 15 ml. of toluene was heated at reflux temperature while a slow stream of nitrogen was bubbled through the solution until the evolution of dimethylamine had ceased (about 20 hr.). The mixture was cooled, unreacted sodium was removed, and the straw-colored solution was poured into 50 ml. of cold 0.25*N* hydrochloric acid. Treatment of the mixture in a manner similar to that described for the preparation of IV afforded 3.31 g. of crude XII. The crude ester was suspended in a solution of 3.0 g. (0.075 mole) of sodium hydroxide in 50 ml. of water and 15 ml. of ethanol and the mixture was heated under reflux for 6 hr. Treatment of the reaction mixture in a manner similar to that described for the preparation of IV afforded 2.17 g. of a yellow oil which crystallized upon manipulation after the addition of a small amount of ethylene dichloride. The crude product amounted to 1.83 g. (106% based on VII). Recrystallization from a mixture of 15 ml. of ethylene dichloride and 3 ml. of glacial acetic acid yielded 1.12 g. (65% based on VII) of XI, pink rectangular prisms, m.p. 152° (dec.).

A sample recrystallized for analysis melted at 154° (dec.).

Anal. Calcd. for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 55.85; H, 4.59; N, 5.24.

β-[3-(5-Methoxyindolyl]-DL-lactic acid (VI). A mixture of 1.23 g. (0.0044 mole) of XI, 12.9 g. (0.1 mole) of redistilled quinoline and 0.1 g. of copper powder was heated in an oil bath at 155° for 1 hr. while a stream of nitrogen was passed over the solution. The temperature was then gradually raised to 170° over a period of 30 min. (evolution of CO_2 ceased after the first hour of heating at 155°). Treatment of the resulting straw-colored reaction mixture in a manner similar to that described for the preparation of V afforded a yellow oil which crystallized after the addition of a few drops of ethylene dichloride followed by scratching. The crude, tan-colored solid was collected and dried; yield, 0.74 g. (72%), m.p. 126–128°. Recrystallization from a mixture of 8 ml. of ethylene dichloride and 1 ml. of glacial acetic acid afforded 0.59 g. of light buff-colored rectangular prisms of VI, m.p. 128–129°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.70; H, 5.72; N, 5.80.

β-[3-(5-Benzyloxyindolyl)]-α-hydroxy-α-carboxypropionic acid (XIII). With a procedure similar to that used for the preparation of IV, 7.01 g. (0.025 mole) of IX,[14] 8.73 g. (0.040 mole) of II, and three small pieces (1 mm.[3]) of sodium in 75 ml. of toluene were allowed to react, and the mixture was worked up to yield 18.74 g. of crude XIV. The crude XIV was suspended in a solution of 12.0 g. (0.30 mole) of sodium hydroxide in 100 ml. of water and 50 ml. of ethanol, and the mixture was heated at reflux temperature for 6.5 hr. The condenser was set for distillation; 75 ml. of distillate was collected and discarded, and the residual alkaline solution was extracted with ether (2 × 200 ml.). The aqueous phase was then cooled in ice and acidified to *p*H 1 by the careful addition of cold dilute hydrochloric acid. The mixture was then extracted with ethyl acetate (4 × 100 ml.), and the combined ethyl acetate extracts were extracted with saturated sodium bicarbonate solution (4 × 100 ml.). The combined bicarbonate extracts were treated with Norite (room temperature) and filtered through Celite. The amber filtrate was cooled in ice and acidified carefully (CO_2 evolved) to *p*H 1.8 by the careful addition of 6*N* hydrochloric acid. The resulting mixture was extracted with ethyl acetate (4 × 100 ml.), the combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* (bath temp. below 45°). The red-brown oil which was obtained crystallized to a paste when seeded with some crystals obtained by scratching a small portion of the oil suspended in ethylene dichloride. The paste was washed three times with 5-ml. portions of cold nitroethane. The crude product amounted to 5.81 g. (66% based on IX), m.p. 140° (dec.). After recrystallization from 15 ml. of nitroethane, 4.50 g. (51%) of gray XIII was obtained, m.p. 140° (dec.).

A sample was recrystallized for analysis from a mixture of ethylene dichloride and glacial acetic acid (25:1), m.p. 140° (dec.).

Anal. Calcd. for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 63.72; H, 4.75; N, 3.80.

β-[3-(5-Benzyloxyindolyl)]-DL-lactic acid (VIII). A mixture of 2.0 g. (0.0056 mole) of XIII, 27 g. (0.23 mole) of redistilled quinoline, and 0.1 g. of copper powder was heated at 200° for 45 min. under a slow stream of nitrogen. The clear, straw-colored solution was cooled and poured into 125 ml. of cold 2.5*N* hydrochloric acid and treated in a manner similar to that described for the preparation of V. The resulting oil crystallized to a light tan solid; 1.60 g. (92%). Recrystallization from 10 ml. of ethylene dichloride afforded 1.44 g. of small, tan, rectangular prisms of VIII, m.p. 121–122°.

A sample recrystallized for analysis melted at 124–125°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 70.17; H, 5.39; N, 4.41.

β-[3-(5-Hydroxyindolyl)]-DL-lactic acid (X). A mixture of 0.31 g. (0.001 mole) of VIII, 0.02 g. of 5% Pd/C catalyst, and 15 ml. of 95% ethanol was subjected to hydrogenation at atmospheric pressure and room temperature for 6.5 hr. The catalyst was removed by filtration under nitrogen and the ethanol solution was concentrated to a small volume (2 to 3 ml.). Attempts to isolate a solid product resulted in rapid decomposition with the formation of colored oils. Paper chromatographic studies on the ethanol concentrate indicated that pure X was obtained; R_F 0.28, isopropyl alcohol-aq. NH_3-H_2O, 8:1:1; maroon color with diazotized sulfanilic acid,[21] blue color with acidic *p*-dimethylaminobenzaldehyde,[21] dark gray with ammoniacal silver nitrate,[21] and an immediate lavender color with a α-nitrosonaphthol reagent.[22]

DL-β-Phenyllactic acid: Procedure A. (Condensation of II with *N,N*-dimethylbenzylamine.) A mixture of 6.76 g. (0.05 mole) of *N,N*-dimethylbenzylamine, 16.36 g. (0.075 mole) of II, a trace (piece 1 mm.[3]) of sodium, and 40 ml. of toluene was heated at reflux temperature under a stream of nitrogen for 24 hr. Evolution of volatile amine was not detectable. The toluene was removed and the residue then heated at 185–190° for an additional 36 hr. (The evolution of volatile amine was observed with moist *p*H paper.) Treat-

(20) Prepared in 75% yield by a method similar to that described for the preparation of 5-benzyloxygramine; See ref. 14. Compare with J. B. Bell, Jr., and H. G. Lindwall, *J. Org. Chem.*, **13**, 547 (1948).

(21) H. K. Berry, H. E. Sutton, L. Cain, and J. S. Berry, *Univ. Texas Pub.*, No. 5109, 22 (1951).

(22) S. Udenfriend, H. Weissbach, and C. T. Clark, *J. Biol. Chem.*, **215**, 337 (1955).

ment of the dark brown reaction mixture in a manner similar to that described for IV afforded 24.7 g. of a dark red-brown oil. Saponification of this oil with alcoholic sodium hydroxide followed by acidification and decarboxylation afforded 3.7 g. of a yellow oil. On treatment with benzene there was obtained 0.18 g. (2% based on amine) of DL-β-phenyllactic acid, m.p. 91–94°, undepressed on admixture with authentic DL-β-phenyllactic acid.

Procedure B. (Condensation of II with benzyl chloride.) From a mixture of 22.70 g. (0.104 mole) of II, 12.64 g. (0.100 mole) of benzyl chloride, 2.30 g. (0.100 g.-atom) of sodium, and 50 ml. of absolute ethanol heated at reflux temperature for 67 hr. was obtained 24.8 g. of a yellow oil. Saponification of this oil with alcoholic sodium hydroxide followed by acidification and decarboxylation of the dicarboxylic hydroxy acid with quinoline (at 105°) afforded 1.65 g. (10% based on benzyl chloride) of DL-β-phenyllactic acid, m.p. 93–95°.

SALT LAKE CITY, UTAH

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

3,16β-Dihydroxy-$\Delta^{1,3,5}$-estratrien-17-one and Related Compounds[1]

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Received April 25, 1957

The preparation of 3,16β-dihydroxy-$\Delta^{1,3,5}$-estratriene-17-one (IIb) and the diacetate (IIa) are described. Reduction with lithium aluminum hydride yielded $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol (IVb). The factors involved in the reduction of ring D ketols are briefly discussed.

In view of the fact that ring D ketols appear to be potential intermediates in the biochemical transformation of the estrogenic hormone as well as end products of its metabolism, satisfactory syntheses for these compounds were desired. In a prior report from these laboratories a ready synthesis for 3,16α-diacetoxy-$\Delta^{1,3,5}$-estratriene-17-one (IIIa) was described and this compound was employed as an intermediate in the preparation of estriol.[2] In the present communication, synthesis of the epimeric 3,16β-dihydroxy-$\Delta^{1,3,5}$-estratriene-17-one (IIb) and a means for preparation of the naturally occurring metabolite, $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol (IVb) are described. At the same time it was possible to characterize IIIb more completely and, as an extension of the investigation, to identify a previously reported minor reaction product obtained from the lithium aluminum hydride reduction of IIIa.

The preparation of IIa is a direct application of the investigations of Johnson, Gastambide and Pappo[3] who described a stereoselective oxidation of the enol acetate of isoandrosterone to yield 3β,16β-diacetoxyandrostane-17-one. When the reaction conditions described by these authors were employed with estrone-enol diacetate (I) a 42% yield of IIa was obtained. The compound crystallized in at least two polymorphic modifications but the physical constants, and especially the infrared spectrum clearly distinguished the product from IIIa. The compound was readily rearranged by means of either alkali or acid to the stable isomer 3,17β-dihydroxy-$\Delta^{1,3,5}$-estratriene-16-one (VIb). Reduction of IIa by means of lithium aluminum hydride yielded only the known $\Delta^{1,3,5}$-estriene-3,16β,17β-triol (IVb).[4] Despite intensive search no evidence was obtained for the presence of the as yet undescribed fourth isomer of estriol, *i.e.* $\Delta^{1,3,5}$-estratriene-3,16β,17α-triol.

The virtual stereospecificity observed in the metal hydride reduction of IIa may be ascribed to the interposition of the C-18 methyl group and the complex of the reagent with the C-16β-oriented oxygen to the approach of the hydride toward C-17. On the other hand, when IIIa was reduced with lithium aluminum hydride, in addition to the major product, estriol, about 10% of the epimeric $\Delta^{1,3,5}$-estratriene-3,16α,17α-triol (Vb) was formed. The latter was reported earlier[2] as an unidentified component in the reduction of IIIa. The lesser stereoselectivity toward lithium aluminum hydride in the case of IIIa is explicable in the same terms except that the C-16 hydroxyl is on the opposite side of the molecule. The transposition of this group may facilitate formation of the 17α-hydroxy isomer both by removal of a shield over the β face of C-17 and through a cyclic complex of the metal with the two oxygen atoms at C-16 and C-17. The C-18 methyl group appears to be an important factor in obstructing the β attack of C-17 by the metal hydride since reduction of estrone by

(1) This investigation was supported in part by a grant from the American Cancer Society, and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, 76, 2948 (1954).

(3) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, 79, 1991 (1957).

(4) G. F. Marrian, E. J. D. Watson, and M. Panattoni, *Biochem. J.*, 65, 12 (1957); M. N. Huffman and H. H. Darby, *J. Am. Chem. Soc.*, 66, 150 (1944).

the same reagents affords a very high yield of estradiol-17β.[5]

The stereoselectivity of the reaction of lead tetraacetate with the enol diester of estrone was investigated. The total product resulting from the oxidation by lead tetraacetate without isolation or further manipulation was treated immediately with an excess of lithium aluminum hydride in order to "freeze" the hydroxyl group at C-16 in the orientation resultant from the action of the reagent. Isolation of the reaction product by direct crystallization and countercurrent distribution of the residual material revealed that $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol (IVb) was the major product of the reaction. There was, however, a relatively small amount of $\Delta^{1,3,5}$-estratriene-3,16α,17β-triol present. It is thus established that while the introduction of an acetoxy group at C-16 in this way is not stereospecific in the strict sense, it is highly stereoselective, a conclusion in accord with that reached by Johnson and his colleagues.

EXPERIMENTAL[6]

3,16β-Diacetoxy-$\Delta^{1,3,5}$-estratriene-17-one (IIa). To a solution of 2.00 g. of estrone–enol diacetate, m.p. 143–148.5°,[7] in 40 ml. of glacial acetic acid and 2 ml. of acetic anhydride was added 2.50 g. of freshly recrystallized lead tetraacetate. Solution was complete at the end of 2 hr. After 18 hr. at room temperature the starch-iodide test was negative; the solvent was then evaporated under reduced pressure at 30–35°, benzene was added and the solution was washed successively with water, 5% sodium bicarbonate solution, and water. The solution, after drying over anhydrous sodium sulfate was concentrated and the product was chromatographed on alumina. The chromatogram yielded 0.151 g. of estrone–enol diacetate, m.p. 148–152°, 0.812 g. (42% based on unrecovered enol diacetate) of 3,16β-diacetoxy-$\Delta^{1,3,5}$-estratriene-17-one, m.p. 140–148°, and 0.187 g. of less pure material, m.p. 119–135°; the infrared spectrum showed that this also was principally IIa.

An analytical sample was recrystallized from petroleum ether as clusters of blunt prisms, m.p. 148–149°,[8] $[\alpha]_D^{24}$ +130.4° (ethanol). The infrared spectrum in carbon tetrachloride solution exhibited bands at 1764 (carbonyl stretching vibrations of phenolic acetate and the C-17 ketone, displaced from its normal position at 1745), at 1750 (carbonyl stretching vibrations of ketol acetate displaced from normal acetoxy band at 1742–1737) and at 1608 and 1492 cm.$^{-1}$ (carbon:carbon stretching vibrations of aromatic ring). The absence of absorption between 1425 and 1400 cm.$^{-1}$ is indicative that there was no unsubstituted methylene group adjacent to the ketone function. In carbon disulfide solution there were bands at 1228 (ketol acetate, displaced from normal acetoxy bands at 1245) and 1206 cm.$^{-1}$ (phenolic acetate).

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 71.33; H, 7.07. Found: C, 71.57; H, 7.10.

3-Acetoxy-17β-hydroxy-$\Delta^{1,3,5}$-estratriene-16-one. Further elution of the column with methanol gave 0.230 g. of oily material which partially crystallized from acetone–petroleum ether. Repeated recrystallization gave 10 mg. of a compound, m.p. 166–177° (appearance of melt suggested polymorphism); $[\alpha]_D^{28.5}$ −68.7° ($CHCl_3$). The infrared spectrum supported the structure of the rearrangement product, 3-acetoxy-17β-hydroxy-$\Delta^{1,3,5}$-estratriene-16-one. The diacetate, prepared with acetic anhydride and pyridine gave an infrared spectrum identical with that of authentic 3,17β-diacetoxy-$\Delta^{1,3,5}$-estratriene-16-one (VIa).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.29; H, 7.51.

3,16β-Dihydroxy-$\Delta^{1,3,5}$-estratriene-17-one (IIb). Hydrolysis of IIa yielded IIb which was recrystallized from ethanol. The melting point was not sharp although some crystals melted at 213–216°. Heating under reduced pressure to remove solvent of crystallization did not improve the melting point. An additional recrystallization from alcohol, however, produced the analytical sample in the form of fine needles, m.p. 219–221°, $[\alpha]_D^{26}$ +173.7° (ethanol) after drying at 0.1 mm. and 70° for 1 hr.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.40; H, 7.66.

The product exhibits polymorphism as evidenced by the melting behavior and infrared spectrum in potassium bromide dispersion. Major differences in spectra were observed in four regions: 1800–1700, 1500–1425, 1300–1100 and 900–650 cm.$^{-1}$. A further description of these spectral alterations will be published elsewhere.

The material moved as a single spot on paper in the system chloroform:formamide. In this system IIb is the most polar (*i.e.* nearest to the origin), VIb is intermediate, and IIIb moves nearest to the solvent front.

$\Delta^{1,3,5}$-Estratriene-3,16β,17β-triol (IVb). A solution of 100 mg. of IIa, m.p. 143–146°, in 25 ml. of dry ether was slowly added to a suspension of 100 mg. of powdered lithium aluminum hydride in 100 ml. of dry ether. A white fluffy precipitate formed and when addition was complete, the suspension was refluxed for 2 hr. The excess reagent was destroyed with ethyl acetate. After washing with cold water, the ether solution was dried and the ether was evaporated leaving a white solid which was recrystallized from ethanol. Two crops (60 mg.; 78%) of $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol, m.p. 281–289° (285–289° in an evacuated capillary) were obtained. The same triol was prepared by lithium aluminum hydride reduction of VIa. There was no depression of the melting point when the triols from the two sources were mixed; infrared spectra of the triacetates were identical; paper chromatograms in the system chloroform:formamide showed the same rate of migration and no contamination with other products.

Stereochemistry of the reaction of $\Delta^{1,3,5,15}$-estratetraene-3,17-diol diacetate (I) *with lead tetraacetate.* Two grams of estrone–enol diacetate was oxidized with 2.80 g. of lead tetraacetate according to the above procedure. The reaction product, without isolation, was dissolved in 300 ml. of dry ether and 1.00 g. of powdered lithium aluminum hydride was carefully added. After heating under reflux for 2 hr., the excess reagent was destroyed with ethyl acetate followed by water and dilute hydrochloric acid. Ethyl acetate was added and the organic layer was separated, washed with saturated salt solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent left a semisolid residue which was recrystallized from ethanol to give 0.669 g. (42% based upon the enol diacetate) of $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol (IVb), m.p. 265–275°. Paper chromatography indicated that the compound was essentially pure. The material which remained in the filtrate, 0.954 g., was separated in a 99-tube countercurrent distribution in the system cyclohexane-ethyl acetate (1:1) upper layer, and ethanol-water (1:1) lower layer. The separation is shown in Figure 1. There were four definite but overlapping areas which were identified from the K values of known compounds. These were estriol (peak tube 28), $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol (peak tube

(5) A. C. Ott and M. F. Murray, Abstracts of the 113th Meeting, AMERICAN CHEMICAL SOCIETY, Chicago, 1948.

(6) Melting points were taken on a Kofler-type hot stage melting point apparatus unless otherwise indicated, and are corrected.

(7) One sample resolidified and then melted 150–152°.

(8) In subsequent preparations a second polymorphic form was obtained, m.p. 140–141.5°.

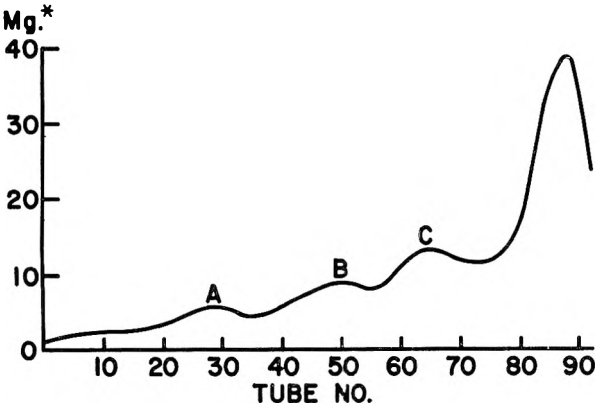


FIG. 1. COUNTERCURRENT DISTRIBUTION OF 954 MG. OF REDUCTION MIXTURE REMAINING AFTER REMOVAL OF A FIRST CROP OF IVb IN: upper layer, cyclohexane–ethyl acetate (1:1); lower layer, ethanol–water (1:1); *, based on ϵ_{2800} = 2100. A = estriol-16α,17β; B = estriol-16β,17β; C = estradiol-17β.

49), and estradiol-17β (peak tube 65); the major portion of relatively nonpolar material was present in tubes 80–94.

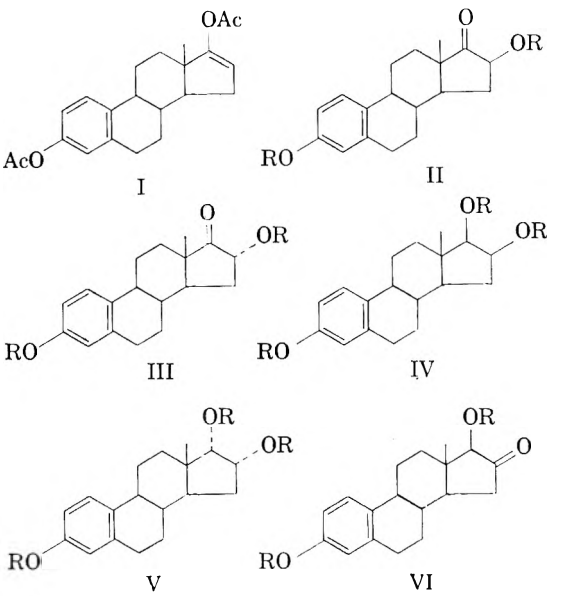
The combined material in tubes 20–36 (estriol fraction), weighed 86 mg. This was acetylated and chromatographed on alumina to yield 50 mg. of estriol triacetate identified from the infrared spectrum. An additional 100 mg. of $\Delta^{1,3,5}$-estratriene-3,16β,17β-triol was obtained from the combined contents of tubes 40–53. The remainder of the material was discarded.

3,16α-Dihydroxy-$\Delta^{1,3,5}$-estratriene-17-one (IIIb). A solution of 1.00 g. of 16α,17α-epoxy-$\Delta^{1,3,5}$-estratriene-3,17β-diol diacetate, m.p. 150–153°, in 150 ml. of methanol and 25 ml. of 6*N* sulfuric acid was allowed to stand at room temperature for 3 days. The solution was concentrated under vacuum at room temperature to one third of its original volume. The suspension was cooled in an ice bath and filtered to give 0.703 g. of IIIb (91%), m.p. 205–228° after drying to constant weight in a desiccator. Recrystallization from acetone–petroleum ether gave a first crop of 0.520 g., m.p. 210–235° and a second crop of 0.128 g., m.p. 190–232°. The compound crystallized with a molecule of acetone of crystallization as shown by analysis and melting behavior. Repeated recrystallization from acetone–petroleum ether, followed by drying at 0.1 mm. and 100° for 8 hr. to remove acetone of crystallization, gave the analytical sample, m.p. 205–206.5°, $[\alpha]_D^{28.5}$ +168.8° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.38; H, 7.73.

In spite of the fact that two types of crystals were observed,[9] clusters of needles and hexagonal plates, the compound was chromatographically pure in the system chloroform:formamide. The infrared spectrum in potassium bromide dispersion exhibited bands at 3540 and 3340 (O—H stretching vibrations), 1717 (carbonyl stretching), 1615, 1577, and 1495 (aromatic ring) cm.$^{-1}$ The absence of absorption between 1425 and 1400 cm.$^{-1}$ indicated that there was no unsubstituted methylene group adjacent to the ketone function.

$\Delta^{1,3,5}$-Estratriene-3,16α,17α-triol (Vb). A previously reported synthesis of estriol[2] also produced a side product having a K value of 0.98 in the system cyclohexane–ethyl acetate (1:1), upper layer; ethanol-water (1:1), lower layer. The compound isolated from tubes 40–55 of the countercurrent distribution melted at 230–235°; the melting point was not depressed upon admixture with authentic $\Delta^{1,3,5}$-estratriene-3,16α,17α-triol[10] and the infrared spectra of the compounds from the two sources were identical.



II,III,IV,V,VI a R = Ac
II,III,IV,V,VI b R = H

Acknowledgments. We wish to express our thanks to Dr. William S. Johnson, University of Wisconsin, for his kindness in giving us a copy of his manuscript prior to publication. We are also grateful to Dr. Glyn Roberts of this Institute for his help with infrared spectrometry and to Mrs. Rosemarie Lehman for technical assistance.

NEW YORK 21, N. Y.

(9) This compound was previously prepared in these laboratories by Dr. D. K. Fukushima as a higher-melting modification, m.p. 222–223.5°, by crystallization from ethyl acetate.

(10) Prepared in these laboratories by Dr. Stephen Kraychy according to the Procedure of V. Prelog, L. Ruzicka, and P. Wieland, *Helv. Chim. Acta*, 27, 250 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VIII. Azabicyclo[3.2.1] octane Derivatives[1]

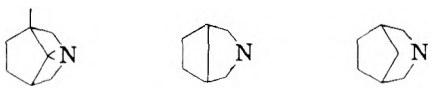
CHARLES H. GROGAN[2] AND LEONARD M. RICE[3]

Received June 3, 1957

A series of *N*-dialkylaminoalkyl-3-azabicyclo[3.2.1]octane-2,4-diones have been prepared employing *cis*-1,3-cyclopentane dicarboxylic anhydride, obtained by permanganate oxidation of norbornylene, and appropriate dialkylaminoalkylamines. These diones were smoothly reduced to the corresponding *N*-dialkylaminoalkyl-3-azabicyclo[3.2.1]octanes by means of lithium aluminum hydride in ether solution. Monohydrochlorides and monomethiodides were prepared from the imides and dihydrochlorides and dimethiodides from the bases. All simple acid addition and quaternary salts were screened for hypotensive activity in dogs. The bis-quaternary salts possessed a good hypotensive action and a favorable therapeutic index.

In our studies of the preparation of fused ring nitrogen heterocycles, and their use as one or both of the bridgehead groups in symmetrical and unsymmetrical bis-quaternary salts, we have recently reported the synthesis and hypotensive properties of compounds of these types containing the 3-aza-1,8,8,-trimethylbicyclo[3.2.1]octane (camphidine) nucleus.[4] Since these compounds proved to be very potent hypotensive agents at low dosage levels either by oral or parenteral administration,[5] we decided to vary the size of the fused ring system and bridging within the rings and study such variations in relation to physiological activity. To this end we have prepared and evaluated series of compounds of this type in which the 3-azabicyclo-[3.2.0]heptane nucleus, II, was thus employed.[6]

The present communication deals with the synthesis and evaluation of series of compounds derived from the 3-azabicyclo[3.2.1]octane nucleus, III. It will be noted from structures I and III that this series is similar to the camphidine series, I, except that the methyl substituents at positions 1 and 8 have been removed. On comparison with the camphidine series, I, the present series, III, might



I II III

be considered as derived from norapocamphidine. In the azabicycloheptane series, II, both the methyl substituents and the central bridging carbon atom have been removed.

The desired bases in other series previously studied[4-8] were readily accessible by a two-step process from the dicarboxylic acid anhydride and the appropriate primary amine. The key intermediate in the present series was likewise the dicarboxylic acid anhydride. The anhydride of *cis*-1,3-cyclopentane dicarboxylic acid was obtained by the oxidation of norbornylene by means of sodium permanganate according to the procedure of Birch *et al.*[9] and treatment of the resultant dicarboxylic acid with acetyl chloride and acetic anhydride.

This anhydride was reacted with appropriate dialkylaminoalkylamines to yield the corresponding amic acids. Reaction of the amine and anhydride in this case proceeded less readily than in previous series,[4,6] including that derived from camphoric anhydride. It was necessary to apply heat to the reaction mixture to obtain a clear melt of anhydride and amine. The resultant amic acids were cyclized to the imides by heating at 170–180° for several hours and isolated from the reaction flask by vacuum distillation. Several imides thus prepared are listed in Table I and their corresponding monohydrochlorides and monomethiodides in Table II.

Reduction of the diones (imides) with lithium aluminum hydride in ether solution proceeded smoothly to give the expected bicyclic bases in good yield. The bases were also conveniently isolated by vacuum distillation. Representative bases are listed in Table III and their dihydrochlorides and bismethiodides in Table IV. The dihydrochlorides were readily obtained in the usual manner; but in order to obtain the bismethiodides it was necessary to heat the base with methyl iodide in methanol at 100° in a bomb tube for several hours. Thus, the reaction of the bases derived from norapocamphoric anhydride (cyclopentane-1,3-dicarboxylic anhydride) was similar to that of those derived from camphoric anhydride in the relative difficulty of bisquaternization.

(1) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

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(4) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 22, 185 (1957).

(5) L. M. Rice and C. H. Grogan, U. S. Patent 2,786,834, March 26, 1957.

(6) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, in press.

(7) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, 75, 4911 (1953).

(8) C. H. Grogan and L. M. Rice, U. S. Patent 2,784,199, March 5, 1957.

(9) S. F. Birch, W. J. Oldham, and E. A. Johnson, *J. Chem. Soc.*, 818 (1947).

TABLE I

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.1]OCTANE-2,4-DIONES

Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
Dimethylaminoethyl	$C_{11}H_{18}N_2O_2$	110–113	0.5	62.83	63.07	8.63	8.53	13.32	13.40	1.4985
Dimethylaminopropyl	$C_{12}H_{20}N_2O_2$	130–135	0.5	64.25	64.43	8.99	9.00	12.49	12.71	1.4968
Diethylaminoethyl	$C_{13}H_{22}N_2O_2$	116–119	0.5	65.51	65.66	9.31	9.20	11.76	11.53	1.4940
Diethylaminopropyl	$C_{14}H_{24}N_2O_2$	138–142	0.6	66.63	66.78	9.59	9.70	11.10	10.82	1.4968
Morpholinopropyl	$C_{14}H_{22}N_2O_3$	145–150	0.4	63.13	63.07	8.33	8.43	10.52	10.40	...

TABLE II

DERIVATIVES OF COMPOUNDS IN TABLE I

Hydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Methiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
$C_{11}H_{19}ClN_2O_2$	188–189	14.37	14.53	$C_{12}H_{21}IN_2O_2$	236–237	36.03	36.08
$C_{12}H_{21}ClN_2O_2$	184–185	13.60	13.83	$C_{13}H_{23}IN_2O_2$	225–226	34.65	34.40
$C_{13}H_{23}ClN_2O_2$	116–117	12.90	13.04	$C_{14}H_{26}IN_2O_2$	165–166	33.37	33.37
$C_{14}H_{25}ClN_2O_2$	141–142	12.28	12.49	$C_{15}H_{27}IN_2O_2$	179–180	32.19	32.40
$C_{14}H_{23}ClN_2O_3$	200–201	11.71	11.63	$C_{15}H_{25}IN_2O_3$	211–213	31.08	31.02

TABLE III

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.1]OCTANES

Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
Dimethylaminoethyl	$C_{11}H_{22}N_2$	69–72	3.5	72.47	72.61	12.16	11.85	15.37	15.30	1.4792
Dimethylaminopropyl	$C_{12}H_{24}N_2$	60	0.3	73.41	73.56	12.32	12.14	14.27	14.30	1.4772
Diethylaminoethyl	$C_{13}H_{26}N_2$	91–94	6.0	74.22	74.19	12.46	12.37	13.32	12.89	1.4782
Diethylaminopropyl	$C_{14}H_{28}N_2$	68	0.3	74.94	75.12	12.58	12.73	12.48	12.25	1.4784
Morpholinopropyl	$C_{14}H_{26}N_2O$	78–82	0.04	70.54	70.59	10.99	11.14	11.75	11.85	1.4976

TABLE IV

DERIVATIVES OF COMPOUNDS IN TABLE III

Dihydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Dimethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
$C_{11}H_{24}Cl_2N_2$	295–297	27.78	27.58	$C_{13}H_{28}I_2N_2$	235–237	54.45	54.85
$C_{12}H_{26}Cl_2N_2$	280–282	26.33	26.53	$C_{14}H_{30}I_2N_2$	270–272	52.85	52.86
$C_{13}H_{28}Cl_2N_2$	242–244	25.03	25.03	$C_{15}H_{32}I_2N_2$	222–223	51.36	51.44
$C_{14}H_{30}Cl_2N_2$	227–228	23.85	24.14	$C_{16}H_{34}I_2N_2$	235–237	49.94	49.89
$C_{14}H_{28}Cl_2N_2O$	299–301	22.78	22.72	$C_{16}H_{32}I_2N_2O$	251–252	48.60	48.45

The compounds prepared in the present series were screened for hypotensive activity in dogs by techniques previously outlined.[4,6] The imides, as their monohydrochlorides or monomethiodides, and the bases as their dihydrochlorides were inactive. The bismethonium salts of the bases produced a good hypotensive response and possessed a favorable therapeutic index. The dimethiodide of the dimethylaminopropyl base had an LD_{50} of 400 mg./kg. on intraperitoneal administration to rats.

EXPERIMENTAL

The following examples will illustrate the general synthetic procedures employed on this series.

N-Dimethylaminopropyl-3-azabicyclo[3.2.1]octane-2,4-dione. Into a 50 ml. round bottom flask was placed 15 g. (0.107 mole) of powdered cyclopentane-1,3-dicarboxylic anhydride. Dimethylaminopropylamine, 11.5 g. (0.113 mole) was added in one portion. The reaction mixture was heated gently until a clear melt was obtained and then at 170–180° in an oil bath for 2 hr. The reaction mixture was fractionated *in vacuo* to yield 14.8 g., 62%, of an oil with b.p. 130–135°/0.5 mm., n_D^{20} 1.4968.

The *imide hydrochloride* was readily obtained in isopropyl alcohol and precipitated with ether, m.p. 172–175°. Recrystallization from isopropyl alcohol-ether raised the m.p. to 184–185°.

The *imide methiodide* was prepared in isopropyl alcohol and precipitated with ether. Recrystallization was from isopropyl alcohol-ether, m.p. 225–226°.

N-Dimethylaminopropyl-3-azabicyclo[3.2.1]octane. Into a 1-liter, 3-necked, reaction flask fitted with stirrer, dropping

funnel, and reflux condenser, protected from moisture with a soda lime tube, were placed 8 g. of lithium aluminum hydride and 500 ml. of anhydrous ether. When solution had been effected a solution of 14.8 g. (0.066 mole) of *N*-dimethylaminopropyl-3-azabicyclo[3.2.1]octane-2,4-dione in 200 ml. of anhydrous ether was added over a period of 10 min. The reaction mixture was stirred for 3 hr. and then decomposed by slow addition of water. A slight excess of water was added, the mixture stirred for 0.5 hr., and inorganic solids filtered off. The solid cake was well washed with ether. The ethereal solutions were combined and dried over sodium sulfate, the ether stripped off, and the resultant oil distilled *in vacuo* to yield 9.6 g., 74%, of base boiling at 60°/0.3 mm., n_D^{20} 1.4772. The *dihydrochloride*, prepared in the usual manner by treating an isopropyl alcohol solution with ethanolic-HCl, melted after recrystallization from methanol-ether at 280–282°. The *dimethiodide* was not formed by refluxing the base with excess methyl iodide in methanol. The following procedure was employed. Into a bomb tube were placed 4 g. of the base, 20 ml. of absolute methanol, and 10 ml. of methyl iodide. The tube was sealed and heated at 100° for 4 hr. On cooling much crystalline material separated. The tube was opened and the crystalline residue dissolved in boiling methanol, filtered, and refrigerated. Most of the bis-quaternary salt precipitated on cooling. The remainder was precipitated with ether. After recrystallization from methanol-ether it melted at 270–272° dec.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF A. H. ROBINS COMPANY, INC.]

Preparation of 4-Amino-1-butanols and Some Derivatives of Pharmacological Interest

CARL D. LUNSFORD, ROBERT S. MURPHEY, AND EDWARD K. ROSE

Received February 18, 1957

The 4-alkylamino and 4-dialkylamino-1-butanols are prepared in good yields by lithium aluminum hydride reduction of the reaction product of equimolar amounts of butyrolactone and a primary or secondary amine. The use of two moles of amine results in the formation of *N,N'*-symmetrically substituted putrescines. The 3-aminopropanols are prepared in a similar manner by the substitution of propiolactone for butyrolactone. The 3,4,5-trimethoxybenzoates, the diphenylacetates, and the benzhydryl ethers of several of the aminobutanols and of *N*-3-hydroxypropylpiperidine and their quaternary salts have been prepared and their pharmacological activity examined.

In view of the fact that the reserpine structure contains a hydroxyl group esterified with 3,4,5-trimethoxybenzoic acid separated from a tertiary amino group by four carbon atoms it seemed of interest to examine several derivatives of the 4-dialkylamino-1-butanols for pharmacological activity. A similarly inspired investigation[1] has recently led to the synthesis of aminoethyl-, aminopropyl-, and aminomethylcyclohexyl-3,4,5-trimethoxybenzoates. Although little interest has been directed toward the 4-amino-1-butanol system some derivatives have been reported to possess pharmacological activity. For example, the diphenylacetate of 4-morpholinebutanol[2] has been reported to be 60% as effective as papaverine in its antispasmodic action on the isolated guinea pig ileum. In addition, it has been reported that tests in laboratory animals indicated the *p*-aminobenzoate of 4-diethylamino-1-butanol[3] to be a more effective local anesthetic than cocaine.

The present work is concerned with the synthesis of the 3,4,5-trimethoxybenzoate and diphenylacetate esters as well as the benzhydryl, and *p*-chlorobenzhydryl ethers of some of the 4-dialkylamino-1-butanols. The detailed pharmacology of the compounds will be the subject of separate communications.[4]

The *N*-substituted 4-amino-1-butanols have generally been prepared by (1) the alkylation of amines with 4-halo-1-butanol[2,5] or its esters[3] and (2) by the lithium aluminum hydride reduction of *N,N*-dialkylsuccinamates[7] or succinamic acids.[8] Catalytic hydrogenation of β-carbethoxypropionylpiperidine to 4-piperidinobutane-1-ol has also been successful.[9]

The disadvantages of the alkylation method are obvious since mixtures are usually obtained. By an adaptation of the reduction method it has been found that the 4-dialkylamino-1-butanols are easily prepared in yields of the order of 60% from the readily available starting materials: butyrolactone,

(1) F. M. Miller and M. S. Weinberg, Abstracts, Atlantic City Meeting, AMERICAN CHEMICAL SOCIETY, p. 11N (1956).

(2) L. C. Cheney and W. G. Bywater, *J. Am. Chem. Soc.*, **64**, 970 (1942).

(3) M. G. Kartvelishvili, *Farmakol. i. Toksikol.*, **8**, No. 3, 32 (1945); *Chem. Abstr.* **40**, 6683 (1946).

(4) The pharmacological studies were carried out by Hazleton Laboratories, Inc., Falls Church, Va., and by Doctor J. M. Little and associates, Department of Pharmacology and Physiology, The Bowman-Gray School of Medicine, Winston-Salem, N. C., and will be the subject of separate communications.

(5) E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951).

(6) (a) E. Szarvasi, *Bull. soc. chim. France*, 647 (1949); (b) L. M. Smorgonskii and Y. L. Gol'dfarb, *J. Gen. Chem. (USSR)*, **10**, 1113 (1940); *Chem. Abstr.*, **35**, 4011 (1941).

(7) A. W. D. Avison, *J. Applied Chem. (London)*, **1**, 469 (1951).

(8) R. E. Holmen and D. D. Carroll, *J. Am. Chem. Soc.*, **73**, 1859 (1951).

(9) J. C. Sauer and H. Adkins, *J. Am. Chem. Soc.*, **60**, 402 (1938).

the dialkylamine, and lithium aluminum hydride. The method appears to be general and can also be used for the preparation of the monoalkylaminobutanols, although in our hands the yields have averaged slightly lower than is the case for the dialkyl derivatives. However, the yields compare favorably with those reported for previous methods.

The method consists of the reaction of butyrolactone with an amine to give the γ-hydroxybutyramide (I)[10] and probably the γ-aminobutyric acid (II), and the reduction of the crude reaction mixture to the aminobutanol (III).

Spath[10] has isolated γ-hydroxybutyramides from the reaction of butyrolactone and amines by distillation; however, the reaction mixture must also contain some of the amino acid, possibly in equilibrium with the hydroxyamide *per se* or through the intermediate *N*-alkylbutyrolactam, because when an excess of amine is used there is also formed the γ-dialkylaminobutyramide (IV). The evidence for the presence of IV is the formation of the tetrasubstituted putrescine (V) when the mixture is reduced with lithium aluminum hydride. Tetramethylputrescine and 1,4-bis(1-piperidino)butane have been prepared in this manner. A general method is thus provided for the preparation of *N,N,N',N'-tetrasubstituted putrescines.*

The 3-aminopropanols may be prepared in a similar manner by the substitution of propiolactone for butyrolactone. 3-Hydroxypropylpiperidine was prepared in 68% overall yield from propiolactone, piperidine, and lithium aluminum hydride.

The aminobutanols prepared by this method and their properties are given in Table I.

The diphenylacetates and 3,4,5-trimethoxybenzoates were prepared from the amino alcohol and the acid chloride; the benzhydryl ethers, from the amino alcohol and the benzhydryl halide. These compounds and their properties are given in Tables II and III.

PHARMACOLOGY[4]

The benzhydryl ether of 4-hydroxybutylpiperidine and the diphenylacetate of 3-hydroxypropylpiperidine completely relaxed the histamine-induced contraction of the isolated guinea pig tracheal chain at a dilution of 1:100,000, and the citrate salt of the *p*-chlorobenzhydryl ether of diethylaminobutanol was active at the same concentration against egg white-induced contraction. The other tertiary aminobenzhydryl ethers and diphenylacetates were essentially devoid of antihistaminic or bronchodilator activity. The most significant activity of the quaternary salts of these compounds was the enhancement of the adrenalin response in the anesthetized dog.

The trimethoxybenzoates were devoid of any reserpine-like activity as indicated by their failure to prolong the hexobarbital sleeping time in mice and their failure to effect the fall-off time of rats from a rotating rod.

EXPERIMENTAL[11]

The 4-amino-1-butanols were all prepared in essentially the same manner. A typical procedure is illustrated by the synthesis of *4-dibutylamino-1-butanol.* A mixture of 68.8 g. (0.8 mole) of butyrolactone and 104 g. (0.8 mole) of di-*n*-butylamine was heated at 150° for 4 hr. The resulting mixture, usually a sirup, was dissolved in ether and added dropwise to a stirred solution of 25.1 g. (0.68 mole) of lithium aluminum hydride in 800 ml. of ether. After complete addition the reaction mixture was stirred and refluxed for 1 hr. The excess hydride was decomposed with water, and the mixture was filtered. The filtrate was concentrated, and the residue was fractionally distilled at reduced pressure. Yield 97.4 g. (62%); b.p. 172–175° (40 mm.).

When the starting amine boiled below 150° the reaction with butyrolactone was carried out at reflux until the pot temperature reached 150° where it was maintained for 4 hr. When the starting amine was dimethylamine or diethylamine the reaction was run in a sealed tube at 150°. The properties of the aminobutanols thus prepared are given in Table I.

N,N,N',N'-Tetramethylputrescine.[12] A mixture of 172 g. (2.0 mole) of butyrolactone and 180 g. (4.0 mole) of dimethylamine was heated in two sealed tubes at 200° for 4 hr. The resulting reaction mixture was heated to 125° *in vacuo*, and reduced with 125 g. of lithium aluminum hydride, as described above. There was obtained 86 g. (30%) of *N,N,N',N'*-tetramethylputrescine, b.p. 78–80° (28 mm.); n_D^{25} 1.4261; d^{27} 0.7864.

Anal. Calcd. for $C_8H_{20}N_2$: C, 66.60; H, 13.97. Found: C, 66.78; H, 13.95.

The dipicrate melted 203–205° (Lit.[12] 198°).

Anal. Calcd. for $C_{20}H_{26}N_8O_{14}$: C, 40.17; H, 4.35. Found: C, 40.35; H, 4.26.

(10) E. Spath and J. Lintner, *Ber.*, 69*B*, 2727 (1936).

(11) All melting points are corrected. Carbon and hydrogen analyses by Schwarzkopf Microanalytical Laboratory, 56-19 37th Avenue, Woodside 77, New York.

(12) R. Willstätter and W. Huebner, *Ber.*, 40, 3869 (1907).

TABLE I

4-DIALKYLAMINO-1-BUTANOLS, $RR'NCH_2CH_2CH_2CH_2OH$

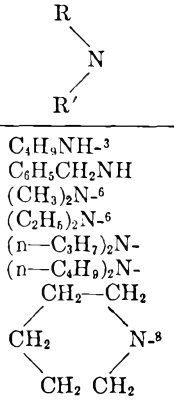
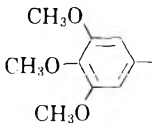
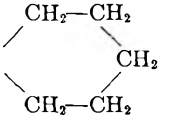
R, R′	B.P. °C.	B.P. Mm.	Yield, %	n_D^{25}	d^t	Formula	Analysis N Calcd.	N Found	C Calcd.	C Found	H Calcd.	H Found
C_4H_9NH-[3]	80–80.5	0.2	44	1.4503	0.8900^{28}	$C_8H_{19}NO$	9.64	9.30	66.15	66.25	13.18	12.98
$C_6H_5CH_2NH$	137–140	0.8	56	1.5288		$C_{11}H_{16}NO$	7.81	7.90	73.70	73.48	9.56	9.57
$(CH_3)_2N$-[6]	98	22	56	1.4390	0.8798^{25}	$C_6H_{15}NO$			61.49	61.58	12.90	12.84
$(C_2H_5)_2N$-[6]	83–85	0.8	80	1.4460	0.8653^{27}	$C_8H_{19}NO$	9.64	9.93	66.15	66.37	13.18	13.22
$(n\text{—}C_3H_7)_2N$-	114	4.3	77	1.4472	0.8723^{26}	$C_{10}H_{23}NO$	8.08	7.90	69.31	69.22	13.88	13.50
$(n\text{—}C_4H_9)_2N$-	135	0.3	62	1.4502	0.8616^{27}	$C_{12}H_{27}NO$	6.96	7.02	71.58	71.69	13.52	13.44
 -[8]	75	0.2	71	1.4733	0.9471^{27}	$C_9H_{19}NO$	8.91	8.72	68.74	68.53	12.18	12.01

TABLE II

$RCOOCH_2CH_2CH_2CH_2\overset{+}{N}R''(R')_2\ X^-$

R	R′	R″	X^-	M.P., °C.	Yield, %[a]	Formula	Analysis, Halogen Calcd.	Halogen Found
	CH_3	H	Cl	122–124[b]	75	$C_{16}H_{25}NO_5\cdot HCl$	10.20	10.17
"	C_2H_5	H	Cl	140–141[b]	97	$C_{18}H_{29}NO_5\cdot HCl$	9.44	9.42
"	C_2H_5	CH_3	I	142.5–144[c]	78	$C_{18}H_{29}NO_5\cdot CH_3I$	26.40	26.10
"	$n\text{—}C_3H_7$	H	Cl	118–119[d]	35	$C_{20}H_{33}NO_5\cdot HCl$	8.78	8.44
"	$n\text{—}C_3H_7$	CH_3	I	115–117[d]	37	$C_{20}H_{32}NO_5\cdot CH_3I$	24.95	24.67
"		H	Cl	156.5–157[d]	83	$C_{19}H_{29}NO_5\cdot HCl$	9.14	9.17
"	"	CH_3	I	171–173[c]	35	$C_{19}H_{29}NO_5\cdot CH_3I$	25.73	25.79
$(C_6H_5)_2CH$—	"	H	Cl	148–150[b]	53	$C_{23}H_{29}NO_2\cdot HCl$	9.15	9.13
"	"	CH_3	I	69–72[e]	34	$C_{23}H_{29}NO_2\cdot CH_3I$	25.77	25.55
"	"	CH_3	Br	144–146[e]	61	$C_{23}H_{29}NO_2\cdot CH_3Br$	17.93	17.90

[a] The yields reported are generally the results of a single trial; [b] recrystallized from isopropyl alcohol; [c] absolute ethanol; [d] absolute ethanol–ether; and [e] butanone.

There was also obtained a higher boiling fraction which proved to be 4-dimethylamino-1-butanol (60 g., 25.5%); b.p. 103–105° (28 mm.).

1,4-Bis(1-piperidino)butane. In a manner similar to that described for the tetramethylputrescine, 17.2 g. (0.2 mole) of butyrolactone, 34.0 g. (0.4 mole) of piperidine, and 11.4 g. (0.3 mole) of lithium aluminum hydride were used to make 25 g. (56%) of 1,4-bis(1-piperidino)butane; b.p. 117–118° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{28}N_2$: Neut. Equiv. 112 mg./m. eq. Found: Neut. Equiv. 114 mg./m. eq.

The hydrochloride was prepared by addition of ethereal hydrogen chloride to the base. It melted above 300°.

Anal. Calcd. for $C_{14}H_{28}N_2\cdot HCl$: Cl^-, 23.85. Found: Cl^-, 23.75.

1-Piperidinepropanol. Propiolactone 28.4 g. (0.40 mole) was added dropwise to 34.0 g. (0.40 mole) of piperidine with continuous stirring and ice bath cooling so that the temperature was maintained at 5–10°. Near the end of the addition the mixture was allowed to warm to 20°. The resulting sirup was dissolved in 100 ml. of tetrahydrofuran, and the solution was reduced with 11.4 g. (0.30 mole) of lithium aluminum hydride in the usual manner. The excess hydride was decomposed with water, and the mixture was filtered. The filtrate was concentrated, and the residue was fractionally distilled at reduced pressure. Yield 31 g. (68%); b.p. 117–122° (25 mm.); n_D^{25} 1.4750; d_{25}^{25} 0.9585 (Lit.[13] b.p. 108–109°) (20–21 mm.); n_D^{25} 1.4742; d_{25}^{25} 0.9529.

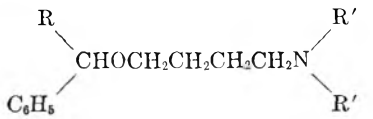
The preparation of the benzhydryl ethers of the 4-dialkylamino-1-butanols. A typical synthesis is illustrated by the following:

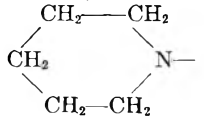
N-(4-Benzhydryloxybutyl)-N,N-di-n-propylamine. A solution of 49.3 g. (0.20 mole) of benzhydryl bromide and 69.2 g. (0.40 mole) of 4-di-*n*-propylamino-1-butanol in 200 ml. of toluene was refluxed 15 hr., concentrated *in vacuo*, and partitioned between 5% sodium hydroxide and ether. The ethereal extract was extracted with 5% hydrochloric acid. This was made alkaline with 20% sodium hydroxide and extracted with ether. This ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was distilled. Thirty-nine grams of dipropylaminobutanol were recovered. The yield of the benzhydryl ether was 26 g. (38.4%); b.p. 175–177° (1.5 mm.).

Anal. Calcd. for $C_{23}H_{33}NO$: C, 81.36; H, 9.80; N, 4.13. Found: C, 81.12; H, 10.03; N, 4.10.

(13) O. A. Barnes and R. Adams, *J. Am. Chem. Soc.*, 49, 1307 (1927).

TABLE III



R	R′ N— R′	Salt	B.P., °C. (M.P., °C.)	Yield, Mm	Yield, %[a]	Formula	Analysis Calcd.	Analysis Found
C_6H_5	$(C_2H_5)_2N$—		202–205	1.4	68	$C_{21}H_{27}NO$	N, 4.51	4.52
C_6H_5	$(C_2H_5)_2N$—	HBr	(109–111.5)[b]			$C_{21}H_{27}NO\cdot HBr$	Br, 20.38	20.53
C_6H_5	$(C_2H_5)_2N$—	CH_3Br	(120–121)[b]		81	$C_{21}H_{27}NO\cdot CH_3Br$	Br, 19.68	19.68
C_6H_5	$(n\text{-}C_3H_7)_2N$—		175–177	1.5	38	$C_{23}H_{33}NO$[d]	N, 4.13	4.10
C_6H_5	$(n\text{-}C_4H_9)_2N$—		192–194	1.5	38	$C_{25}H_{37}NO$[e]	N, 3.82	3.86
C_6H_5			217–220	2.0	46	$C_{22}H_{29}NO$		
C_6H_5		HCl	(135.5–137)[b]			$C_{22}H_{29}NO\cdot HCl$	Cl, 9.85	9.80
C_6H_5		CH_3I	(126–126.5)[b]		73	$C_{22}H_{29}NO\cdot CH_3I$	I, 27.28	27.30
p-ClC_6H_4-	$(C_2H_5)_2N$—	Citrate	(123–124)[c]		62	$C_{21}H_{28}ClNO\cdot C_6H_8O_7$[f]	N, 2.60	2.75

[a] The yields reported are generally the results of a single trial; [b] recrystallized from butanone and [c] absolute ethanol. [d] Calcd.: C, 81.36: H, 9.80. Found: C, 81.12; H, 10.03. [e] Calcd.: C, 81.69; H, 10.15. Found: C, 81.59; H, 9.97. [f] Calcd.: C, 60.27; H, 6.74. Found: C, 60.35; H, 6.66.

The preparations of the 3,4,5-trimethoxybenzoic acid and diphenylacetic acid esters were accomplished by the reaction of the acid chloride with the aminoalcohol and are illustrated by the following:

4-Dimethylaminobutyl 3,4,5-trimethoxybenzoate hydrochloride. To a cooled solution of 23 g. (0.10 mole) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of chloroform was added 11.7 g. (0.10 mole) of 4-dimethylamino-1-butanol in several portions and the solution was refluxed 2 hr. and concentrated. The residue was partitioned between dilute hydrochloric acid and ether. The acid extract was made alkaline with 20% sodium hydroxide and extracted with ether. This ethereal extract was washed with water, dried over sodium sulfate, filtered, and acidified with ethereal hydrogen chloride. The oil which separated was crystallized from isopropyl alcohol or butanone. Yield 26 g. (75%); m.p. 122–124°.

Anal. Calcd. for $C_{16}H_{25}NO_5\cdot HCl$: Cl^-, 10.20. Found: Cl^-, 10.17.

The quaternary salts of both the esters and the ethers were prepared by the addition of methyl iodide or methyl bromide to an ethereal solution of the base. When crystallization did not occur spontaneously the ether was decanted and the oil was crystallized from a suitable solvent.

The following derivatives of 1-piperidinepropanol were prepared in the same manner as has been described for the aminobutanols.

3-(1-Piperidino)propyl 3,4,5-trimethoxybenzoate hydrochloride. Yield 51%; m.p. 169–171° when crystallized from absolute ethanol-ether.

Anal. Calcd. for $C_{18}H_{27}NO_5\cdot HCl$: Cl^-, 9.48. Found: Cl^-, 9.63.

3-(1-Piperidino)propyl diphenylacetate nitrate. Yield 90%; m.p. 115–116° when crystallized from water.

Anal. Calcd. for $C_{22}H_{27}NO_2\cdot HNO_3$: N, 7.00. Found: N, 7.04.

3-(1-Piperidino)propyl diphenylacetate methiodide. M.p. 144.5–146° when crystallized from absolute ethanol.

Anal. Calcd. for $C_{22}H_{27}NO_2\cdot CH_3I$: I^-, 26.48. Found: I^-, 26.50.

3-(1-Piperidino)propyl diphenylacetate methobromide. M.p. 165–166° when crystallized from isopropyl alcohol.

Anal. Calcd. for $C_{29}H_{27}NO_2\cdot CH_3Br$: Br^-, 18.50. Found: Br^-, 18.50.

RICHMOND, VA.

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and Its Derived Compounds. XXVII.[1] Synthesis in the Syringyl Series[2,3]

IRWIN A. PEARL

Received May 20, 1957

Vanillin was converted to syringaldehyde by way of 5-iodovanillin in large-scale reactions. Electrolytic reduction of syringaldehyde yielded hydrosyringoin which in turn yielded syringil upon oxidation with cupric hydroxide in acetic acid solution. Syringil was subjected to reduction under several reducing conditions to yield almost all of the possible monomolecular reduction products. Propiosyringone was reduced in alkaline solution with sodium amalgam to yield α,α'-diethylhydrosyringoin.

During the past decade many sulfite pulp mills in the Middle West have ceased pulping the difficultly obtained conifers and are now pulping indigenous deciduous woods, especially quaking aspen (*Populus tremuloides*) and bigtooth aspen (*Populus grandidentata*). The spent liquor from the sulfite pulping of these deciduous woods offers a great potential source of syringyl compounds, the most important being syringaldehyde. A fundamental study of the chemical utilization of this spent liquor necessitated the production of large quantities of syringaldehyde and its conversion to a number of model compounds and anticipated reaction products. The present paper reports the large-scale synthesis of syringaldehyde from vanillin and a number of experiments in the bisyringyl series.

Several methods for the synthesis of syringaldehyde (I) from vanillin (II) in relatively small amounts have been reported recently,[4-7] but, in most cases, the many steps involved precluded their use for large-scale laboratory preparations. Of these, only the procedure of Pepper and MacDonald,[6] comprising the iodination of vanillin to 5-iodovanillin (III) and reaction of the latter compound with sodium methoxide under pressure in the presence of a copper catalyst, appeared adaptable to large-scale operation.

III was prepared in molar quantities by a modification of the method of Erdtman,[8] and was obtained in yields of 95%.

The results of Pepper and MacDonald[6] on the conversion of III to I were repeated easily in the 13-g. amounts employed by these authors. However, attempts to scale up the reaction to 600–700 g. resulted in much lower yields of I with II as the unwanted by-product of the reaction. A desire to overcome the reducing action of the catalyst led to use of other copper catalysts, but in all cases, yields of I were lower than with the British Drug Houses precipitated copper powder employed by Pepper and MacDonald, and in many instances other by-products were noted in the reaction mixtures. Therefore, the British Drug Houses copper was used in large-scale experiments, and conditions were evolved for production of I in yields of 75–80% with II as the only by-product.

During the work-up of some of the experiments using Copper Brilliant 104[9] fractions containing less than 65% I (as determined by paper chromatography) were upgraded before purification by crystallization. Solutions of reaction products in chloroform or mixtures of chloroform and Skellysolve C were saturated with dry ammonia gas. Both II and I precipitated as ammonium salts, but other by-products did not. The precipitate was filtered, washed with clean solvent, allowed to dry, stirred into absolute ethanol, and filtered to give a precipitate of pure ammonium syringaldehyde, which was acidified and crystallized from chloroform to give pure I. The ammoniated filtrate noted above was evaporated to dryness and recrystallized from Skellysolve C to give colorless crystals of an iodine-containing compound which appears to be 5-iodovanillyl methyl ether (IV). McIvor and Pepper[4] obtained 5-bromovanillyl methyl ether from a similar reaction of 5-bromovanillin and sodium methoxide in methanol in the presence of a copper catalyst. Thus, Copper Brilliant 104 acted as both a reducing agent for the aldehyde group and a methylating agent in this reaction.

An experiment employing Pale Gold Brilliant 111[9] gave dehydrodivanillin V as the chief by-product indicating a type of Ullman reaction under

(1) Paper XXVI of this series: I. A. Pearl, *J. Am. Chem. Soc.*, **77**, 2826 (1955).

(2) Presented before the Division of Organic Chemistry at the 131st Meeting of the AMERICAN CHEMICAL SOCIETY, Miami, Fla., April, 1957.

(3) A portion of this paper represents results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the league by The Institute of Paper Chemistry. Acknowledgment is made by the institute for permission on the part of the league to publish these results.

(4) R. A. McIvor and J. M. Pepper, *Can. J. Chem.*, **31**, 298 (1953).

(5) I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.*, **74**, 4262 (1952).

(6) J. M. Pepper and J. A. MacDonald, *Can. J. Chem.*, **31**, 476 (1953).

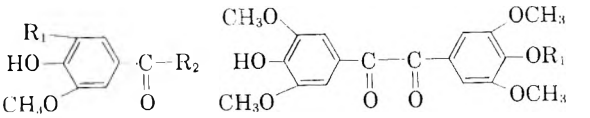
(7) K. Kratzl, T. Horejschi, and G. Billik, *Monatsh.*, **85**, 1165 (1954).

(8) H. Erdtman, *Svensk Kem. Tidskr.*, **47**, 228 (1953).

(9) A copper pigment manufactured by Crescent Bronze Co., Chicago.

these conditions. Two other unidentified by-products were isolated in crystalline form. The data of a large number of preparative experiments led us to the conclusion that the transformation of III to I by reaction with sodium methoxide under pressure in the presence of a copper catalyst is a complex reaction, and that conditions of reactant ratios, temperature, and time are not alone in determining the course of the reaction. Changes in results obtained when all operating conditions were ostensibly alike indicated that the catalyst (which in this case was the copper plus any impurities in the reactants or in the stirring autoclave) determined the course of the reaction, and was responsible for completion of either the double decomposition to I or the reduction of II. The formation of the by-products would be still another reaction or reactions.

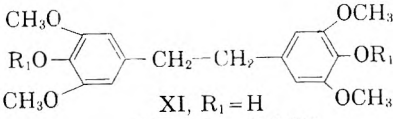
Electrolytic reduction of I in a manner already reported for II[10] yielded the desired hydrosyringoin (VI), and oxidation with cupric hydroxide in glacial acetic acid gave syringil (VII). Reduction of VII under a variety of conditions employed earlier on vanillil[11] yielded most of the monomolecular reduction products of VII, although there appeared to be very little correlation between the reduction of vanillil and that of VII. The reduction products of VII were characterized by their methyl ethers and their acetates. 4,4′-Dihydroxy-3,3′,5,5′-tetramethoxystilbene (VIII) and 1,2-bis(4-hydroxy-3,5-dimethoxyphenyl)ethanol (IX) could not be prepared directly from VII, but were readily prepared by reduction with sodium borohydride or sodium trimethoxyborohydride of deoxysyringoin (X), an intermediate easily prepared by reduction of VII with tin amalgam in ethanolic hydrochloric acid or with zinc in acetic acid. Bisyringyl (XI) and VIII were the only two reduction products of VII previously known.[12] All of the bis-syringyl compounds prepared in this study will be employed as intermediates in hardwood lignin model compound studies.



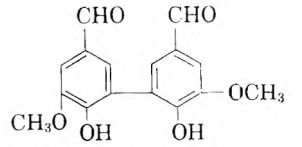
I, R_1 = CH_3O; R_2 = H
II, R_1 = R_2 = H
III, R_1 = I; R_2 = H
XXII, R_1 = CH_3O; R_2 = CH_3CH_2

VII, R_1 = H
XIV, R_1 = CH_3CO
XV, R_1 = CH_3

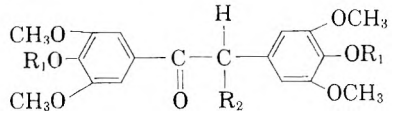
IV



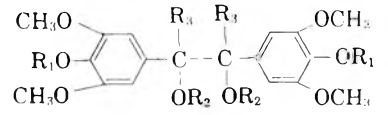
XI, R_1 = H
XIX, R_1 = CH_3CO
XX, R_1 = CH_3



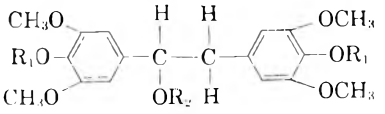
V

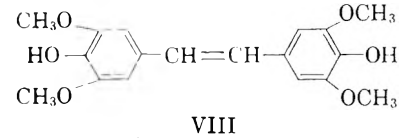


X, R_1 = R_2 = H
XVI, R_1 = H; R_2 = OH
XVII, R_1 = CH_3CO; R_2 = H
XVIII, R_1 = CH_3; R_2 = H



VI, R_1 = R_2 = R_3 = H
XII, R_1 = R_2 = CH_3CO; R_3 = H
XIII, R_1 = CH_3; R_2 = R_3 = H
XXIII, R_1 = R_2 = H; R_3 = CH_3CH_2





VIII

IX, R_1 = R_2 = H
XXI, R_1 = R_2 = CH_3CO

EXPERIMENTAL

All melting points are uncorrected, and ultraviolet spectral data are for solutions in 95% ethanol (concentration, 0.02 g. per liter).

Syringaldehyde I. A freshly prepared solution of 450 g. of sodium metal in 12,500 ml. of acetone-free methanol was alpced in a 5-gallon stainless steel autoclave equipped with automatic temperature control and a stirring device, and treated with 650 g. of crude III[8] and 125 g. of British Drug Houses precipitated copper. The autoclave was sealed and, while stirring, heated to 130° in 1 hr., maintained at 130° for 5 hr., and allowed to cool. The reaction mixture was filtered and the precipitate was washed with water. The water washings were acidified, and the precipitate was filtered to give fraction A-1. The filtrate was extracted with chloroform, and the chloroform was dried and distilled to give fraction A-2. The original methanolic filtrate was concentrated under reduced pressure until the heavy precipitate prevented further distillation, and filtered. The precipitate was dissolved in water, acidified with hydrochloric acid, and extracted with chloroform. Drying and distillation of the chloroform gave fraction B. The methanolic filtrate was again concentrated and processed as before to give fraction C. The final methanolic filtrate was diluted with water and extracted with chloroform. This chloroform extract was dried and distilled to yield fraction D. The several fractions obtained were analyzed quantitatively by the procedure of Pepper and MacDonald.[6] A typical experiment is illustrated by the data of Table I.

Extracts containing I in amounts of 65% or greater could be crystallized from chloroform or mixtures of chloroform and Skellysolve C to give crystals of pure I melting at 110°. Extracts containing less than 65% I (filtrates from the crystallization of pure I noted directly above are included

(10) I. A. Pearl, *J. Am. Chem. Soc.*, **74**, 4260 (1952).
(11) I. A. Pearl, *J. Am. Chem. Soc.*, **74**, 4593 (1952).
(12) H. Richtzenhain, *Ber.*, **77**, 409 (1944).

TABLE I

REACTION OF 5-IODOVANILLIN WITH SODIUM METHYLATE

Fraction	Syringaldehyde, g.	Vanillin, g.	5-Iodovanillin, g.
A-1	80		20
A-2	27		
B	154	17	
C	16	4	
D	65	36	
Total	342 (80%)	57 (16%)	20 (3%)

in this category) were upgraded before crystallization. Solutions containing I, II, and possibly by-products in chloroform or mixtures of chloroform and Skellysolve C were saturated with dry ammonia gas. Both I and II precipitated as ammonium salts, but by-product material remained in solution. The precipitate was filtered, washed with clean solvent, and air-dried. The dry mixture of ammonium salts was stirred into absolute ethanol and filtered. The precipitate consisted substantially of the ammonium salt of I, and the filtrate contained the ammonium salt of II with some I. The ammonium salt of I was dissolved in water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform was concentrated to a small volume and cooled to yield crystals of pure I melting at 110°. Hunter and Hibbert[13] noted the difference in the solubilities in ethanol of the ammonium salts of I and II. I was compared with authentic I[4] by mixed melting point.

In an experiment employing Copper Brilliant 104[9] as a catalyst the ammoniated filtrate from the precipitation of I and II was evaporated to dryness at room temperature, and the residue was boiled with Skellysolve C and filtered hot. Cooling of the filtrate yielded colorless crystals melting at 93–94°. These crystals contained iodine, had a butyl alcohol–2% aqueous ammonia R_f at 20° of 0.85, and gave positive reactions with bisdiazotized benzidine and ferric chloride, but not with the Mäule or with 2,4-dinitrophenylhydrazine spray reagents. A configuration corresponding with the analytical data and with the observed chemical reactions is that of IV: λ_{max} 215 mμ, ε 30000; λ_{max} 290 mμ, ε 2620.

Anal. Calcd. for $C_9H_{11}O_3I$: C, 37.09; H, 3.77; CH_3O, 21.11. Found: C, 37.38; H, 3.89; CH_3O, 20.88.

The residue from the Skellysolve boiling was washed successively with boiling benzene, ethanol, and toluene to leave colorless crystals melting at 278–279°. These crystals possess the syringyl group as indicated by the positive Mäule reaction and lack of reaction with bisdiazotized benzidine. Analysis indicates a compound with the formula $C_{22}H_{24}O_9$ with two methoxyl groups, but as yet no structure has been assigned. The ultraviolet absorption spectrum indicated the following maxima: λ_{max} 215 mμ, ε 42200; λ_{max} 286 mμ, ε 6260.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59; CH_3O, 14.35. Found: C, 60.90, 60.92; H, 5.63, 5.53; CH_3O, 14.3, 14.5.

The boiling benzene washings from the above experiment were diluted with petroleum ether (b.r. 65–110°), and the yellow precipitate was recrystallized from benzene–Skellysolve C to give yellow crystals melting at 137–141°. Recrystallization did not raise its melting point. Acetylation with acetic anhydride in pyridine and recrystallization of the acetate from ethanol gave bright yellow crystals melting at 145–146°.

Analysis indicated C, 61.56; H, 5.26; and CH_3O, 21.5, but no structure has been assigned to the product.

An experiment using Pale Gold Brilliant 111[9] yielded over 3% of by-product in fraction D. The dry fraction was covered with ether and filtered. The insoluble material was washed with ether and recrystallized from acetic acid to give dehydrodivanillin melting at 302–304° and not depressing the melting point of authentic V.[14]

Hydrosyringoin (VI). A warm (60°) mixture of 100 g. of I and 64 g. of sodium hydroxide in 1600 ml. of water was placed in the cathode compartment of the electrolysis cell described earlier.[10] The anode compartment was filled with a solution of 16 g. of sodium hydroxide in 400 ml. of water. A current of 3.6 amperes was maintained across the cell for 7.5 hr. at which time the temperature had dropped to 25°. During the last hour of electrolysis a precipitate separated in the cathode compartment. The catholyte was filtered, and the precipitate was washed thoroughly with water. The combined filtrate and washings were acidified with sulfur dioxide. The resulting white precipitate was filtered, washed with water, and air-dried to give 70 g. of crude VI melting at 245–251°. Recrystallizations from acetic acid gave colorless crystals melting at 265–266°: λ_{max} 250 mμ, ε 20150; λ_{max} 369 mμ, ε 35100.

Anal. Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 58.85; H, 6.12.

The tetraacetate XII was prepared with acetic anhydride in pyridine and was obtained as white crystals from ethanol melting at 203–204°: λ_{max} 274 mμ, ε 2960; λ_{max} 360 mμ, ε 160.

Anal. Calcd. for $C_{26}H_{30}O_{12}$: C, 58.42; H, 5.66. Found: C, 58.49; H, 5.68.

Methylation of VI with dimethyl sulfate in alkaline solution and recrystallization first from ethanol and then from methanol yielded 3,3′,4,4′,5,5′-hexamethoxyhydrobenzoin XIII melting at 215–216° and identical with authentic XIII.[15]

Springil (VII). A mixture of 184 g. (0.5 mole) of hydrosyringoin, 234 g. (2.4 moles) of commercial copper hydrate powder, and 3000 ml. of glacial acetic acid was boiled under reflux with stirring for 6 hr. and allowed to cool. The mixture was diluted with water and filtered. The precipitate was leached thoroughly with dilute sodium hydroxide solution and then with water. The combined washings and leachings were acidified with dilute sulfuric acid, and the precipitate was filtered, washed, and air-dried to yield 101 g. of crude VII melting at 194–197°. Recrystallization from acetic acid yielded fluffy yellow needles melting at 198–199° which proved to be the dihydrate of VII.

Anal. Calcd. for $C_{18}H_{22}O_{10}$: C, 54.27; H, 5.57. Found: C, 54.30; H, 5.57.

Pure VII was obtained by boiling crude VII in xylene under a water-separator, filtering, and allowing to cool. These crystals melted at 198° and their ultraviolet absorption spectrum was identical with that of the dihydrate and indicated the following maximum: λ_{max} 330 mμ, ε 21270.

Anal. Calcd. for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01. Found: C, 59.69; H, 4.98.

Bland[16] reported a melting point of 198° for VII prepared by essentially the same procedure,[10] but recorded no intermediates.

Acetylation yielded the diacetate of VII (XIV) as light yellow needles from ethanol melting at 192–193°: λ_{max} 215 mμ, ε 42200; λ_{max} 297 mμ, ε 18500.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 59.19; H, 4.97; CH_3O, 27.8. Found: C, 59.16; H, 4.94; CH_3O, 27.8.

Methylation of VII and recrystallization from either methanol or ethanol yielded 3,3′,4,4′,5,5′-hexamethoxybenzil (XV) melting at 192–193° and identical with authentic XV.[15]

Syringoin (XVI). A solution of 5 g. of VII in 350 ml. of warm *N* sodium hydroxide was treated with sodium hydrosulfite powder and heated on the steam bath until almost

(13) M. J. Hunter and H. Hibbert, *J. Am. Chem. Soc.*, **61**, 2190 (1939).

(14) K. Elbs and H. Lerch, *J. prakt. Chem.*, **93**, 1 (1916).

(15) M. Marx, *Ann.*, **263**, 249 (1891).

(16) D. E. Bland, *Australian J. Appl. Sci.*, **6**, 511 (1955).

neutral in reaction. The mixture was made alkaline with sodium hydroxide and cooled. The cool mixture was filtered, and the precipitate was dissolved in boiling water and acidified with dilute sulfuric acid. The precipitate was filtered, washed with water, and recrystallized twice from ethanol to give 3 g. of pure XV melting at 165–166°: λ_{max} 310 mμ, ε 13170.

Anal. Calcd. for $C_{18}H_{20}O_8$: C, 59.33; H, 5.53. Found: C, 59.21; H, 5.49.

Methylation with dimethyl sulfate in alkaline solution yielded XV instead of the desired 3,3′,4,4′,5,5′-hexamethoxybenzoin just as vanilloin yielded veratril under the same conditions.[11]

Syringoin was also prepared by the reduction of VII with iron and acetic acid.

Deoxysyringoin (X). One hundred grams of tin amalgam[17] was covered with 800 ml. of ethanol, treated with 25 g. of VII, and heated to boiling under reflux on the steam bath. The boiling solution was treated portionwise with 200 ml. of concentrated hydrochloric acid through the reflux condenser, and boiling was continued 6 hr. The warm mixture was filtered, and the filtrate was diluted with water and concentrated in a rotating evaporator. The concentrated solution deposited a crystalline precipitate which was filtered and recrystallized from ethanol to yield 22 g. of X as colorless crystals melting at 185–186°: λ_{max} 306 mμ, ε 12080.

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.09; H, 5.79.

Acetylation gave the diacetate (XVII) as colorless crystals from toluene melting at 200–201°: λ_{max} 300 mμ, ε 21750.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 60.82; H, 5.58.

Methylation yielded 3,3′,4,4′,5,5′-hexamethoxydesoxybenzoin (XVIII) melting at 165–166°, not depressing the melting point of XVIII prepared by reduction of XV with zinc and acetic acid,[15] and having the following maximum in its ultraviolet absorption spectrum: λ_{max} 283 mμ, ε 11070.

Anal. Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.75; H, 6.35.

X was also prepared by reduction of VII with zinc in acetic acid and as a by-product in the reduction of VII with sodium hydrosulfite in alkaline solution.

Bisyringyl (XI). A boiling mixture of 5 g. of VII, 300 ml. of 95% ethanol, and 10 g. of zinc dust was removed from the hot plate and treated gradually with 40 ml. of concentrated hydrochloric acid. The colorless solution was filtered immediately and concentrated under reduced pressure with gradual addition of water. Finally, the concentrated mixture was diluted to one liter with water and allowed to cool. The white precipitate was filtered and recrystallized from ethanol to give 4 g. of XI melting at 176–177°: λ_{max} 215 mμ, ε 35400; λ_{max} 274 mμ, ε 2875; λ_{max} 335 mμ, ε 435.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.67; H, 6.63.

Acetylation yielded the diacetate of XI melting at 165–166° (from ethanol): λ_{max} 271 mμ, ε 2460.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.08; H, 6.17.

Methylation and recrystallization of the product from dilute ethanol gave 3,3′,4,4′,5,5′-hexamethoxybibenzyl (XX) melting at 136–137° which agrees with the m.p. 138–139° reported for XX by Richtzenhain[12] who prepared XI by dehydrogenation of 4-methyl-2,6-dimethoxyphenol. Richtzenhain reported melting points of 179° and 157–158° for XI and XIX, respectively.

Hydrosyringoin (VI) *by reduction of* VII. Reduction of VII with Raney nickel alloy in alkaline solution[11] or with excess sodium trimethoxyborohydride in aqueous alkaline solution yielded VI, identical with that prepared by electrolytic reduction of I.

Unsuccessful reductions of VII. Attempted reductions of VII with zinc in ethanolic acetic acid[11] and with sodium trimethoxyborohydride in tetrahydrofuran yielded only the starting material.

1,2-Bis(4-hydroxy-3,5-dimethoxyphenyl)ethanol (IX). A solution of 10.5 g. (0.03 mole) of X in 500 ml. of absolute methanol was cooled under tap water and treated portionwise with 3.5 g. (0.09 mole) of sodium borohydride. After addition was complete, the mixture was allowed to stand 2 hr. During this time the solution turned green in color, and colorless crystals separated from solution after 30 min. The reaction mixture was concentrated almost to dryness in a rotating evaporator, and the yellowish residue was covered with 500 ml. of water, and filtered. The yellowish crystals melted at 227–228° and amounted to 7 g. Recrystallization from ethanol yielded very light pink crystals of IX melting at 231–232°: λ_{max} 273 mμ, ε 2660.

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.60; H, 6.32.

Reduction of 10 g. of X in 250 ml. of dilute sodium hydroxide solution with 10 g. of powdered sodium trimethoxyborohydride for 30 min. and acidification with carbon dioxide of the filtered reaction mixture gave crude IX which was recrystallized from benzene to give crystals melting at 231–232° which did not depress the melting point of IX prepared above.

Acetylation of IX gave the triacetate, 3,3′,5,5′-tetramethoxy-α,4,4′-triacetoxybibenzyl (XXI) melting at 175–176° (from ethanol): λ_{max} 270 mμ, ε 1547.

Anal. Calcd. for $C_{24}H_{28}O_{10}$: C, 60.50; H, 5.92. Found: C, 60.51; H, 6.20.

4,4′-Dihydroxy-3,3′,5,5′-tetramethoxystilbene (VIII). Treatment of IX or X in warm methanol with excess sodium borohydride caused dehydration of IX to form VIII. The resulting warm methanol solution was evaporated to dryness in a rotating evaporator, and the residue was recrystallized from acetic acid to yield light pink crystals of VIII melting at 246–247°: λ_{max} 328 mμ, ε 14170.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C 64.90; H, 6.11.

Richtzenhain[12] reported 242° as the melting point of VIII and also reported that the compound turned pink in air.

Propiosyringone (XXII). Propiosyringone was prepared by the rearrangement of the propionate of pyrogallol 1,3-dimethyl ether with aluminum chloride in nitrobenzene solution in accordance with the procedure of Hunter, Cramer, and Hibbert[18] and was obtained in 30% yield as crystals melting at 109–110°.

α,α′-Diethylhydrosyringoin (XXIII). A suspension of 35 g. of XXII in 500 ml. of water was treated with 250 g. of 3% sodium amalgam, and the warm mixture was stirred for 7 hr. After 2 hr., the foamy mixture became clear and dark in color. After standing overnight, the mixture was filtered, and the clear filtrate was acidified with sulfur dioxide and filtered. The precipitate was covered with benzene and boiled under a water separator until all water was removed. Cooling of the benzene yielded a granular precipitate. This was filtered to give 13.8 g. of product melting at 118–120° which, when crystallized from dilute ethanol, yielded colorless needles melting at 104–105° with gas evolution. These crystals appear to be the dihydrate of XXIII.

Anal. Calcd. for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47. Found: C, 58.02; H, 7.19.

Acknowledgment. The author wishes to thank the Analytical Department of the Institute of Paper Chemistry for the analyses and spectra reported in this paper.

APPLETON, WIS.

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[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Reduction of Methyl Benzoyldiazoacetate. A New Synthesis of Allophenylserine[1]

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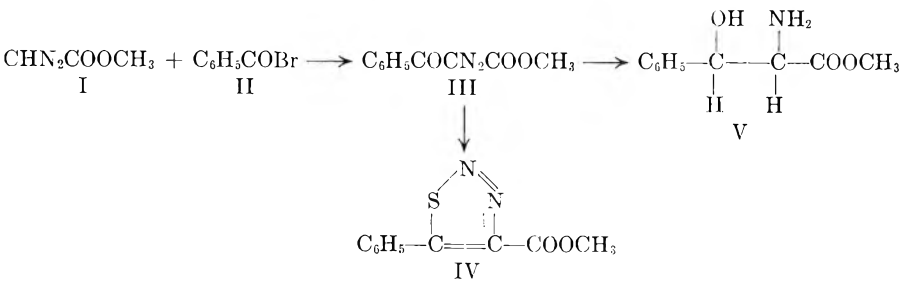
Received May 20, 1957

A synthesis of allophenylserine (DL-*erythro*-β-phenylserine) by catalytic reduction of methyl benzoyldiazoacetate is reported. Chemical reduction of methyl benzoyldiazoacetate with aluminum amalgam in moist ether gives a complex mixture of products, including methyl benzoylacetate.

The reaction of methyl diazoacetate (I) with benzoyl bromide (II) to give methyl benzoyldiazoacetate (III) has long been known.[3] The present paper reports the results of an investigation which had as its principal objective the reduction of III to give either a phenylalanine or a β-phenylserine ester.



The attempted reduction of III by a variety of chemical reducing agents led either to recovery of III, or, in the case of aluminum amalgam, to a complex mixture of products (sequel). Conversion of III to the known thiadiazole IV, followed by attempted reduction with either sodium hydrosulfite or Raney nickel (desulfurization) gave only recovered IV. Hence, a catalytic procedure was investigated. Reduction of III in 70% acetic acid over 5% palladium-on-charcoal gave allophenylserine methyl ester (V), isolated in 82% yield as the hydrochloride. The over-all yield of the hydrochloride of V from II was 64%. Conversion of V to allophenylserine (VI) by a known procedure, followed by fractionation of VI by the method of Shaw and Fox[4] did not reveal any of the diastereomeric *threo* form. It is evident that the reduction of III is highly stereospecific, and compares favorably with recently reported syntheses of VI from ethyl benzoylacetate *via* either the oximino[5] or the acetamido[6] derivative. This appears to be the first stereospecific reduction of an acyl- or aroyldiazoacetic ester, although a mixture of the diastereomeric threonines was reported by Birkofer[7] through catalytic reduction of ethyl acetyldiazoacetate. While this investigation was in progress, Fodor and coworkers reported a β-keto-α-amino acid ester from catalytic reduction of ethyl α-bromopalmitoyldiazoacetate,[8] and effected further reduction to the serine derivative with sodium borohydride.

In contrast to the satisfactory yield of V obtained in the catalytic reduction procedure, reaction of III with aluminum amalgam in moist ether gave no yield of the arylserine ester. Two principal fractions, A and B, were isolated from the reaction mixture. The ether-insoluble Fraction A appeared reasonably homogeneous, and after recrystallization from dimethylformamide-water was obtained in a colorless, crystalline condition, m.p. 222–223°. Elemental analysis, combined with Rast molecular weight determination, indicated a molecular formula of $C_{20}H_{22}O_6$ for the pure ester (VII). Alkaline hydrolysis of VII gave the acid, $C_{18}H_{18}O_6$ (VIII),[9] reconverted by ethereal diazomethane to VII. The stability of VIII as the free acid precludes the pos-

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(2) DuPont Teaching Assistant, 1953–54.

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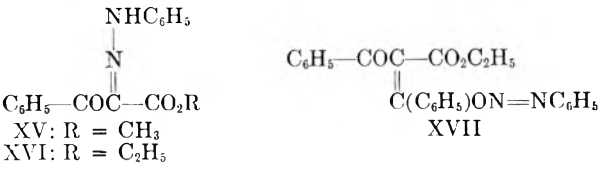
(9) The analytical data are satisfactory also for an acid with formula $C_{15}H_{16}O_5$. However, this interpretation would require that the ester precursor of such a monobasic acid have a molecular formula of $C_{16}H_{18}O_5$. Although the molecular weight determination is in agreement with the latter formula, the carbon value would be seriously in error. The Rast procedure would appear to be subject to greater error than the carbon determination.

sibility that VIII is DL-β,β'-diphenyl-β,β'-dihydroxyadipic acid (IXa), which is known to lactonize spontaneously.[10] Although meso-β,β'-diphenyl-β,β'-dihydroxyadipic acid (IXb) is known in the free state, it loses water to give a lactone so readily that it cannot be purified by crystallization.[11] The acid VIII was recrystallized easily from dilute methanol. A dimethyl ester (X) of either IXa or IXb was considered as a possible reduction product, since it could be formed by pinacol reduction of the intermediate methyl benzoylacetate (XII), previously formed by reductive cleavage of III with loss of nitrogen. Attempts to acetylate VII under a variety of conditions were unsuccessful, even though the infrared spectrum revealed the presence of the hydroxyl function. Repeated attempts to obtain useful products for assigning structure by oxidation procedures gave either recovery of starting material or benzoic acid.

In contrast to Fraction A, the ether-soluble Fraction B was obtained as an oil, which could not be induced to crystallize. Fraction B was reacted with 2,4-dinitrophenylhydrazine(XI) in order to isolate derivatives of any substances containing suitably reactive carbonyl groups. There was obtained a crystalline derivative which gave a nitrogen analysis satisfactory for the known 2,4-dinitrophenylhydrazone of methyl benzoylacetate (XII). However, it was observed concurrently that the readily available ethyl dibenzoylacetate underwent cleavage of a benzoyl group during reaction with XI, to give the same derivative obtained from ethyl benzoylacetate and XI. Accordingly it was apparent that Fraction B could contain either XII or methyl dibenzoylacetate (XIII), or both XII and XIII. It is considered reasonable to assume that XII and XIII would be very similar chemically to ethyl benzoyl- and dibenzoylacetate, respectively.

A partial solution of the problem involving the composition of Fraction B was obtained by reacting it with benzenediazonium chloride (XIV). Although the reaction product was an orange-colored oil which did not crystallize, chromatography of the product on silicic acid–Celite gave, together with other fractions, a crystalline yellow substance, m.p. 74–75°, which was stable on the adsorbent. It was shown concurrently that while XVI (from commercially available ethyl benzoylacetate and XIV) appeared stable on silicic acid–Celite, XVII (from ethyl dibenzoylacetate and XIV) is not. Hence, it is considered reasonably certain that the yellow compound, m.p. 74–75°, is the phenylhydrazone (XV) reported[12] to melt at 76°, formed by tautomerization of the initially formed benzenediazonium coupling product of methyl benzoylacetate, which was present in Fraction B. In addition to XV, chromatography of the reaction product of Fraction B and XIV gave two resinous



fractions. Also, there was present a compound which moved rapidly down the adsorbent column into the effluent. No crystalline material proved isolable from the effluent, however, and the identity of this substance remains obscure. It is apparent that only one substance, methyl benzoylacetate, has been identified among the aluminum amalgam reduction products of III. However, a sufficiently thorough study has been made to indicate that the reduction is not useful for preparing any one product in satisfactory yield. Further study is not anticipated.

In the course of this work, the infrared spectra of the aroyldiazo ester (III) and the 1,2,3-thiadiazole (IV) were investigated. The spectrum of III in Nujol showed a strong, sharp band at 2165 cm.$^{-1}$ and in carbon tetrachloride solution at 2147 cm.$^{-1}$ This band is attributed to the aliphatic diazo group, on the basis of the presence of similar absorption maxima in the infrared spectra of other aliphatic diazo compounds. Thus diazomethane[13] shows an infrared maximum at 2101 cm.$^{-1}$, diazocyclopentadiene[14] at 2082 cm.$^{-1}$ (carbon tetrachloride), azaserine[15] at 2146 cm.$^{-1}$ (Nujol), and α-diazo-*o*-methoxyacetophenone[16] at 2080 cm.$^{-1}$ (chloroform). A band in the vicinity of 2000–2200 cm.$^{-1}$ in the spectrum of IV is lacking. It is apparent that the —N=N— grouping absorbs completely differently from the true aliphatic diazo grouping.[17] Also, the presence of the diazo band in the spectrum of III affords physical evidence that methyl benzoyldiazoacetate is not a 1,2,3-oxadiazole.

EXPERIMENTAL

Melting points are uncorrected. Nitrogen analyses (Dumas method) were performed by D.N.T. Other microanalyses were carried out by Clark Microanalytical Laboratories or by Micro-Tech Laboratories. The infrared spectra (of Nujol mulls unless otherwise specified) were recorded with a Perkin-Elmer Model 21 spectrophotometer using an

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NaCl prism. Only medium and strong absorption bands are reported herein.

Silicic acid used in chromatographic procedures is Merck reagent grade, approximate formula H_2SiO_3. Celite 535 was employed in all chromatographic work. Chemicals for which preparations are not given are commercially available.

Methyl diazoacetate. This diazo ester was prepared from glycine methyl ester hydrochloride by the method of Womack and Nelson.[18]

Methyl benzoyldiazoacetate. This compound was prepared in 78% yield by the method of Staudinger and coworkers[3]; m.p. 84–85° (lit.[3] m.p., 83–84°).

The infrared spectrum of methyl benzoyldiazoacetate shows absorption maxima at 2165, 1725, 1618, 1442, 1345, 1268, 1130, and 746 cm.$^{-1}$ In carbon tetrachloride solution, maxima were displayed at 2147, 1728, 1633, and 1120 cm.$^{-1}$

Allophenylserine. To a solution of 10 g. of methyl benzoyldiazoacetate in 70 ml. of glacial acetic acid was added 0.5 g. of 5% palladium on charcoal. A 30-ml. quantity of water was added, and the reaction vessel was attached immediately to the hydrogen line. Hydrogenation was carried out at 40 p.s.i.g. hydrogen, and was permitted to continue until the theoretical quantity was absorbed (*ca.* 5 hr.). After catalyst removal, the reaction mixture was concentrated to 35 ml., cooled to 5°, basified to litmus with concentrated ammonium hydroxide, and extracted with ten 150-ml. portions of ether. Dry hydrogen chloride gas was passed into the dried, combined ether extracts, and the resulting precipitate collected by filtration, washed with dry ether, and dried *in vacuo* over potassium hydroxide; yield, 9.3 g. (82%), m.p. 178–182° (dec.). Recrystallization from methanol-ether gave the colorless allophenylserine methyl ester hydrochloride, m.p. 182° (dec.) [lit. m.p.,[4] 180° (dec.)].

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: N, 6.05. Found: N, 6.12.

The following procedure is essentially that used by Shaw and Fox in preparing allophenylserine from its ethyl ester hydrochloride.[19] Allophenylserine methyl ester hydrochloride (5.7 g.) was hydrolyzed at room temperature by solution in 25 ml. of 2*N* sodium hydroxide containing 1.5 ml. of methanol. After 2 hr., the resulting clear solution was neutralized with concentrated hydrochloric acid and allowed to stand overnight at 5°. Collection of the white needles present, which were then washed with ice water and dried *in vacuo*, yielded 3.38 g. (75%) (from the ester hydrochloride) of allophenylserine, m.p. 189–191° (dec.). This melting point is in agreement with the observation of Shaw and Fox[19] that samples of allophenylserine decompose in the range 189–193°, depending on heating rate and initial bath temperature.

Anal. Calcd. for $C_9H_{11}NO_3$: N, 7.73. Found: N, 7.68.

Application of the fractionation procedure of Shaw and Fox to the isolated acid gave a dioxane complex, characteristic of allophenylserine. No *threo*-β-phenylserine proved isolable.

Allophenylserine methyl ester. Application of the method of Shaw and Fox,[19] for liberating the methyl ester of phenylserine from its hydrochloride, to 2.5 g. of allophenylserine methyl ester hydrochloride gave 1.7 g. of the free methyl ester, which, after recrystallization from ether–petroleum ether (b.p. 30–60°), gave m.p. 108.5° (lit.[4] m.p. 110°).

Anal. Calcd. for $C_{10}H_{13}NO_3$: N, 7.18. Found: N, 7.08.

The methyl ester was obtained also by the general method outlined for preparing the hydrochloride from methyl benzoyldiazoacetate, except that the ether extracts of the basified hydrogenation mixture were evaporated to dryness to give the cream-colored crude ester, m.p. 105–107°. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 6.6 g. (68%) of white plates of allophenylserine methyl ester, m.p. 108–109°.

Reduction of methyl benzoyldiazoacetate by aluminum amalgam in moist ether. Isolation of fractions. The aluminum amalgam was prepared by permitting 7.5 g. of ether-washed aluminum turnings to stand in a 5% solution of mercuric chloride for 5 min. The amalgamated turnings were washed thoroughly with distilled water and then covered with technical ether.

In a one-l., wide-mouthed Erlenmeyer flask, 31 g. of methyl benzoyldiazoacetate was dissolved in 750 ml. of technical ether. The aluminum amalgam was introduced into the solution in a perforated glass test tube (3 × 12 cm.), suspended in the solution by a wire to permit the aluminum hydroxide formed to fall away from the active surface of the metal. The reaction commenced immediately, with vigorous evolution of gas. Ether was added to the reaction during the course of the run to maintain the volume of the solution at 750 ml. During the course of the reaction, a piece of moist litmus paper indicated the presence of ammonia in the evolved gases. The reaction was continued until the yellow solution had turned almost colorless; usually this required 4 to 6 hours.

Upon completion of the reduction, any excess aluminum was removed, and then the heterogeneous mixture was poured into a 5.5 × 27.5 cm. chromatographic tube, where the aluminum hydroxide was eluted with two additional liters of ether. From this ether solution there was precipitated, upon standing, a white crystalline solid which was collected by filtration. Evaporation of the ether filtrate yielded a yellow oil and additional solid material. This solid was removed by filtration, washed with dry ether, and added to the first crop. The total yield of solid (Fraction A) was 1.4 g.

The residual yellow oil was suspended in water and extracted continuously with fresh ether to yield a yellow ether solution, which was dried over Drierite. The aqueous layer was still yellow in color and was retained. Distillation of the ether under reduced pressure left a viscous, reddish-orange oil; yield, 11.6 g. (Fraction B).

The yellow aqueous layer was subjected to continuous extraction with *n*-butyl alcohol for 3 days. The butanol then was removed by distillation under reduced pressure to give a residual yellow oil which did not crystallize and was not investigated further.

Characterization of fraction A. Fraction A was a white, crystalline solid, insoluble in most common organic solvents. It was recrystallized from dimethyl formamide–water to give the ester VII with a constant m.p. of 222–223°. A ferric chloride test with VII was negative.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19; mol. wt., 358. Found: C, 67.34; H, 6.41; mol. wt. (Rast), 272, 293.

The infrared spectrum of VII showed absorption maxima at 3500, 1737, 1700, 1350, 1207, 1183, 1159, 1068, 1015, 999, 750, and 703 cm.$^{-1}$ The band at 3500 cm.$^{-1}$ is attributed to presence of the hydroxyl function, the band at 1737 cm.$^{-1}$ to the ester function.[20]

The ester VII (0.3 g.) was hydrolyzed with 10 ml. of 5% potassium hydroxide at room temperature. After standing overnight, the clear solution was acidified and the resulting product collected by filtration. Two recrystallizations from methanol-water yielded 0.24 g. of the acid VIII, m.p. 191–192°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.64; H, 5.75.

When the acid VIII was treated with excess ethereal diazomethane, the ester VII was again obtained, m.p. and mixed m.p., 222–223°.

The infrared spectrum of VIII showed absorption maxima at 3515, 1682, 1444, 1355, 1223, 950, and 697 cm.$^{-1}$ The band at 3515 cm.$^{-1}$ is attributed to the hydroxyl function, the band at 1682 cm.$^{-1}$ to the carboxyl carbonyl group.[20]

(18) E. B. Womack and A. B. Nelson, *Org. Syntheses*, **24**, 56 (1944).

(19) K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3417 (1953).

(20) F. Miller in *Organic Chemistry*, Vol. III, edited by Gilman, John Wiley and Sons, Inc., New York, 1953, pp. 140–141, 143–150.

Characterization of fraction B. A. Preparation of 2,4-nitrophenylhydrazone. 2,4-Dinitrophenylhydrazine reagent was prepared according to the directions of Shriner and Fuson.[21] A 0.25-ml. quantity of Fraction B in 5 ml. of 95% ethanol was added to the reagent. The solution was allowed to stand 1 hr., and the orange-colored 2,4-dinitrophenylhydrazone present was collected by filtration. One recrystallization from ethanol–ethyl acetate gave orange plates of the 2,4-dinitrophenylhydrazone of methyl benzoylacetate, m.p. 166–167° (dec.) (lit.[22] m.p. 169–170°).

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: N, 15.64. Found: N, 15.44.

Ethyl dibenzoylacetate (prepared by the method of Wright and McEwen[23]) was reacted with the 2,4-dinitrophenylhydrazine reagent. There was obtained, after one recrystallization from ethanol–ethyl acetate, orange plates, m.p. 161–162° (dec.)[24], which gave an analysis satisfactory for the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate.

Anal. Calcd. for $C_{17}H_{16}N_4O_6$: N, 15.05. Found: N, 15.04, 15.01.

The 2,4-dinitrophenylhydrazone of ethyl benzoylacetate was prepared by the same procedure; m.p. and mixed m.p. with the product for which analysis is given immediately above, 161–162°.

B. Chromatographic study of coupling product with benzenediazonium chloride. A 0.5-g. quantity of oily Fraction B was coupled with benzenediazonium chloride according to the procedure of Bülow and Neber[25] as modified by Bolhofer.[6] The quantities of reactants employed were based on the assumption that Fraction B was pure methyl benzoylacetate. Attempts to isolate the coupling product in a crystalline condition direct from the reaction mixture by addition of ice were unsuccessful. There was obtained instead a reddish-orange oil (Residue I), by decanting the aqueous supernatant layer. The decantate slowly deposited additional insoluble oily material, which was not further investigated because of its unpromising, tarry appearance. Residue I resisted all attempts at crystallization from benzene–iso-octane and ethyl acetate–iso-octane, and was dried in a vacuum desiccator over phosphorus pentoxide for several days.

Residue I (145 mg.) in benzene solution was chromatographed on 65 g. of silicic acid–Celite (5:1 wt.), adsorbent column dimensions 33 × 130 mm. The column was developed with benzene-ethanol (500:1 vol.) under a water pump vacuum over a 45-min. period. There was formed during the early stages of development of the chromatogram a pale yellow, fast-moving zone which moved into the column effluent and was retained. Upon completion of development, there was present at the top of the column a stationary zone, which contained resinous material and was discarded. There were present two additional bands, an orange-brown one, 2 mm. in width, with trailing edge 13 mm. from the top of the adsorbent column, and a yellow one, 53 mm. in width, with trailing edge 46 mm. from the top of the adsorbent column. The column was extruded and the bands cut out. Elution of the former with acetone gave a resinous material which resisted all attempts at crystallization.

Elution of the latter B with acetone yielded a yellow oil which was dried thoroughly in a vacuum desiccator. The product then was rubbed repeatedly with iso-octane, with mechanical removal of tar, to give a yellow solid. The latter was dissolved in pure *n*-hexane and the resulting solution permitted to evaporate slowly at room temperature to give the pure coupling product, XV; m.p. 74–75° (lit.[12] m.p. 76°), yield 34 mg. (two crops).

The isolation of crystalline material from the column effluent did not prove feasible. Solvent removal gave an intractable oil.

Chromatography of coupling product (XVII) *from ethyl dibenzoylacetate and benzenediazonium chloride.* The coupling product XVII was prepared by the method outlined by Bülow and Hailer.[26]

A 200-mg. quantity of XVII in benzene solution was chromatographed on 64 g. of silicic acid–Celite (5:1 wt.), adsorbent column dimensions 33 × 132 mm. The chromatogram was developed with benzene-ethanol (500:1 vol.) over a 50–55-min. period under a water-pump vacuum. Initially, a fairly sharp, bright yellow band formed, which then moved down the column quite rapidly, becoming more diffuse as development progressed. After completion of the development period, the trailing edge of the single diffuse zone (28 mm. wide) was 85 mm. from the top of the adsorbent column. The zone was such a faint yellow that it was hardly discernible. The adsorbent column was extruded. The single zone was cut out and eluted with acetone. The faint color was restricted to the outer zone surface, which was exposed to the air. The acetone eluate was poured onto *ca.* 700 ml. of ice-water mixture. A considerable quantity of material solidified during this operation, and was removed mechanically with the aid of a spatula. On standing, the solid mixture melted to give two phases, which were separated in a separatory funnel. The upper phase (apparently containing benzene as solvent) was retained and permitted to evaporate at room temperature overnight. The residual solid, obtained in low yield, was suspended in cyclohexane, and then the colorless product present collected by filtration and air-dried. The material burned completely without leaving an ash, and gave m.p. 108–110°. No other crystalline material proved isolable. The column effluent was colorless.

Methyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate. This substance was prepared from 5 g. of methyl benzoyldiazoacetate dissolved in 50 ml. of methanol by the general method of Staudinger and coworkers. The yield of pure product, m.p. 63–63.5° (lit.[3] m.p. 60°), was 5.2 g. (96%).

The infrared spectrum of the thiadiazole derivative showed absorption maxima at 1727, 1335, 1275, 1228, 1208, 1173, 1010, 832, 749, and 687 cm.$^{-1}$

Saponification of the ester with 10% sodium hydroxide gave 5-phenyl-1,2,3-thiadiazole-4-carboxylic acid, m.p. 156–157° (dec.), [lit.[27] m.p. 157° (dec.)]. The infrared spectrum showed absorption maxima at 3455, 1688, 1601, 1252, 835, 756, and 690 cm.$^{-1}$

5-Phenyl-1,2,3-thiadiazole-4-carboxamide. 5-Phenyl-1,2,3-thiadiazole-4-carboxylic acid (2 g.) was heated under reflux with 10 ml. of thionyl chloride until all of the solid had dissolved and there was no further evolution of hydrogen chloride. The excess thionyl chloride was removed under reduced pressure. The remaining solution was cooled in an ice bath and 10 ml. of concentrated ammonium hydroxide

(21) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, 1948, p. 171.

(22) W. J. Croxall, J. O. Van Hook, and H. J. Schneider, *J. Am. Chem. Soc.*, **73**, 2713 (1951).

(23) P. E. Wright and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 4540 (1954).

(24) The melting point of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate has been reported as 246–247° [G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953)]. Johnson used a different procedure [*J. Am. Chem. Soc.*, **73**, 5888 (1951)] than the one employed in the present work, and purified the derivative by repeated crystallization from different solvents. It is apparent that tautomerization of an initially formed dinitrophenylhydrazone is theoretically possible, as well as the existence of geometric isomers. The exact structure of the 2,4-dinitrophenylhydrazone is not critical in the present study. The major interest in the present work is that the same derivative was obtained from both ethyl benzoyl- and dibenzoylacetate with 2,4-dinitrophenylhydrazine.

(25) C. Bülow and P. Neber, *Ber.*, **45**, 3732 (1912).

(26) C. Bülow and E. Hailer, *Ber.*, **35**, 915 (1902).

(27) L. Wolff, *Ann.*, **333**, 1 (1904).

added dropwise. The collected precipitate was recrystallized from absolute ethanol; m.p. 141–142°, yield 1.5 g. (75%).

Anal. Calcd. for $C_9H_7N_3OS$: N, 20.48. Found: N, 20.38.

Acknowledgments. The financial support of this investigation by the Research Corporation of New York through a Frederick Gardner Cottrell grant to the University of Nebraska is gratefully acknowledged. Infrared spectra were determined by C. W. Rook, Dr. W. C. Robison, E. M. Shelton, and E. Magnuson.

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[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Chloroacetates and Dichloroacetates of Flavonol, 7-Hydroxyflavone, and Chrysin[1]

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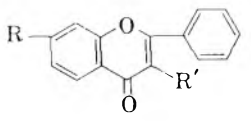
Received April 5, 1957

An improved synthesis of 7-chloroacetoxyflavone is reported. The procedure developed has been applied in the preparation of 7-dichloroacetoxyflavone, 3-chloroacetoxyflavone and 7-dichloroacetylchrysin. The attempted solubilization of 7-chloroacetoxyflavone by conversion to the pyridinium salt is reported.

A broad range of biological activity has been demonstrated by flavonoid materials. The present paper describes a series of chloroacetyl and dichloroacetyl derivatives of flavonol, 7-hydroxyflavone and chrysin, which were prepared for evaluation of possible biological activity. The possibility of solubilizing 7-hydroxyflavone as a pyridinium salt of the chloroacetate has been investigated.



I: R = OH; R′ = H
II: R = CH_2ClCOO; R′ = H
III: R = H; R′ = OH
IV: R = H; R′ = CH_2ClCOO
V: R = $CHCl_2COO$; R′ = H

7-Hydroxyflavone (I) was prepared by the method of Robinson and Venkataraman,[2] as well as by fusion of resacetophenone dibenzoate in the presence of benzoic acid and sodium benzoate. The latter procedure is somewhat similar to the modification introduced by Wheeler and coworkers,[3] but utilizes benzoic acid as the reaction medium instead of glycerol, which is quite hygroscopic. 7-Hydroxyflavone is described[2] as forming long colorless needles, m.p. 240°. The product obtained by the benzoic acid fusion method crystallized in long brilliant yellow needles (Form A), m.p. 244–244.5°. Upon hydrolysis of 7-chloroacetoxyflavone (sequel), colorless 7-hydroxyflavone was obtained. After recrystallization from ethanol, very pale yellow needles (Form B), m.p. 244–245° were obtained. Infrared absorption spectra of the two forms, A and B, showed them to be identical on a molecular basis to each other and to the flavone derivative prepared by the method of Robinson and Venkataraman.[2]

7-Chloroacetoxyflavone (II) has been prepared by Row and Seshadri[4] by heating 7-hydroxyflavone with an excess of chloroacetyl chloride. No yield for this reaction was reported, but it was noted that it was very difficult to remove a green color from the product. This procedure, upon being repeated by the authors, led to a greenish black tar, from which only a small amount of starting material proved isolable in pure form. Although an exhaustive study of the reaction mixture was not made, it appeared likely that recrystallization from methanol caused decomposition of any ester present to give 7-hydroxyflavone (sequel). Further experiments using xylene solutions showed the green color to be due to contact of the warm reactants with air. Accordingly, all succeeding reactions were carried out in xylene in an atmosphere of nitrogen with exclusion of air until all of the excess chloroacetyl chloride had been removed by distillation *in vacuo*. Under these conditions, the green color did not appear and colorless needles of 7-chloroacetoxyflavone were obtained in yields up to 77%.

Under anhydrous conditions, 7-chloroacetoxyflavone reacts with pyridine to give a solid product. Extraction of this product with ether removed unreacted starting material and left a light yellow residual solid with a wide melting range. The product, presumably the crude pyridinium salt, was tested for water solubility. Although the

(1) Abstracted from the M.S. Thesis of Walter Wm. Hanneman, University of Nebraska, 1956.

(2) R. Robinson and K. Venkataraman, *J. Chem. Soc.*, 2344 (1926).

(3) A. T. M. Dunne, J. E. Gowan, J. Keane, B. M. O'Kelly, D. O'Sullivan, M. M. Roche, P. M. Ryan, and T. S. Wheeler, *J. Chem. Soc.*, 1252 (1950).

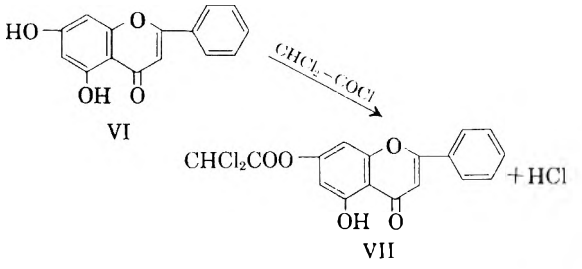
(4) R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 11A, 206 (1940).

salt dissolved instantly, almost immediately there appeared a colloidal precipitate which was shown to be pure 7-hydroxyflavone.

The water-labile nature of the crude pyridinium salt made it necessary to consider the possibility that 7-chloroacetoxyflavone itself was readily hydrolyzed. It was demonstrated that in boiling water hydrolysis began immediately, even though the starting ester was not water-soluble. The rate of hydrolysis depended apparently on the particle size. In boiling absolute methanol, decomposition was complete in less than 30 min. and upon standing overnight at room temperature in methanol, the conversion to 7-hydroxyflavone also was complete.

The procedure developed was extended to flavonol (III) to give 3-chloroacetoxyflavone (IV). Reaction of dichloroacetyl chloride with 7-hydroxyflavone according to the same general procedure led to 7-dichloroacetoxyflavone (V). Reaction mixtures containing dichloroacetyl chloride did not show as great a tendency to turn green as the monochloroacetylation mixtures. The method just outlined did not give a detectable reaction between flavonol and dichloroacetyl chloride. However, the addition of several drops of pyridine to the reaction mixture gave a 63% yield of colorless, crystalline product, m.p. 121–123°, presumably 3-dichloroacetoxyflavone. The latter product was unstable in moist air, undergoing rather rapid conversion to flavonol.

A readily available dihydroxyflavone containing the 4-carbonyl-5-hydroxy system is chrysin (VI), which was prepared by the method of Mentzer and Pillon.[5] The possibility of hydrogen-bonding involving the 5-hydroxyl made it reasonable to expect that substitution at the 7-position could be effected preferentially. By heating chrysin with an excess of dichloroacetyl chloride in xylene under reflux, a 70% yield of the pale yellow 7-dichloroacetylchrysin (VII) was obtained. In contrast to the dichloroacetate of flavonol, the dichloroacetate of chrysin is reasonably stable in a stoppered bottle.



The infrared spectra of both chrysin and 7-hydroxyflavone show a very broad zone of absorption in the region 3200–2100 cm.$^{-1}$ Although the strong C—H band of Nujol obscures the region near 3000 cm.$^{-1}$, definite peaks of moderate intensity occur between 2670–2580 cm.$^{-1}$ The strong bands at 1780 and 1772 cm.$^{-1}$ in the spectra of V and VII, respectively, are attributed to the ester carbonyl groups. In dichloroacetic esters, the shift toward frequencies higher than those of most ester carbonyl bands has been attributed to the inductive effect of the chlorine atoms.[6] The flavone carbonyl bands were present as follows: I, 1625 cm.$^{-1}$; V, 1640 cm.$^{-1}$; VI, 1647 cm.$^{-1}$; VII, 1658 cm.$^{-1}$.

EXPERIMENTAL[7]

All melting points are corrected. Infrared absorption spectra of Nujol mulls in sodium chloride cells were recorded with a Perkin-Elmer Model 21 spectrophotometer.

Resacetophenone. This compound was prepared by the procedure of Cooper.[8]

Resacetophenone dibenzoate. This substance was prepared by the method of Baker,[9] m.p. 80–81° (reported, 80–81°[9]).

7-Hydroxyflavone. In a 500 ml. round bottomed flask, fitted with a stirrer and thermometer, were placed 59 g. of resacetophenone dibenzoate, 48 g. of sodium benzoate, and 175 g. of benzoic acid. The resulting mixture was heated 4 hr. at 200°, cooled, and washed with 2 l. of 5% sodium bicarbonate, which was discarded. The residue was dissolved in 200 ml. of methanol, and a solution of 25 g. of sodium hydroxide in 50 ml. of water was added slowly. After heating under reflux 30 min., the base was neutralized with dilute hydrochloric acid and the alcohol removed by distillation. The residue was dissolved in 500 ml. of 5% sodium hydroxide and the solution saturated with carbon dioxide to precipitate the crude flavone; yield, 14 g. (36%). Recrystallization from ethanol gave long bright yellow needles (Form A), m.p. 244–244.5° (lit.[2] m.p. 240°). Both forms (A and B) showed infrared bands at 2580, 1625, 1609, 1575, 1553, 1512, 1386, 1358, 1286, 1260, 1191, 1173, 1140, 1097, 1047, 1030, 973, 960, 855, 845, 823, 777, 771, 688, and 674 cm.$^{-1}$

7-Chloroacetoxyflavone. A preliminary experiment demonstrated the deleterious effect of contact of the reaction mixture with air. In a 200 ml. round bottomed flask were placed 2 g. of 7-hydroxyflavone, 8 ml. of chloroacetyl chloride, and 50 ml. of xylene. The mixture was heated under reflux for 2 hr. As the reaction proceeded the heterogeneous reaction mixture was converted to a light brown solution. At the end of this time, most of the excess chloroacetyl chloride was removed by distillation, and the residual liquid was poured into a beaker to cool. On contact with air, the solution turned dark green and a tar resulted. Extraction of this tar with 500 ml. of ether and evaporation of the ether gave 400 mg. of crude 7-chloroacetoxyflavone, m.p. 132–138° (lit.[4] m.p. 138–139°).

In a 200 ml. round bottomed flask with a side arm were placed 3 g. of 7-hydroxyflavone, 12 ml. of chloroacetyl chloride, and 75 ml. of xylene. The reaction mixture was heated for 3 hr. in an atmosphere of nitrogen, which was introduced through the side arm. The resulting solution remained light yellow throughout the reflux period. At the end of this period, solvent and excess chloroacetyl chloride were removed by distillation *in vacuo*. Care was taken that all traces of the acid chloride were removed. On cooling,

(5) C. Mentzer and D. Pillon, *Compt. rend.*, **234**, 444 (1952).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 156.

(7) Infrared spectra were determined by E. Magnuson. We are indebted to Myron J. Holm for assistance with chlorine analyses.

(8) S. R. Cooper, *Org. Syntheses*, **21**, 103 (1941).

(9) W. Baker, *J. Chem. Soc.*, 1381 (1933).

the product crystallized without a trace of green color. After extraction with ether, removal of solvent, and recrystallization of the residue from ethyl acetate–cyclohexane, 2.9 g. (77%) of 7-chloroacetoxyflavone was obtained as white needles, m.p. 136–137° (lit.[4] m.p. 138–139°).

Attempted solubilization of 7-chloroacetoxyflavone as the pyridinium salt. One g. of 7-chloroacetoxyflavone was dissolved in 10 ml. of dry pyridine and permitted to stand in a tightly stoppered flask at room temperature for 3 days. Then the reaction flask was opened, placed in a vacuum desiccator over paraffin, concentrated sulfuric acid and phosphorus pentoxide (in separate beakers), and permitted to stand *in vacuo* until excess pyridine was completely removed. The residual yellow powder was extracted with dry ether in a Soxhlet extraction apparatus for 24 hr. to remove unreacted 7-chloroacetoxyflavone. After additional drying *in vacuo* of the ether insoluble fraction, the product gave an indistinct melting point, *ca.* 150–180°. This fraction dissolved immediately upon addition to water, but almost instantly there appeared a water-insoluble substance which was collected by filtration and air dried; m.p. 238–240°. After recrystallization from ethanol, pale yellow needles, m.p. 244–245°, were obtained. Identity of the latter substance (Form B) with 7-hydroxyflavone[2] was shown by infrared absorption spectra and mixed melting point.

Decomposition of 7-chloroacetoxyflavone. A. In methanol: A 100 mg. quantity of 7-chloroacetoxyflavone in 25 ml. of absolute methanol was heated on a steam bath for 30 min. Additional methanol was added from time to time to replace that lost through boiling. The volume of methanol then was reduced to about 5 ml. and allowed to cool. Colorless crystals separated and were collected by filtration; m.p 238–240°. After recrystallization from methanol, the product was shown to be 7-hydroxyflavone by m.p. and mixed m.p. determination.

B. In water: The same general procedure was employed as in Part A, but the heterogeneous nature of the reaction mixture resulted in a slow reaction and only partial conversion to the flavone. The 7-hydroxyflavone was separated mechanically and identified by melting point and mixed melting point determination.

7-(Dichloroacetoxy)flavone. Into a 200 ml. round bottomed three necked flask, fitted with reflux condenser, dropping funnel, and capillary tube for maintaining an atmosphere of nitrogen were placed 75 ml. of xylene and 2 g. of 7-hydroxyflavone. A 10-ml. volume of dichloroacetyl chloride in 50 ml. of xylene was added slowly over a 30-min. period through the dropping funnel. The pale yellow solution was heated under reflux an additional 3 hr. and allowed to stand overnight. Solvent and excess acid chloride were removed by distillation *in vacuo*, and the light yellow residual solid washed with ether. The crude product gave m.p. 130–150°, and was returned to the reaction flask and heated with the previously removed solvent and dichloroacetyl chloride under reflux for an additional 4 hr. Again solvent and excess acid chloride were removed by distillation *in vacuo*. There resulted as residue 1.5 g. (54%) of crude product, m.p. 156–160°. Recrystallization from xylene-cyclohexane gave colorless needles of 7-(dichloroacetoxy)flavone, m.p. 161–162°.

Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: Cl, 20.3. Found: Cl, 20.5.

3-Chloroacetoxyflavone. In a 200 ml. round bottomed flask with side arm (through which a nitrogen atmosphere was maintained) were placed 1.0 g. of flavonol, 0.57 g. of chloroacetyl chloride, and 50 ml. of xylene. The reaction mixture was heated under reflux for 30 min., and then excess acid chloride and solvent were removed by distillation *in vacuo*. The melting point of the residual crude product was 155–160°. Recrystallization from xylene gave 0.94 g. of 3-chloroacetoxyflavone as colorless needles, m.p. 159.5–160.3°.

Anal. Calcd. for $C_{17}H_{11}ClO_4$: Cl, 11.3. Found: Cl, 12.1.

7-Dichloroacetylchrysin. Into a 200 ml. round bottomed flask with side arm (through which a nitrogen atmosphere was maintained) 0.50 g. of chrysin, 0.3 g. of dichloroacetyl chloride, and 75 ml. of xylene were placed and allowed to stand at room temperature for 28 hr. At the end of this time no change was apparent, and the chrysin was recovered upon solvent removal by distillation *in vacuo*.

The recovered chrysin was returned to the reaction flask, and 70 ml. of xylene and 3.60 g. of dichloroacetyl chloride were added. Nitrogen was passed through the flask and the reaction mixture was heated to reflux temperature. After 4 to 5 min., white fumes were evolved for about 1 min. At this point the reaction mixture was homogeneous. Solvent and excess acid chloride were removed under reduced pressure. Upon cooling in Dry Ice, the residual yellowish brown oil formed crystals which were dissolved in 15 ml. of boiling xylene; charcoal was added, and the crystals were removed by filtration. Addition of isooctane to the cooled filtrate gave a brown gum, together with yellow crystals. Upon slow addition of xylene to the heated solution, the yellow crystals dissolved. The brown residue (20 mg.) was removed by filtration and discarded. The clear yellow filtrate produced upon cooling 510 mg. (70%) of yellow needles, m.p. 144–148°. Recrystallization from anhydrous ether (50 ml.) gave the pale yellow 7-dichloroacetylchrysin, m.p. 151–151.5°, which in acetone solution gave a rather pale reddish violet color with alcoholic ferric chloride.[10] In acetone solution, 7-hydroxyflavone gives a negative test with alcoholic ferric chloride.[10]

Anal. Calcd. for $C_{17}H_{10}Cl_2O_5$: Cl, 19.4. Found: Cl, 19.9.

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(10) That production of a color with ferric chloride solution is a property of 3-, 5- or 8-hydroxyflavones, but not of 6-, 7-, or 4′-hydroxyflavones has been reported L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3137 (1951) [additional references are cited by these authors].

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, INSTITUTE OF SCIENCE, UNIVERSITY OF BOMBAY]

Stability of Coumarinic Acids[1]

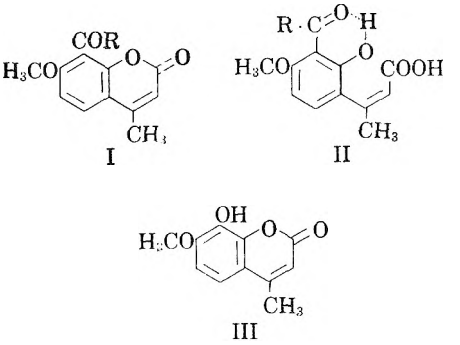
R. M. NAIK AND V. M. THAKOR[2]

Received March 1, 1957

Experimental evidence is furnished to substantiate the interpretation made by Crawford and Rasburn[6] of the stability of the coumarinic acids derived from coumarins having "acidic" substituents in the 8-position. The isomerization of 5-hydroxy-4-methyl-8-nitrocoumarin to 5-hydroxy-4-methyl-6-nitrocoumarin anticipated on the basis of the interpretation has been successfully effected.

Several coumarinic acids have been isolated from coumarins having "acidic" substituents in the 8-position,[3] whereas the isolation of a stable coumarinic acid from coumarins having "acidic" substituents in positions other than 8 has apparently not been accomplished. Dey and Krishnamurty[3d] employed this observation in the effective separation of the mixture of 8-nitro- and 6-nitrocoumarins. During the formylation[4] of some hydroxycoumarin derivatives, we observed that 8-formyl-5,7-dimethoxy-4-methylcoumarin furnished a stable *cis* acid, *viz.* 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid, on warming with alkali and then acidifying, whereas 6-formyl-5,7,-dimethoxy-4-methylcoumarin was recovered on identical treatment. The stability of this and other coumarinic acids derived from coumarins having "acidic"[3c] substituents in the 8-position has been interpreted[5] as due to the failure to lactonize because of the creation of an intromolecular hydrogen bond between the "acidic" (which usually happens to be chelate-forming) substituent in the 8-position and the hydroxyl group generated from the pyrone ring on treatment with alkali. Recently, while the present communication was being prepared, an interesting paper[6] appeared wherein the authors furnish the same interpretation. We record our observations to substantiate this interpretation and also report an isomerization anticipated because of the intramolecular hydrogen bond.

3-Acetyl-4-methoxy-β-methylcoumarinic acid (II, R = CH_3) prepared earlier by Limaye and Sathe[7] along with the corresponding *trans* acid, and 3-formyl-4-methoxy-β-methylcoumarinic acid (II, R = H) revert to their parent coumarins (I) on crystallizing from acetic acid or on standing at room temperature in alcohol containing a few drops of concentrated hydrochloric acid. This is consistent with the view[8] that the intramolecular hydrogen bond is weakened in the presence of protons, *i.e.* in an acidic medium. Dakin oxidation of both these coumarinic acids (II) furnished 8-hydroxy-7-methoxy-4-methylcoumarin (III) and not the corresponding 3-hydroxycoumarinic acid derivative; lactonization has taken place presumably because of the low stability of the *cis* acid resulting from the replacement of the earlier hydrogen bond by a comparatively weak hydrogen bond of the catechol type.



The *cis* acids derived from 8-formyl-5,7-dimethoxy-4-methylcoumarin and 5-methoxy-4-methyl-8-nitrocoumarin (described later) are apparently more stable as they failed to revert to their parent coumarins on crystallizing from acetic acid or on standing in alcoholic hydrochloric acid; however, they reverted in the presence of 80% sulphuric acid. The hydrogen peroxide oxidation of 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid furnished 8-hydroxy-5,7-dimethoxy-4-methylcoumarin.

Interesting evidence in favor of the interpretation is provided by the failure to isolate a stable coumarinic acid (V) from 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (IV) where the hydroxyl group in the 7-position can form a hydrogen bond

(1) This paper comprises a portion of the thesis presented by Mr. R. M. Naik towards the requirement for the degree of Doctor of Philosophy of the University of Bombay, and the work was carried out during the tenure of the Government of India research scholarship awarded to one of us (R.M.N.).

(2) Present address: Department of Chemistry, Gujarat College, Ahmedabad.

(3) (a) W. v. Miller and F. Kinkelin, *Ber.*, *22*, 1706 (1889); (b) A. Clayton, *J. Chem. Soc.*, **97**, 1388 (1910); (c) L. A. Jordan and J. F. Thorpe, *J. Chem. Soc.*, **107**, 387 (1915), (d) B. B. Dey and P. Krishnamurty, *J. Ind. Chem. Soc.*, **4**, 197 (1927).

(4) R. M. Naik and V. M. Thakor, unpublished results.

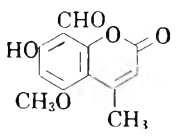
(5) R. M. Naik, Ph.D. thesis, Univ. of Bom., August 1955.

(6) M. Crawford and J. W. Rasburn, *J. Chem. Soc.*, 2155 (1956).

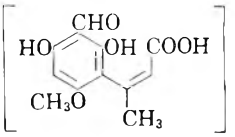
(7) D. B. Limaye and N. R. Sathe, *Rasayanam*, **1**, 30 (1936); *Chem. Abstr.* **31**, 2212 (1937).

(8) V. M. Thakor, *Curr. Sci.*, **22**, 118 (1953).

with the formyl group leaving the hydroxyl group from the pyrone ring free to lactonize.



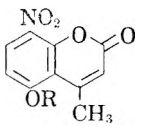
IV



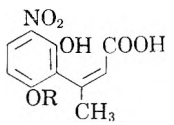
V

Clayton[3b] isolated a stable *cis* acid from 7-hydroxy-8-nitrocoumarin and its stability has been attributed[6] to double chelation as in the case of 2-nitroresorcinol. However, 7-methoxy-4-methyl-8-nitrocoumarin, prepared by Pechmann condensation of 2-nitroresorcinol with ethyl acetoacetate and subsequent methylation, failed to give a stable coumarinic acid. This is in agreement with the recorded[6] failure to isolate a *cis* acid from 7-methyl-8-nitrocoumarin and may be due to the interference of the methoxyl in the 7-position with the coplanarity of the 8-nitro substituent—a condition necessary for maximum chelation.

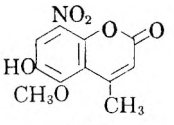
If the stability of the *cis* acids under consideration were to be attributed to the intramolecular hydrogen bond, then complete isomerization of a 5-hydroxycoumarin derivative with a chelate-forming substituent in the 8-position to the corresponding 5-hydroxycoumarin with the substituent in the 6-position by means of alkali would be expected. This would also confirm that the conditions employed consistently throughout led to the formation of *cis* acids only as the isomerization would not be possible in case of the *trans* acid. With these considerations in view, the nitration of 5-hydroxy-4-methylcoumarin was reinvestigated. In contrast to the observations of Parekh and Shah,[9] two mononitro isomers, m.p. 265° and m.p. 188–189°, were isolated. The structure of 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) has been assigned to the isomer, m.p. 265° as (i) its methyl ether (VI, R = CH_3) yielded stable 6-methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3) on treatment with alkali—a characteristic of coumarins with an "acidic" substituent in the 8-position, (ii) the Elbs oxidation of VI (R = CH_3) furnished 6-hydroxy-5-methoxy-4-methyl-8-nitrocoumarin (VIII) in good yield indicating the 6-position to be



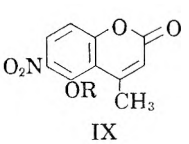
VI



VII



VIII



IX

(9) N. B. Parekh and R. C. Shah, *J. Ind. Chem. Soc.*, **19**, 335 (1942).

vacant, since the oxidation of coumarins[10] proceeds smoothly in the 6-position which is *para* to the hydroxyl group of the pyrone ring.

The alternative structure of 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) has been assigned to the other isomer, m.p. 188–189°. Parekh and Shah[11] prepared this substance by Pechmann condensation of 4-nitroresorcinol with ethyl acetoacetate and gave m.p. 209–210°. However, an attempt to repeat their work using anhydrous aluminum chloride met with failure. The observed demethylation of 5-methoxy-4-methyl-6-nitrocoumarin (IX, R = CH_3) with alkali is unusual; however, instances of such demethylation of the methoxyl groups in *ortho* and sometimes *para* positions to the nitro groups by alkali are known in the literature.[12] The nitration of 5-methoxy-4-methylcoumarin afforded only one isomer, identical with 5-methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3).

When 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) was warmed with alkali and then acidified, 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) alone was isolated, indicating that complete isomerization took place presumably through the *cis* acid (VII, R = H). The hydroxyl in the 5-position takes part in lactonization since the original hydroxyl is involved in hydrogen bond formation. The action of alkali on a 5-hydroxycoumarin derivative with any substituent other than chelate-forming in the 8-position, may also bring about at least partial isomerization due to the greater ease with which the hydroxyl group in the 5-position can lactonize. However, *complete* isomerization and at the same time the formation of the stable coumarinic acid from its methyl ether would be a reliable criterion for the existence of chelation.

EXPERIMENTAL[13]

3-Acetyl-4-methoxy-β-methylcoumarinic acid. (II, R = CH_3) 8-Acetyl-7-methoxy-4-methylcoumarin (2 g.) was heated on a steam bath with sodium hydroxide (20 c.c., 5%) for about 15 min., when the whole of the substance went into solution. The product which separated on cooling and gently acidifying, was crystallized from alcohol as light green flakes, m.p. 162° (decomp.), yield 1.5 g. Limaye and Sathe[7] prepared it along with the *trans* acid by drastic and prolonged boiling with concentrated alkali and gave m.p. 163°. While acidifying, unless care is taken to avoid both generation of heat and addition of excess of hydrochloric acid, the coumarinic acid partially reverts to the parent coumarin. This reversal also takes place when the coumarinic acid is crystallized from acetic acid or on keeping it at room temperature with alcohol containing few drops of hydrochloric acid.

8-Hydroxy-7-methoxy-4-methylcoumarin (III). To the solution of the preceding coumarinic acid (0.4 g.) in sodium hydroxide (4 c.c., 4%) at 0°, hydrogen peroxide (1.6 c.c.,

(10) S. M. Sethna, *Chem. Revs.*, **49**, 91 (1951).

(11) N. B. Parekh and R. C. Shah, *J. Ind. Chem. Soc.*, **19**, 340 (1942).

(12) (a) Robert Burwell, *Chem. Revs.*, **54**, 662 (1954); (b) R. M. Naik *et. al. Proc. Ind. Acad. Sci.*, **38A**, 32 (1953).

(13) Melting points are uncorrected and were taken in open capillary tubes.

30%) was added dropwise with stirring, and the reaction mixture left for 1 hr. when white needles separated. It was acidified and the product which separated was crystallized from alcohol as thin white needles, m.p. 156° (0.2 g.).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.3; H, 4.7.

It does not give any color with alcoholic ferric chloride but dissolves in dilute alkali. It was methylated with dimethyl sulfate by the potassium carbonate-acetone method to the known 7,8-dimethoxy-4-methylcoumarin. Recently Desai and Parghi[14] reported the preparation of 8-hydroxy-7-methoxy-4-methylcoumarin and stated its melting point as 145°. It is probable that their product is a mixture containing traces of 7,8-dihydroxy-4-methylcoumarin.

8-Formyl-7-methoxy-4-methylcoumarin (I, R = H) was prepared by methylation of 8-formyl-7-hydroxy-4-methyl-coumarin and crystallized from alcohol as thin plates, m.p. 242°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.2; H, 4.8.

3-Formyl-4-methoxy-β-methylcoumarinic acid (II, R = H). One gram of I (R = H) was heated for 15 min. on a steam bath with sodium hydroxide (10 c.c., 5%) and the solution was cooled and gently acidified. The pale yellow product which separated was crystallized from alcohol as pale yellow prisms. It shrinks and then melts at 237°, but does not depress the m.p. of 8-formyl-7-methoxy-4-methylcoumarin, presumably indicating the ring closure which takes place before it melts.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 60.7; H, 5.0.

It completely dissolves in sodium bicarbonate with effervescence and gives a purple-brown color with alcoholic ferric chloride. On standing in acetic acid or alcoholic hydrochloric acid, it reverts to the original coumarin (I, R = H).

The Dakin oxidation of 3-formyl-4-methoxy-β-methylcoumarinic acid (II, R = H) (0.2 g.) in sodium hydroxide (4 c.c., 2%) with hydrogen peroxide (1 c.c., 6%) furnished 8-hydroxy-7-methoxy-4-methylcoumarin (III) described earlier.

8-Hydroxy-5,7-dimethoxy-4-methylcoumarin. Hydrogen peroxide (2 c.c., 6%) was added dropwise to a solution of 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid (0.2 g.) in sodium hydroxide (4 c.c., 2%) at 0°, and the reaction mixture was left at 0° for 2 hr. The color changed from orange-red to greenish-brown and later to light yellow. On acidification, a pale yellow product separated, which crystallized from alcohol as brown prisms, 0.08 g., m.p. 258°.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.3; H, 5.0.

With alcoholic ferric chloride it gives a faint brown color which changes to pale green on standing.

Action of sodium hydroxide on 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (IV). The sodium salt which separated on addition of 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (0.5 g.) to sodium hydroxide (5 c.c., 5%), dissolved on heating on a steam bath for 15 min. The salt did not separate on cooling presumably indicating the opening of the pyrone ring. The solution was gently acidified and the product which separated was identified as the original coumarin (IV). No trace of stable coumarinic acid derivative could be isolated.

5-Hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) *and 5-hydroxy-4-methyl-6-nitrocoumarin* (IX, R = H). Nitric acid (2 c.c., *d* 1.42) was added with stirring to 5-hydroxy-4-methylcoumarin (0.2 g.) suspended in glacial acetic acid (5 c.c.) at 10° and the mixture left at 0° for 30 min. The substance slowly went into solution and later yellow glistening needles separated. On pouring the contents in cold water, a yellow product was obtained. It was crystallized from a little excess of acetic acid in clusters of thick needles of 5-hydroxy-4-methyl-8-nitrocoumarin, m.p. 265° (decomp.).

Anal. Calcd. for $C_{10}H_7NO_5$: N, 6.3. Found: N, 6.1.

With alcoholic ferric chloride it gives a pale orange color comparable to that of *p*-nitrophenol. Its methyl ether (VI, R = CH_3) crystallized from acetic acid as flocculent white needles, m.p. 225°.

Anal. Calcd. for $C_{11}H_9NO_5$: N, 6.0. Found: N, 6.2.

The mother liquor from the above crystallization on evaporation yielded 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) which crystallized from alcohol as shining yellow needles. It was twice recrystallized, m.p. 188–189°.

Anal. Calcd. for $C_{10}H_7NO_5$: N, 6.3. Found: N, 6.2.

It gives a blood red color with alcoholic ferric chloride. Parekh and Shah[11] gave m.p. 209–210° for this substance, whereas the melting point of the substance obtained by us could not be raised even after several crystallizations. Its methyl ether (IX, R = CH_3) crystallized from alcohol as thin white needles, m.p. 148°.

Anal. Calcd. for $C_{11}H_9NO_5$: N, 6.0. Found: N, 6.2.

When dissolved in 5% sodium hydroxide by warming on a steam bath, cooled, and then acidified, 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) was isolated indicating the demethylation[12] which took place with alkali.

5-Methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3). 5-Methoxy-4-methylcoumarin (0.2 g.) was added in small lots to nitric acid (2 c.c., *d* 1.42) at 20°. The substance went into solution and the reaction mixture turned greenish-brown. After 15 min., the contents were poured into crushed ice. The product which separated was crystallized twice from acetic acid in needles, m.p. 225°. The melting point was not depressed when mixed with 5-methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3) obtained above. The 6-nitro isomer could not be detected.

6-Methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3), was obtained by heating 5-methoxy-4-methyl-8-nitrocoumarin (0.1 g.) on a steam bath for 15 min. with sodium hydroxide (5 c.c., 5%) and acidifying. The coumarinic acid crystallized from alcohol as crisp yellow plates, m.p. 182° (efferv.).

Anal. Calcd. for $C_{11}H_{11}NO_6$: N, 5.5. Found: N, 5.7.

It gives red color with alcoholic ferric chloride. It reverts to the original coumarin when kept with sulphuric acid (80%).

6-Hydroxy-5-methoxy-4-methyl-8-nitrocoumarin (VIII). To a cooled (0°) solution of 5-methoxy-4-methyl-8-nitrocoumarin (0.7 g.) in sodium hydroxide (6 c.c., 10%) (obtained after warming), a saturated solution of potassium persulfate (0.8 g.) was added dropwise with stirring and the reaction mixture left overnight in a refrigerator. It was acidified and unreacted 6-methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3) was removed by filtration. The filtrate was heated for 1 hr. with more hydrochloric acid when pale yellow crystalline product separated. It crystallized from alcohol as thin light yellow needles, 0.2 g., m.p. 232°.

Anal. Calcd. for $C_{10}H_7NO_6$: N, 5.6. Found: N, 5.8.

It does not give any color with ferric chloride but dissolves in dilute alkali. It does not effervesce with sodium bicarbonate.

Isomerization of 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) *to 5-hydroxy-4-methyl-6-nitrocoumarin* (IX, R = H). 5-Hydroxy-4-methyl-8-nitrocoumarin (0.2 g.) was heated on a steam bath for 15 min., with sodium hydroxide (10 c.c., 5%). The solution was cooled and gently acidified. The product separated was crystallized from alcohol as thin needles, m.p. 188–189°. The melting point was not depressed when mixed with 5-hydroxy-4-methyl-6-nitrocoumarin obtained earlier. No other product could be isolated along with it.

Acknowledgment. The authors express their grateful thanks to Dr. R. C. Shah, F.N.I., for his keen interest in this work.

FORT, BOMBAY,
INDIA

(14) R. D. Desai and J. V. Parghi, *J. Ind. Chem. Soc.*, **33**, 661 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Tribenzotropone from a 1,3-Rearrangement[1]

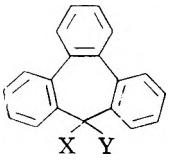
MARTIN STILES AND ARTHUR J. LIBBEY, JR.

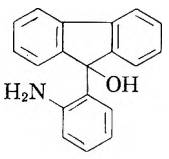
Received June 11, 1957

The decomposition, in acid solution, of the diazonium salt from 9-*o*-aminophenyl-9-fluorenol yields tribenzotropone (I), whose structure was determined by conversion to 4-phenylfluorenone. The properties of I and the corresponding carbinol (II) indicate that the tribenzotropylium ion (III) possesses little if any of the stabilization present in the parent tropylium system.

In connection with our interest in the properties of compounds containing carbon atoms with unusual bond angles we have attempted the synthesis of derivatives of indeno[1,2,3-*jk*]fluorene.[2] This paper describes an unusual rearrangement which was observed in the course of one such attempt. The product of this rearrangement, tribenzotropone (I), and the corresponding carbinol (II) have been examined briefly for evidence of the basic properties associated with other tropone derivatives.

The amino alcohol (IV) was obtained by a method suggested by the work of Gilman and Stuckwisch,[3] who prepared 2,*N*,*N*-trilithioaniline and converted it to anthranilic acid by carbonation. We found that the mixture of organolithium compounds formed when a 3:1 ratio of *n*-butyllithium and *o*-bromoaniline are stirred together at room temperature could be treated with excess fluorenone to yield a complex mixture of products from which IV could be obtained in low yield. The amino alcohol could not be obtained by acid extraction of an ethereal solution of the product, but by hot acid extraction of the tarry residue. This fact may merely reflect the demonstrated low solubility of IV in aqueous acids, but it may mean that IV can be isolated only after the hydrolysis of some condensation product between IV and the excess fluorenone.

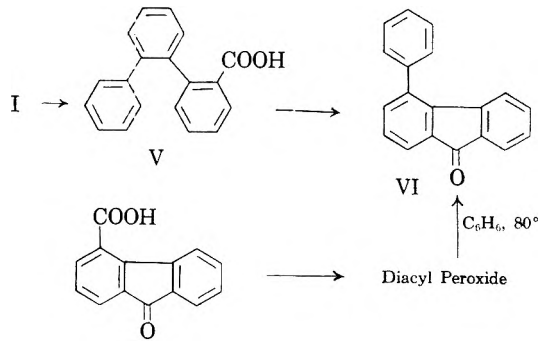




IV

I, X + Y = O
II, X = OH; Y = H
III, X = +; Y = H

The diazonium sulfate of IV decomposed slowly at room temperature and very rapidly on the steam bath to produce, in addition to the usual phenolic product, a 24% yield of tribenzotropone (I). This ketone was identified by alkali fusion to *o*-terphenyl-2-carboxylic acid (V), which could be dehydrated by thionyl chloride to 4-phenylfluorenone (VI).[4] A sample of 4-phenylfluorenone for comparison purposes was prepared by a method which we had previously found suitable for preparing 1-phenylfluorenone, *i.e.* the decomposition of the diacyl peroxide from the appropriate fluorenonecarboxylic acid. Since this appears to be the first example of the use of a ketoperoxide as an arylating agent and since the synthesis of the 1-phenyl isomer was studied in more detail, both reactions are described in the Experimental section.



The work of DeTar[5] indicates that the decomposition of aryldiazonium salts in acid solution to give cyclic products or phenols involves ionic intermediates. Thus, the rearrangement of the hydroxy diazonium salt, which further work has shown occurs in a number of related compounds,[6] appears to be an example of the 1,3-shift of an aryl group to an electron-deficient carbon atom, a type of rearrangement which, so far as we know, has not been reported before. A discussion of the detailed mechanism of this reaction including the factors responsible for its occurrence will be de-

(1) Presented before the Division of Organic Chemistry at the 131st Meeting, AMERICAN CHEMICAL SOCIETY, Miami, Fla., April 3–12, 1957.

(2) The synthesis of the closely related but less strained 2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene has recently been reported by H. Rapoport and J. Z. Pasky [*J. Am. Chem. Soc.*, **78**, 3788 (1956)] who have reviewed the prior attempts to prepare these compounds.

(3) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **71**, 2933 (1949).

(4) K. Alder, J. Haydn, K. Heimbach, K. Neufang, G. Hansen, and W. Gerhard, *Ann.*, **586**, 110 (1954).

(5) D. F. DeTar and S. V. Sagmanli, *J. Am. Chem. Soc.*, **72**, 965 (1950); D. F. DeTar and D. I. Relyea, *J. Am. Chem. Soc.*, **76**, 1680 (1954).

(6) Unpublished results of Anthony J. Sisti in this laboratory.

ferred until later. It seems clear that in the present case, however, the cyclization was effectively prevented by the severe strain which would be present in the resulting ring system. It is anticipated that the rearrangement may occur to a major extent only in compounds which cannot readily cyclize.

The properties of tribenzotropone (I) are in accord with the theoretical prediction[7] and the other experimental observations[8,9] that fusion of benzene nuclei onto the 7-membered ring decreases the stabilization provided by the 7-carbon π-electron system. In Figs. 1 and 2 the ultraviolet absorption curves of I in ethanol and in formic acid are seen to be similar, and those of the carbinol (II) in these two solvents nearly identical. In this respect I and II differ sharply from derivatives of 2,3- and 4,5-benzotropones,[10,11] which are decidedly basic toward formic acid. Both I and II are colored in concentrated sulfuric acid solution (yellow and rose, respectively). The intensity of the visible absorption bands (410 and 560 mμ) of the solutions of II in sulfuric acid more dilute than 90% is distinctly less than that of the solution in concentrated acid, indicating that pK_{R^+}[12] is approximately -15.[13] This lack of stability for the tribenzotropylium ion (III) compared to tropylium[14] (pK_{R^+} 4.8), benzotropylium[10] (pK_{R^+} 1.6), dibenzo[*ae*]tropylium[9] (pK_{R^+} -3.7) and diphenylcarbonium[12] (pK_{R^+} -13.3) ions is much more pronounced than would have been expected on electronic grounds. It is suggested that an important factor is the resistance to planarity arising from interference of the *ortho*- hydrogens as well as from the angular strain of a planar 7-membered ring.

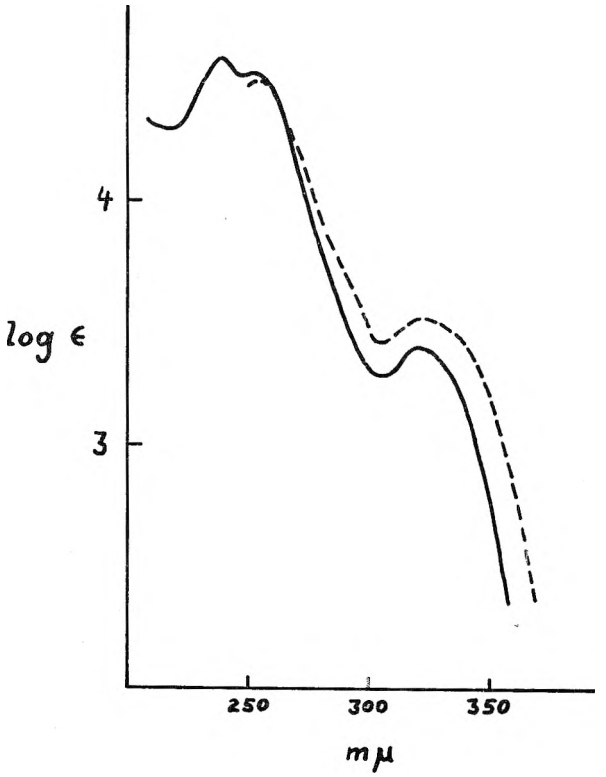


FIG. 1. ULTRAVIOLET SPECTRUM OF I IN 95% ETHANOL (——) AND IN FORMIC ACID (– – –)

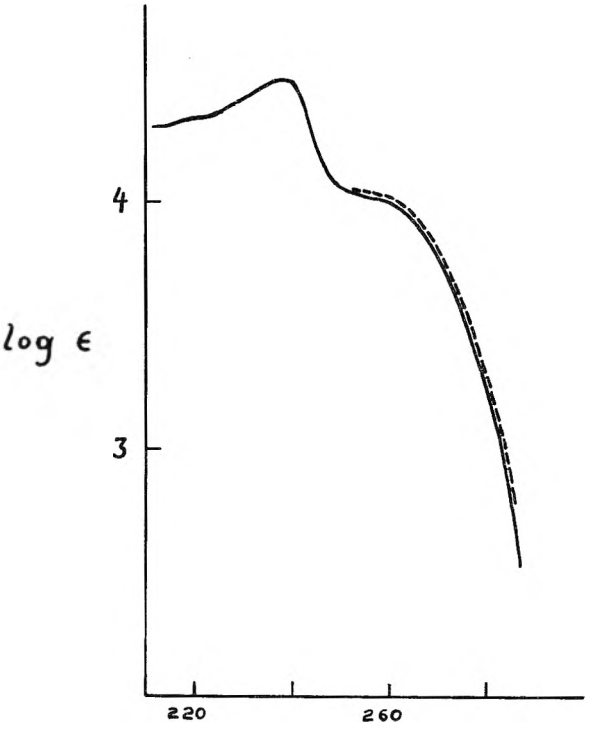


FIG. 2. ULTRAVIOLET SPECTRUM OF II IN 95% ETHANOL (——) AND IN FORMIC ACID (– – –)

The infrared spectrum of I indicates that the carbonyl group (1668 cm.$^{-1}$) differs little from that in 2,3,6,7,-dibenzotropone[15] and normal diaryl ketones[16] and does not resemble the highly polar carbonyl group apparently present in tropone[17] (1638 cm.$^{-1}$), 2,3-benzotropone[11] (1644 cm.$^{-1}$), 4,5-benzotropone[11] (1633), and 2,7-dimethyl-4,5-benzotropone[11] (1625 cm.$^{-1}$).

(7) J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *J. Am. Chem. Soc.*, **74**, 4579 (1952).
(8) P. L. Pauson, *Chem. Revs.*, **55**, 9 (1955).
(9) G. Berti, *J. Org. Chem.*, **22**, 231 (1957).
(10) H. H. Rennhard, E. Heilbronner, and A. Eschenmoser, *Chemistry and Industry*, 415 (1955).
(11) E. Kloster-Jensen, N. Tarköy, A. Eschenmoser, and E. Heilbronner, *Helv. Chim. Acta*, **39**, 786 (1956).
(12) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3047 (1955).
(13) A more accurate determination of pK_{R^+} was prevented by the behavior of the solutions on standing; see Experimental.
(14) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).
(15) E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman, and B. Pullman, *Bull. soc. chim. France*, 689 (1951).
(16) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley & Sons, Inc., New York, 1954, p. 114.
(17) W. von E. Doering and F. L. Detert, *J. Am. Chem. Soc.*, **73**, 876 (1951).

EXPERIMENTAL[18]

9-o-Aminophenyl-9-fluorenol. Under an atmosphere of dry nitrogen 365 ml. (0.398 mole) of a 1.09*M* ethereal solution of *n*-butyllithium[19] was added with stirring to 25.8 g. (0.150 mole) of *o*-bromoaniline in 100 ml. ether over a 1-hr. period at room temperature. The vigorous gas evolution slackened abruptly after the addition of 140 ml. of solution and the rate of addition was greatly increased at this point. The brown solution was stirred for an additional 30 min. before the addition of 36 g. (0.20 mole) of fluorenone dissolved in 500 ml. ether. The addition of the ketone required 1 hr. The mixture was allowed to stand overnight prior to hydrolysis by the addition of water. The ether layer was separated, washed with water, and extracted with 500 ml. of 10% HCl in five portions. No solid material was obtained from the acid extract upon treatment with excess alkali.

The dried ether solution was evaporated to a thick brown residue which was digested with a mixture of 100 ml. alcohol and 400 ml. 10% HCl on the steam bath for 30 min. The hot acid solution was decanted, treated with charcoal, filtered, cooled, and made alkaline. The digestion was repeated with fresh portions of acid as long as significant quantities of amine were extracted. The amine was taken up in ether and dried, and the solution was evaporated to 6.4 g. of a thick oil. The oil crystallized from benzene to give 2.28 g. of light crystalline powder, m.p. 141–143°. The analytical sample, m.p. 142.5–143.0°, was colorless.

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.50; H, 5.53; N, 5.13. Found: C, 83.39; H, 5.48; N, 5.02.

Deamination of 9-o-aminophenyl-9-fluorenol. The amino alcohol (2.05 g., 0.0075 mole) was finely powdered and suspended in 70 ml. of 10% sulfuric acid. Diazotization by the addition of a portion of 0.52 g. (0.0075 mole) sodium nitrite in 5 ml. water was very slow at 0°, so most of the solution was added at room temperature, over a 45-min. period. Under these conditions some nitrogen was evolved and a small amount of oil separated during the diazotization. The mixture was then heated on the steam bath until the evolution of nitrogen ceased. The precipitated oil was taken up in ether, washed with water, and extracted with 150 ml. of 5% NaOH in three portions. The neutral material obtained by evaporation of the dried ether solution was dissolved in 1:1 benzene-petroleum ether and adsorbed on a column of alumina. Elution with more of the same solvent yielded 0.457 g. of colorless crystals of I melting at 178–179° after crystallization from benzene. λ_{max}^{EtOH} 238 (log ϵ 4.58), 254 (4.52), 321 (3.40).

Anal. Calcd. for $C_{19}H_{12}O$: C, 89.04; H, 4.72. Found: C, 89.05, 89.15; H, 5.02, 4.72.

The *oxime*, prepared in the usual way and recrystallized from benzene melted at 196–197°.

Anal. Calcd. for $C_{19}H_{13}NO$: N, 5.16. Found: N, 4.91, 4.87.

The alkaline extract of the crude deamination product yielded, upon acidification, 0.604 g. of resinous material, presumably *9-o-hydroxyphenyl-9-fluorenol*, which crystallized from chloroform-petroleum ether as light amber prisms, m.p. 133–134°. Material of this melting point could be obtained only with considerable loss in weight, and its purity is apparently low.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 82.59; H, 5.32.

Alkali fusion of tribenzotropone. The ketone (0.121 g., 0.00047 mole) was added in portions to 2 g. molten KOH at a temperature just high enough to maintain the flux. After cooling, the solid was dissolved in water and the solution was filtered and acidified. The crude acid was taken up in ether, dried, and isolated as 0.080 g. (61%) of a thick, nearly colorless oil. *S-benzylthiuronium salt*, m.p. 154.5–155.0°.

Anal. Calcd. for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.49; N, 6.36. Found: C, 73.68; H, 5.61; N, 6.40.

On the basis of the following experiment the acid was assigned the structure *o-terphenyl-2-carboxylic acid*, IV.

Ring closure of the acid, IV. Treatment of 0.080 g. (0.00029 mole) of IV with 2 ml. of thionyl chloride on the steam bath overnight produced, after removal of excess $SOCl_2$, a yellow residue which was adsorbed on 4 g. of alumina. Elution with a 1:2 mixture of benzene-petroleum ether yielded 0.043 g. of yellow crystals, m.p. 116–117° alone and when mixed with a sample of 4-phenylfluorenone prepared as described below. The two samples exhibited the same infrared spectrum.

1-Phenylfluorenone. Fluorenone-1-carboxylic acid[20] was converted to the acid chloride, m.p. 134–135°, as described by Goldschmiedt[21] who reported the melting point as 140°. The acid chloride (3.60 g., 0.0148 mole) was dissolved in the minimum quantity of chloroform and treated for 1.5 hr. at 0° with a cold solution of excess Na_2O_2. The precipitated crude product was washed with cold water, methanol, and chloroform, and dried in air. The yellow *peroxide* melted at 157° with decomposition, and was very slightly soluble in the common organic solvents. Recrystallization was therefore impractical. Iodometric titration required 75–80% of the theoretical quantity of thiosulfate.

The crude peroxide (2.21 g.) was suspended in benzene and refluxed 48 hr., at which time the yellow solid had disappeared. After extraction of the dark benzene solution with alkali, chromatography on alumina yielded 0.796 g. of yellow crystalline material which melted at 120–121° after crystallization from ethanol. λ_{max}^{EtOH} 253 (log ϵ 4.71), 273 (4.34), 329 (3.45).

Anal. Calcd. for $C_{19}H_{12}O$: C, 89.04; H, 4.72; Mol. Wt., 256. Found: C, 89.47, 89.26; H, 5.24, 5.21; Mol. Wt. (Rast), 266.

The *oxime* melted at 235–236°.

Anal. Calcd. for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.92; H, 5.01; N, 5.09.

From the alkaline extract of the crude product there was obtained 0.857 g. of fluorenone-1-carboxylic acid, m.p. 199–201°.

4-Phenylfluorenone, V. Fluorenone-4-carboxylic acid[22] was converted to the acid chloride[23] which, when treated in the manner described above, gave a 65% yield of yellow crystals, m.p. 116–117° when crystallized from methanol (reported[4] m.p. 112°). λ_{max}^{EtOH} 250 (4.53), 258 (4.60), 304 (shoulder, 3.52), 333 (shoulder, 3.15).

Anal. Calcd. for $C_{19}H_{12}O$: C, 89.04; H, 4.72. Found: C, 89.15; H, 4.75.

The intermediate *peroxide*, m.p. 167° (dec.), was not purified.

Tribenzotropyl alcohol (II). The ketone (I) was reduced by sodium borohydride in either methanol or 95% ethanol to yield fine colorless needles, m.p. 118–119° (80%); λ_{max}^{alc} 222 (shoulder, log ϵ 4.34), 238 (4.51), 256 (shoulder, 4.04). Principal infrared bands of a chloroform solution were at 3577, 1487, 1479, 1438, 1190, 1126, 1063, and 1047 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{14}O$: C, 88.35; H, 5.46. Found: C, 88.26; H, 5.47.

Solutions of II *in sulfuric acid.* In order to measure pK_{R^+}, solutions of II were prepared in 6 different concentrations of sulfuric acid, ranging from 84 to 96%, and the absorption

(18) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(19) H. Gilman and R. G. Jones, *Org. Reactions*, **6**, 352 (1951). The concentration of alkyllithium was determined as described by H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(20) J. Forrest and S. H. Tucker, *J. Chem. Soc.*, 1137 (1948); L. F. Fieser and A. Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

(21) G. Goldschmiedt, *Monatsh.*, **23**, 886 (1902).

(22) R. Götz, *Monatsh.*, **23**, 32 (1904).

(23) C. Graebe and Ch. Aubin, *Ber.*, **20**, 845 (1887).

at 410 mμ was measured in 1-cm. cells with a Cary Model 11 Spectrophotometer. It was found that the absorption of solutions in 92–96% H_2SO_4 increased over a period of hours and then slowly fell. The maximum value of A/c for each solution was in the range (0.9–1.2) × 10^4 liters/mole. Solutions of II in 86–89% H_2SO_4 absorbed more weakly and the intensity of the 410 mμ band began to decrease immediately, falling to nearly zero over a period of a few hours. The color of a solution in 84% H_2SO_4 was barely discernible, A/c = 6 × 10^2 at 410 mμ. An approximate value of −15 for pK_{R^+} may be calculated from these data. A more precise determination was not attempted due to poor reproducibility. Similar behavior has been reported[12] for other rather unstable carbonium ions.

Acknowledgment. This work was supported by a grant-in-aid from the Carbide and Carbon Chemicals Company.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

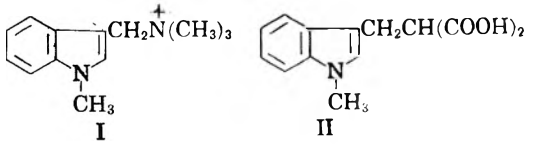
Certain Alkylations with the Methiodide of *N,N*-Dimethylaminomethylferrocene. Synthesis of an α-Amino Acid Having the Ferrocene Group[1]

CHARLES R. HAUSER AND JACQUE K. LINDSAY

Received April 29, 1957

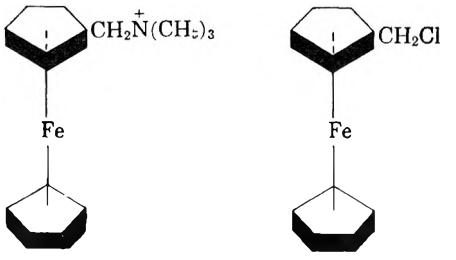
Alkylations of sodio malonic ester and sodio ethyl acetamidocyanoacetate with the methiodide of *N,N*-dimethylaminomethylferrocene were effected, and the products hydrolyzed and decarboxylated to form the corresponding monocarboxylic acids. The latter overall reaction produced an α-amino acid having the ferrocene group, which may be regarded as an analogue of phenylalanine.

Certain quaternary ammonium ions have been more available than the corresponding alkyl halides, and have been employed successfully in the alkylations of the sodium derivatives of active hydrogen compounds.[2] For example, quaternary ammonium ion I, which is prepared by the methylation of 1-methylgramine, has been used in the alkylation of sodio malonic ester to form II (after saponification).[3]



I II

In the present investigation quaternary ammonium ion III was employed in the alkylations of sodio malonic ester and sodio ethyl acetamidocyanoacetate. This quaternary ammonium ion was readily prepared by the aminomethylation of ferrocene, followed by the methylation of the resulting tertiary amine.[4] On the other hand attempts to prepare the corresponding chloride (IV) by treatment of hydroxymethylferrocene[4] with thionyl chloride or hydrogen chloride produced material that failed to give the Beilstein test for halogen. Similarly the product from hydroxymethylferrocene and phosphorus tribromide appeared not to contain halogen.



III IV

The alkylation of sodio malonic ester with quaternary ion III was effected in ethanol, and the resulting alkylation product was saponified to form dicarboxylic acid V in 67% yield. This dicarboxylic acid was decarboxylated to give monocarboxylic acid VI in 85% yield, the overall yield from III being 57%.

Similarly the alkylation of sodio ethyl acetamidocyanoacetate was effected with quaternary ion III, and the alkylation product hydrolyzed and decarboxylated to form amino acid VII in 67% yield. This α-amino acid was isolated as the monohydrate and in the anhydrous condition. It may be considered as an analog of phenylalanine.

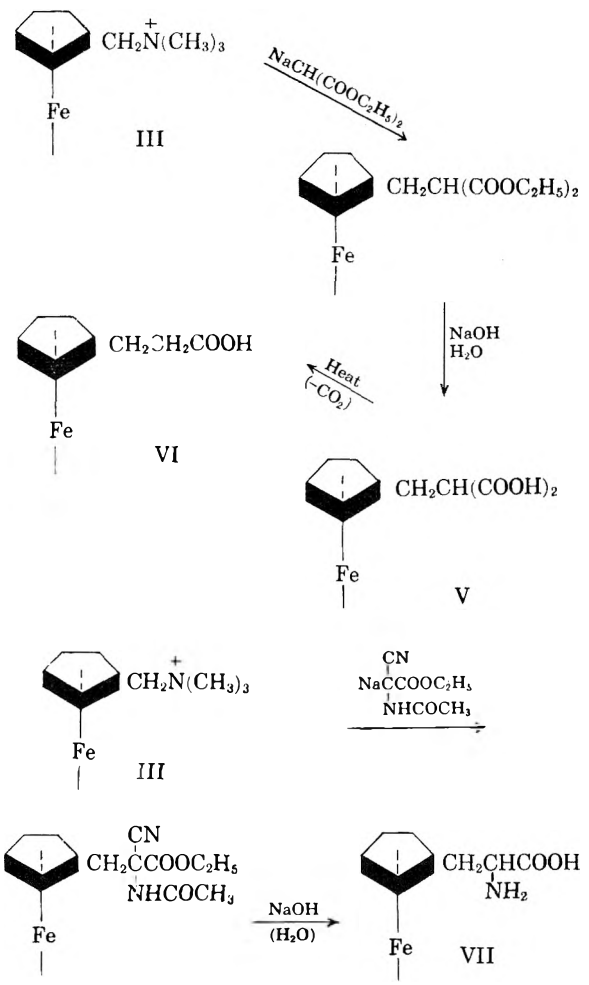
It should be mentioned that sodio acetonitrile, prepared by means of sodium amide in a mixture of liquid ammonia and ether, failed to undergo alkylation with quaternary ammonium ion III within one hour in this medium (at −33°). Since the quaternary ammonium salt was recovered, higher temperatures appear to be required for such alkylations.

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) See H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Am. Chem. Soc.*, 66, 200 (1944).

(3) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 663 (1949); *see also, Org. Reactions*, **VII**, 99 (1953).

(4) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).



EXPERIMENTAL[5]

Alkylation of malonic ester with quaternary ion III. Dicarboxylic acid V and monocarboxylic acid VI. The methiodide of *N,N*-dimethylaminomethylferrocene (III) was prepared as described previously[4] by the aminomethylation of ferrocene (dicyclopentadienyliron)[6] with formaldehyde and dimethylamine followed by the methylation of the resulting tertiary amine with methyl iodide.

A solution of sodium ethoxide was prepared under nitrogen from 2.3 g. (0.1 mole) of freshly cut sodium and 100 ml. of absolute ethanol, and a solution of 16.0 g. (0.1 mole) of redistilled diethyl malonate in 20 ml. of absolute ethanol was added.

To the resulting sodio malonic ester (0.1 mole) was added, with stirring, 38.5 g. (0.1 mole) of the solid methiodide (III), and the solution stirred and refluxed for 43 hr. The odor of trimethylamine was detected at the top of the condenser. After cooling, the reaction mixture was poured onto crushed ice, acidified carefully with 1*N* hydrochloric acid, and extracted three times with ether. The combined ethereal extract was washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. After filtering, the solvent was removed to leave 34 g. of the alkylation product as a clear amber oil which crystallized slowly.

To 30.0 g. of this crude alkylation product was added 10 ml. of 95% ethanol and 50 ml. of 30% potassium hydroxide solution, and the resulting mixture was refluxed for 8 hr. After cooling, diluting with four volumes of water, and extracting with ether, the alkaline solution was acidified carefully with 6*N* hydrochloric acid to precipitate dicarboxylic acid V which was collected on a funnel, washed with water, and dried. This acid (18 g., 67%) melted at 130–133° (dec.). A sample of the solid acid was boiled with water, and the resulting emulsion was filtered and cooled rapidly to produce fine golden plates m.p. 133–134° (dec.) (sample immersed in the melting point bath at 120°).

Anal. Calcd. for $C_{14}H_{14}O_4Fe$: C, 55.66; H, 4.67; Fe, 18.49; Neut. equiv., 151. Found: C, 56.07; H, 4.77; Fe, 18.23; Neut. equiv., 148.

A 7 g. (0.023 mole) sample of dicarboxylic acid V was heated in a flask immersed in an oil bath at 145–150° until frothing ceased (20 min.). The resulting residue was dissolved in 1*N* sodium hydroxide and the solution boiled with decolorizing carbon. After filtering, the solution was cooled and acidified with 6*N* hydrochloric acid to precipitate monocarboxylic acid VI which was collected on a funnel, washed with water, dried, and recrystallized from *n*-heptane. There was obtained 5 g. (84%) of acid VI as fine orange needles, m.p. 116–118°.[7]

Anal.[8] Calcd. for $C_{13}H_{14}O_2Fe$: C, 60.49; H, 5.47; Fe, 21.64. Found: C, 60.50; H, 5.39; Fe, 21.28.

Alkylation of ethyl acetamidocyanoacetate with quaternary ion III. Amino acid VII. This alkylation was carried out in ethanol essentially as described above for malonic ester employing 0.1 mole each of sodium ethoxide, ethyl acetamidocyanoacetate, and the methiodide (III). After stirring and refluxing for 43 hr. (odor of trimethylamine), the reaction mixture was cooled, and the solvent removed partially (water aspirator). Four volumes of water were added, and the mixture extracted three times with ether. The combined ethereal extract was washed with water until neutral to litmus, and dried over magnesium sulfate. After filtering, the solvent was removed to give 30.0 g. of yellow powder, m.p. 172–178°.

This crude alkylation product was hydrolyzed and decarboxylated to form amino acid VII in one step essentially as described by Herz, Dittmer, and Cristol.[9]

To 20.0 g. of the crude alkylation product was added a solution of 20 g. of sodium hydroxide in 200 ml. of water, and the resulting mixture was refluxed for 20 hr. After cooling, and filtering, the reaction mixture was acidified with 1*M* phosphoric acid to *p*H6. The resulting mixture was chilled in an ice bath, and the precipitate collected on a funnel, washed with ice water, and dried. There was obtained 13 g. (67% overall yield calculated as the monohydrate) of crude amino acid VII (yellow powder). It gave the ninhydrin test for α-amino acids. A sample of the yellow powder was recrystallized from a mixture of equal amounts of 95% ethanol and water to give golden plates of the monohydrate of amino acid VII, m.p. 321–333° (dec.).

Anal. Calcd. for $C_{13}H_{17}O_3NFe$: C, 53.63; H, 5.89; N, 4.81; Fe, 19.18. Found: C, 53.66; H, 5.92; N, 4.64; Fe, 19.24.

A sample of the monohydrate was dried at 110° to give yellow plates of anhydrous VII, m.p. 321–333° (dec.).

Anal. Calcd. for $C_{13}H_{15}O_2NFe$: C, 57.17; H, 5.54; N, 5.13; Fe, 20.45. Found: C, 57.29; H, 5.67; N, 5.13; Fe, 20.18.

DURHAM, N. C.

(5) Melting points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn.

(6) We are indebted to Linde Air Products Co., Tonawanda, N. Y., (Dr. R. L. Pruett) for a generous sample of this compound.

(7) This melting point was not depressed on admixture with a sample of acid VI kindly furnished by Dr. K. L. Rinehart of the University of Illinois who prepared it by the carbethoxylation of acetylferrocene, followed by hydrogenation and saponification.

(8) Galbraith Laboratories reported that this acid was too insoluble for a neutralization equivalent.

(9) W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

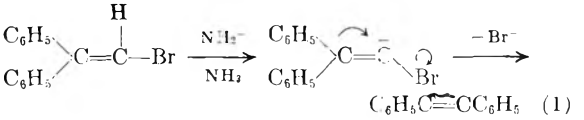
Reaction of 9-Bromomethylenefluorene with Potassium Amide in Liquid Ammonia. Dimerization[1]

CHARLES R. HAUSER AND DANIEL LEDNICER

Received June 17, 1957

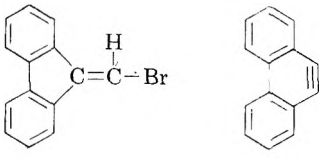
9-Bromomethylenefluorene reacted with potassium amide in liquid ammonia to form a brick-red cumulene and a white product, both of which still contained the fluorene nucleus. No phenanthrene derivative which might have been produced through α-elimination and rearrangement, was found. Mechanisms are considered. An improved method of synthesis is described for the α,β-unsaturated acid employed in the preparation of the 9-bromomethylenefluorene.

Coleman and coworkers[2] have shown that 1,1-diaryl-2-haloethenes undergo with potassium amide in liquid ammonia the α-elimination of hydrogen halide accompanied by the rearrangement of an aryl group to form tolanes. The mechanism has been considered to involve the ionization of the α-hydrogen of the halide by the amide ion, and rearrangement of the resulting carbanion as illustrated below for the bromoethene (Equation 1).[3,4]



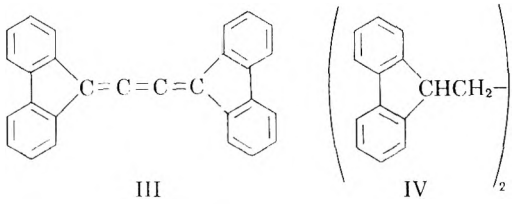
(1)

In the present investigation a study was made of the reaction of the analogous compound in the fluorene series, bromide I, with this reagent. The corresponding rearrangement of bromide I would involve ring enlargement to form a phenanthrene derivative, possibly through intermediate II which would be the phenanthrene analog of benzyne.[5]



I II

However, no phenanthrene derivative was found. Instead, the brick-red solid, cumulene III, and a white solid were obtained. The cumulene (III), which has previously been prepared in other ways,[6,7] was readily identified by its melting point,[6] visible spectrum,[7] and by reduction to IV.[6]

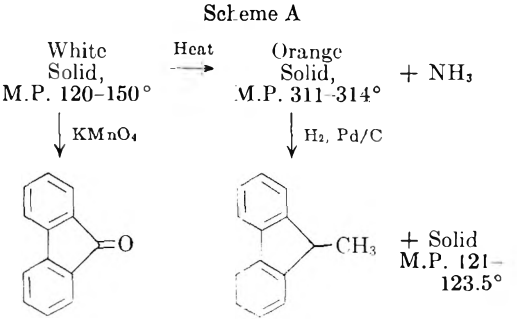


III IV

The white solid, which contained nitrogen but no halogen, exhibited an infrared absorption peak due to the N—H group and apparently also one due to a C=N group. It decomposed slowly at room temperatures and rapidly at its melting point, about 120–150°, eliminating ammonia to form a higher-melting orange solid. The latter product showed the same infrared absorption peak assumed for the C=N group but the peak for the N—H group was absent. The analytical values for the orange product, as well as the "neutralization equivalent" of the ammonia eliminated in its formation, suggests that it has the molecular formula $C_{70}H_{47}N_3$ (a pentamer).

Although neither the white solid nor the orange solid derived from it were identified, they both evidently contained the fluorene nucleus since oxidation of the former and reduction of the latter produced fluorenone and 9-methylfluorene, respectively. Also, another product was formed in the latter reaction. These results are summarized in Scheme A.

Scheme A



The yield of cumulene III from bromide I, as well as that of the white product, was dependent on the mode of addition of the reactants. Thus, III was obtained in 95% yield when the potassium amide in liquid ammonia was added slowly to the

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) G. H. Coleman and R. D. Maxwell, *J. Am. Chem. Soc.*, **56**, 132 (1934); G. H. Coleman, W. H. Holst, and R. D. Maxwell, *J. Am. Chem. Soc.*, **58**, 2310 (1936).

(3) C. R. Hauser, *J. Am. Chem. Soc.*, 62, 933 (1940).

(4) A. A. Bothner-By, *J. Am. Chem. Soc.*, **77**, 3293 (1955).

(5) See J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *J. Am. Chem. Soc*, **78**, 611 (1956).

(6) D. Lavie and E. D. Bergman, *J. Org. Chem.*, **18**, 367 (1953).

(7) R. Kuhn and G. Platzer, *Ber.*, **73B**, 1410 (1940).

bromide whereas the yield of this compound was decreased to only 12% when the bromide was added slowly to the reagent. The white solid was the main product under the latter conditions, in which the amide ion was always present in excess. Also, under these conditions some of the cumulene III appeared to be destroyed since, in a blank experiment, only 52% of this compound was recovered after it had been treated with potassium amide in liquid ammonia for one hour.

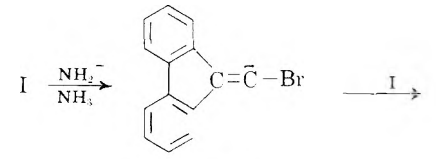
While potassium amide produced a 95% yield of cumulene III under the most suitable conditions, sodium amide gave only a 51% yield of this product under similar conditions. In a single experiment, lithium amide produced mainly tar.

The conversion of bromide I to cumulene III appears to be analogous to that of α-phenylalkyl halides to dimeric olefins which has been shown to involve a self-alkylation β-elimination mechanism[8,9] as illustrated below with benzyl chloride (Equation 2). In fact, intermediate dimeric halides, such as V, have been isolated.[9]

$$C_6H_5CH_2Cl \xrightarrow[NH_3]{NH_2^-} C_6H_5\bar{C}(H)-Cl \xrightarrow{C_6H_5CH_2Cl} C_6H_5CH_2-CH(Cl)C_6H_5 \xrightarrow{-HCl} C_6H_5CH=CHC_6H_5 \quad (2)$$

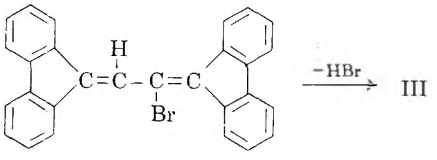
V

The analogous self-alkylation of bromide I to produce cumulene III, which may be regarded as a dimeric olefin, would involve the intermediate formations of carbanion VI and dimeric halide VII (Equation 3).



VI

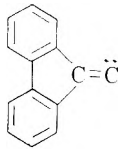
(3)



VII

Whereas the addition of one half of an equivalent of sodium amide to benzyl chloride produced dimeric halide V in good yield,[9] these conditions failed to yield dimeric halide VII, the only isolable material being cumulene III (23%) and recovered bromide I (43%). However, this does not necessarily mean that dimeric halide VII is not an intermediate since its dehydrohalogenation (β-elimination) might be expected to proceed faster than the self-alkylation of bromide I which is a vinyl type halide.

An alternative mechanism would involve the loss of bromide ion from intermediate carbanion VI to form carbene VIII which undergoes dimerization to give cumulene III. This mechanism of formation of cumulene III appears less likely than



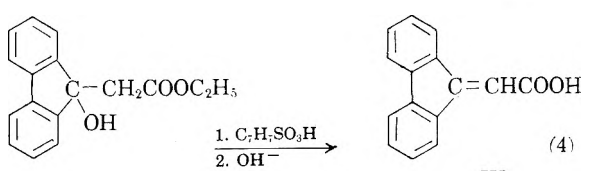
VIII

that involving self-alkylation (Equation 3) since such a carbene as VIII might be expected to add the elements of ammonia, which is present in large excess, more readily than undergo dimerization. On the other hand, the formation of the white product mentioned above might have involved the addition of ammonia or the amide ion to carbene VIII to form an enamine which underwent further reaction. Thus, not only did the white product contain nitrogen but its formation was favored when the amide ion was present in excess and the halide in minimum amounts.

It is of interest that, regardless of the mechanisms, the formations of cumulene III and of the white product did not involve the type of rearrangement exhibited by 1,1-diphenyl-2-bromoethene to which bromide I is structurally analogous. Apparently the energetics that would be involved in the enlargement of the five-membered ring within carbanion VI to form the phenanthryne (II) are unfavorable.

Finally, it should be mentioned that α,β-unsaturated acid IX from which bromide I was prepared was synthesized more conveniently than previously.[10] This was accomplished in an over-all yield of 72% from 9-fluorenone by an adaptation of the method developed recently in this laboratory[11] employing two equivalents of lithium amide to one of ethyl acetate and one of the ketone (Equation 4). α,β-Unsaturated acid IX was converted to bromide I by the method of DeTar and co-workers.[10]

$$CH_3COOC_2H_5 \xrightarrow{2\ LiNH_2} LiCH_2COOC_2H_5 \xrightarrow{\text{fluorenone}}$$



IX

(4)

(8) M. S. Kharasch, W. Nudenberg and E. K. Fields, *J. Am. Chem. Soc.*, **66**, 1276 (1944).

(9) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(10) See D. R. F. DeTar, E. Broderick, G. Foster and B. D. Hilton, *J. Am. Chem. Soc.*, **72**, 2183 (1950).

(11) C. R. Hauser and J. K. Lindsay, *J. Am. Chem. Soc.*, **77**, 1055 (1955).

EXPERIMENTAL[12]

9-Fluorenylideneacetic acid (IX) Ethyl acetate (17.6 g., 0.20 mole) in 80 ml. of ether was added to a suspension of 0.44 mole of lithium amide (from 3.0 g. of lithium), in 600 ml. of liquid ammonia.[11] After stirring for 10 min., a solution of 36.0 g. (0.20 mole) of 9-fluorenone in 400 ml. of ether was added to the grey suspension. When all the ketone had been added the ammonia was displaced by 160 ml. of ether and the greenish grey suspension stirred under reflux for 2 hr. The mixture was allowed to cool and treated with 200 ml. of cold dilute hydrochloric acid; the organic layer was separated, washed with water, with saturated sodium bicarbonate solution, and again with water. The ethereal solution was then dried over sodium sulfate and the solvent was removed to leave behind 51.0 g. of an amber oil.

The product of the above reaction and 2.5 g. of *p*-toluenesulfonic acid in 500 ml. of benzene was brought to reflux. After the evolution of water had ceased (70 min.) solid sodium bicarbonate was added, the solution was washed with water, and the solvent was removed *in vacuo*. On cooling, the residue formed a crystalline mass.

This solid was dissolved in 180 ml. of ethanol containing 20 g. of sodium hydroxide and 20 ml. of water. The resulting blue solution was heated under reflux for 2.5 hr. At the end of this time the solution was poured into 1.2 l. of water, and this was washed with ether. Acidification of the alkaline aqueous solution afforded a yellow precipitate. The acid thus obtained was collected by filtration, dried, and recrystallized from ethanol to yield 32.0 g. (72%) of acid IX, m.p. 223.5–224.5°, lit.[13] 227–228°.

Conversion of acid IX *to bromide* I. Acid IX (5.56 g., 0.025 mole) was dibrominated and then the dibromide treated with aqueous base in the manner described by DeTar and co-workers[10] to afford 3.80 g. of (I), m.p. 73.5–74.5°, and a second crop of 1.23 g., m.p. 71–73° (total yield, 78%).

Reaction of bromide I *with potassium amide. A. Inverse addition procedure.* Potassium amide (0.011 mole) was prepared from 0.42 g. of potassium and 100 ml. of liquid ammonia in an inverse addition flask. Over a period of 25 min. the base was added to a solution of 2.44 g. (0.010 mole) of bromide I in 30 ml. of ether and 100 ml. of liquid ammonia. A brick-red solid precipitated as the addition proceeded. After a total reaction time of 40 min., 5 g. of ammonium chloride was added to the mixture and the ammonia allowed to evaporate. The residual solid was washed with water and then ether. After drying, 1.60 g. (95%) of red solid remained. This was recrystallized from anisole to yield 1.37 g. (80%) of cumulene III (red crystals), m.p. 309° (charring) lit.[6] 302°; λ_{max}, 488, 453 mμ (pyridine), lit.[7] λ_{max} 488, 454 mμ.

A suspension of 0.30 g. of the red compound (III) and 0.15 g. of 10% palladium on charcoal in 75 ml. of ethyl acetate was stirred under hydrogen until the theoretical amount (58 ml.) of gas had been taken up. The catalyst was removed by filtration and the solvent evaporated. The residual solid was recrystallized from benzene ethanol to yield 197 mg. of IV, m.p. 228–229°; lit.[6] 223–224°.

B. Addition of bromide I *to potassium amide.* A solution of 5.0 g. (0.02 mole) of the halide in 200 ml. of ether was added to 0.045 mole of potassium amide (from 1.8 g. of potassium) in 400 ml. of liquid ammonia with vigorous stirring over 1.5 hr. After an additional hour ammonium chloride was added and the ammonia allowed to evaporate. The reddish residue was washed with 500 ml. of ether in portions. After the solid was washed with water and dried, 0.42 g. (12%) of the red cumulene III remained.

The ether extracts were then washed with water and taken to dryness under vacuum at room temperature. A white (sometimes yellowish) solid remained, m.p. 125–150° (dec.); λ_{max} 2.90, 3.00, 6.05 μ. Since this solid darkened on standing at room temperature, and more quickly in solution, it could not, in the authors' hands, be further purified, either by crystallization or chromatography. All further reactions of this were undertaken with the material as obtained from the reaction.

Oxidation of white product. A solution of 2.1 g. of the white solid in 50 ml. of acetone was added to a hot solution of 10 g. of potassium permanganate in 100 ml. of water. The reaction was stirred under gentle reflux as in the course of 8 hr. 40 g. of additional potassium permanganate was added. When the reaction had cooled the manganese dioxide was removed by filtration and washed well with water. Concentration of the alkaline washes to 30 ml. and subsequent acidification failed to yield any organic material.

The air dried manganese dioxide was washed well with ether. When this solution was taken to dryness 0.95 g. of reddish gum remained. This was chromatographed on an alumina column to afford 0.50 g. of orange crystals m.p. 82–84°, and 60 mg. m.p. 80–83°. A mixed melting point of the first fraction with an authentic sample of 9-fluorenone was 82–84°.

Deammoniation of white product to form orange compound. A carefully weighed sample (0.7660 g.) of the white solid was heated to 160° under a stream of nitrogen and the exit gas bubbled through water. At the end of 1 hr. the evolution of ammonia had ceased. The "neutralization equivalent" of the water in the trap was 442; calcd. for $C_{70}H_{47}N_3$, 465, (assuming loss of two molar equivalents of ammonia).

The dark solid was recrystallized from anisole to afford 0.51 g. of dark needles, m.p. 304–310° (dec.).

A small sample was recrystallized to constant m.p. 311–314° (dec.); λ_{max} 6.05 μ (red in presence of base and yellow in acid).

Anal. Calcd. for $C_{70}H_{47}N_3$: C, 90.43; H, 5.10; N, 4.52. Found:[14] C, 90.46, 90.39; H, 5.14, 5.04; N, 4.52, 4.57.

Catalytic reduction of orange compound. A suspension of 380 mg. of V and 200 mg. of 10% palladium on charcoal in 20 ml. of ethyl acetate was stirred under hydrogen for 4 hr., with the uptake of 78 ml. of gas (3.4 mmole). The oily gum which remained when the solvent was removed partly crystallized on standing. Recrystallization from methanol afforded 120 mg. of solid m.p. 100–120°. A sample was recrystallized to constant m.p. 121–123.5°.

Anal. Found: C, 89.87; H, 6.23; N, 4.05.

Chromatography of the gums obtained from the mother liquors of the first crystallization afforded 80 mg. of crystals m.p. 41–43°, whose ultraviolet absorption spectrum is identical with that of 9-methylfluorenone.

Attempted isolation of dimeric halide VII. A solution of sodium amide prepared from 0.12 g. (0.0052 mole) of sodium and 100 ml. of liquid ammonia was added to 2.57 g. (0.010 mole) of the bromide I, over 30 min. The red solid came out almost immediately. The reaction mixture was then worked up in the usual manner to afford 0.40 g. (22.5%) of cumulene, m.p. 298°.

The ether washes were taken to dryness to leave behind a tarry partially crystalline residue. This was dissolved in chloroform and passed through a short alumina column to yield 1.10 g. (43%) of starting material, m.p. 68–72°.

In one run where a full equivalent of sodium amide was added to the bromide I, the yield of cumulene obtained was 52%.

DURHAM, N. C.

(12) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) A. Sieglitz and H. Jassoy, *Ber.*, **54**, 2133 (1921).

(14) The two values represent different samples.

Notes

A department for short papers of immediate interest.

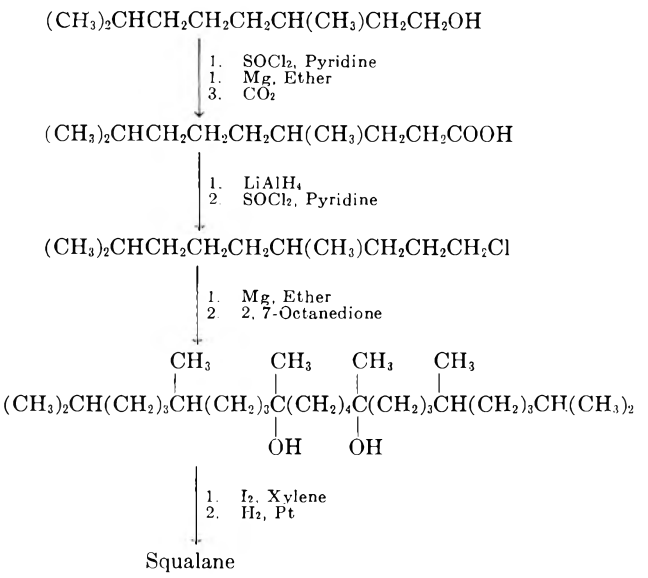
Synthesis of Squalane

KARL J. SAX AND FRED H. STROSS

Received April 16, 1957

Squalane (the mixture of stereoisomers of 2,6,-10,15,19,23-hexamethyltetracosane formed on hydrogenation of squalene) has been tested as a standard for several analytical procedures.[1] During this study a synthetic sample was prepared by a new route to compare its properties with those of hydrogenated squalene. The method of preparation is outlined in Fig. 1.

FIGURE 1.



Although squalane has been prepared by the hydrogenation of both synthetic and natural squalene,[2–6] the reported constants vary considerably. Four reference samples prepared in this work by the hydrogenation of squalene had identical physical properties.[1] The synthetic sample reported here differed slightly in refractive index and viscosity. Mass spectrocopy showed that it contained a small amount of impurity which may have caused the difference. The infrared spectra of the synthetic sample and of hydrogenated squalene were superimposable.

EXPERIMENTAL

Tetrahydrogeraniol. Geraniol was hydrogenated with Raney nickel according to the method of Smith *et al.*[7] The product had a b.p. 107°/10 mm., n_D^{20} 1.4379–1.4381 (reported[7] n_D^{20} 1.4379).

Tetrahydrogeranyl chloride. Tetrahydrogeraniol was converted to the chloride with thionyl chloride and pyridine. Distillation in a packed column at 92–94°/13–15 mm. gave a 66% yield of product, n_D^{20} 1.4364.

Anal. Calcd. for $C_{10}H_{21}Cl$: C, 67.96; H, 11.98; Cl, 20.06. Found: C, 68.2; H, 12.0; Cl, 20.0.

4,8-Dimethylnonanoic acid. A Grignard reagent was prepared from 138.5 g. (0.784 mole) of tetrahydrogeranyl chloride and 19.1 g. (0.785 mole) of magnesium in anhydrous ether. The ether solution was poured onto crushed dry ice and the reaction complex was hydrolyzed with 40 ml. of concentrated sulfuric acid in 600 ml. of water. The ether layer was separated and the aqueous layer was re-extracted with ether. The combined ether extract was washed once with water and the acid was extracted with a solution of 70 g. of potassium hydroxide in 1 liter of water in two portions. The solution of the sodium salt was washed with ether several times, acidified, and the free acid was extracted with ether. The ether was evaporated and the product was distilled through a packed column at 126°/3.5 mm. Fractions with a neutralization equivalent of 186.0–186.5 (calcd. 186.3) were combined; wt. 75.0 g. (51%).

4,8-Dimethylnonanol-1. A solution of 70.4 g. of 4,8-dimethylnonanoic acid in 200 ml. of anhydrous ether was added dropwise, during stirring, to a suspension of 16 g. of

(1) K. J. Sax and F. H. Stross, *Anal. Chem.*, in press.
(2) S. Trippett, *Chemistry and Industry*, **80** (1956).
(3) M. Tsujimoto, *Ind. Eng. Chem.*, **8**, 889 (1916).
(4) A. C. Chapman, *J. Chem. Soc.*, 56 (1917).
(5) A. C. Chapman, *J. Chem. Soc.*, 769 (1923).
(6) I. M. Heilbron, E. D. Kamm and W. M. Owens, *J. Chem. Soc.*, 1631 (1926).
(7) L. I. Smith, H. E. Ungnade, F. L. Austin, W. Pritchard, and J. W. Opie, *J. Org. Chem.*, **4**, 338 (1939).

lithium aluminum hydride in 300 ml. of anhydrous ether. The suspension was stirred overnight, refluxed for 1 hr. and the excess hydride was decomposed with methanol in ether solution. Water was added slowly and the pasty mass was acidified with hydrochloric acid. The aqueous layer was removed and extracted twice with ether. The combined ether extract was washed with dilute sodium hydroxide solution and water. The ether layer was dried over magnesium sulfate, filtered, and evaporated. The yield of product (64.2 g., n_D^{20} 1.4385) was 99%.

Anal. Calcd. for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.39; H, 13.99.

4,8-Dimethylnonyl chloride. A mixture of 94.0 g. (0.546 mole) of 4,8-dimethylnonanol-1 and 41.0 g. (0.519 mole) of pyridine was added slowly to 130 g. (1.09 mole) of thionyl chloride during cooling and shaking in an ice bath. The mixture was refluxed 1.5 hr., cooled, and the upper layer was separated and poured onto crushed ice. The aqueous layer was separated and the product layer was diluted with benzene, washed with water several times, 10% sodium carbonate solution twice and was dried over potassium carbonate. After filtration, the benzene was evaporated and the product was distilled in vacuum at 92–93°/7.5 mm; wt. 98.8 g. (95%). The product was redistilled in a packed column. The major portion boiled at 99°/10 mm., n_D^{20} 1.4396.

Anal. Calcd. for $C_{11}H_{23}Cl$: C, 69.26; H, 12.15; Cl, 18.6. Found: C, 69.29; H, 12.17; Cl, 18.8.

2,7-Octanedione. A Grignard reagent was prepared from 88.7 g. (0.62 mole) of methyl iodide, 15.2 g. (0.63 mole) of magnesium and 250 ml. of ether. The solution was cooled under nitrogen and treated with 62.5 g. of anhydrous cadmium chloride during stirring. A negative Gilman test was obtained after 0.5 hr. The ether was replaced with benzene by distillation until the distillate began to leave a deposit on evaporation.

The dimethylcadmium suspension was cooled and added slowly during stirring to a cooled solution of 49 g. (0.27 mole) of adipyl chloride (Distillation Products Inc.) in 300 ml. of benzene. The mixture was refluxed for 1 hr., cooled and treated with 500 ml. of saturated ammonium chloride. The benzene layer was separated and the aqueous residue was extracted twice with ether. The combined extract was washed with dilute sodium bicarbonate and water and dried over magnesium sulfate. After filtration, the benzene was evaporated and the product was crystallized from benzene-petroleum ether (30–60°). Fractional crystallization from benzene-petroleum ether gave 20.1 g., (53%) m.p. 39.5–40.5.

2,6,10,15,19,23-Hexamethyl-10,15-tetracosanediol. A Grignard reagent was prepared from 57.2 g. (0.3 mole) of 4,8-dimethylnonyl chloride and 7.3 g. (0.3 mole) of magnesium in about 250 ml. of ether at reflux. The solution was assayed by titration of an aliquot and 0.273 mole of Grignard reagent was found. A solution of 14.2 g. (0.1 mole) of 2,7-octanedione in 100 ml. of benzene was added to the ethereal Grignard solution during stirring under nitrogen. The mixture was placed on a steam bath and the ether was replaced with benzene by distillation over an hour's time. The mixture was allowed to stand under nitrogen for 2 days and 500 ml. of 20% sulfuric acid was added during cooling and stirring. The benzene layer was separated and washed with water and sodium bicarbonate until neutral. The aqueous layers were washed with benzene and the combined benzene extract was dried over magnesium sulfate, filtered, and concentrated in vacuum. The infrared absorption spectrum of the residue, 42 g. (92% based on diketone) indicated the presence of tertiary hydroxyl groups.

Anal. Calcd. for $C_{30}H_{62}O_2$: C, 79.22; H, 13.74. Found: C, 78.95; H, 13.65.

Octahydrosqualene. A solution of 30 g. of the above diol in 350 ml. of xylene was treated with 0.1 g. of iodine and was distilled slowly for 1 hr. Another 0.1 g. portion of iodine was added each hour for 12 hr. as the distillation was continued. The xylene was removed by distillation in vacuum and the residue was dissolved in petroleum ether and passed through a 170 × 66 mm. alumina column. A total of 29.0 g. was isolated in the first 500 ml. of petroleum ether eluate; a colored zone remained on the column. The product was heated at 100°/4 mm. for 0.5 hr. and 26.1 g. of product (94%) was obtained.

Anal. Calcd. for $C_{30}H_{56}$: C, 86.04; H, 13.96. Found: C, 86.0; H, 13.9.

Squalane. A mixture of 23.0 g. of octahydrosqualene was placed in a hydrogenation bottle with 0.5 g. of platinum oxide. The mixture was shaken under hydrogen until the theoretical amount of hydrogen was absorbed. Shaking was continued for several hours without further hydrogen uptake. The product was diluted with benzene and filtered. Evaporation of the benzene gave a residue of 17.5 g., n_D^{20} 1.45200. It was passed through a 20 × 200 mm. silica gel column with isopentane; 17.0 g., n_D^{20} 1.45195. Distillation in a molecular still gave about 1.0 g. of forerun, n_D^{20} 1.4511 and a main fraction, n_D^{20} 1.4520, viscosity at 100°F., 20.21 cs. The ultraviolet and infrared absorption spectra showed traces of a monosubstituted benzene. The product was passed through a twelve-foot column of silica gel with isopentane and the eluate was examined in an ultraviolet spectrophotometer. No absorption was noted. The cuts were combined and evaporated. The product, 7.0 g., n_D^{20} 1.45189 gave an infrared absorption spectrum identical with the reference curve. The viscosity was essentially unchanged.

Anal. Calcd. for $C_{30}H_{62}$: C, 85.22; H, 14.78. Found: C, 85.26; H, 14.76.

SHELL DEVELOPMENT CO.
EMERYVILLE, CALIF.

Vinyl Derivatives of the Metals. V. Free Radical Addition Reactions of Triethylvinyltin[1]

DIETMAR SEYFERTH

Received May 27, 1957

In Part II of this series[2] it was shown that hydrogen bromide and mercaptans, which undergo free radical, peroxide-catalyzed addition to vinylsilicon compounds, cleave the vinyl-tin bond. The fact that even mercaptans reacted in this manner seemed to indicate that any reagent capable of electrophilic attack on the *alpha*-carbon atom of the vinyl group attached to tin would undergo this reaction in preference to the double bond addition reaction. Thus a rather severe limit was set on the types of compounds that could conceivably add to the vinyl-tin system.

The polyhalomethanes[3] and hydrogenchlorosilanes[4] are known to add to vinylsilanes. It would

(1) Part IV, D. Seyferth, *J. Am. Chem. Soc.*, **79**, 2738 (1957).

(2) D. Seyferth, *J. Am. Chem. Soc.*, **79**, 2133 (1957).

(3) (a) P. Tarrant, WADC Technical Report 55-220, August 1955; (b) A. F. Gordon, U. S. Patent 2,715,113 (August 1955); *Chem. Abstr.*, **50**, 7131 (1956); (c) A. D. Petrov, E. A. Chernyshev and M. Bisku, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nouk*, 1445 (1956).

(4) (a) C. A. Burkhard and R. H. Krieble, *J. Am. Chem. Soc.*, **69**, 2687 (1947); (b) M. Kanazashi, *Bull. Chem. Soc. Japan*, **26**, 493 (1953); (c) D. Seyferth and E. G. Rochow, *J. Org. Chem.*, **20**, 250 (1955).

not be expected that these reagents would cause vinyltin bond cleavage, hence a study of their action on vinyltin compounds was undertaken.

We have found that polyhalomethanes do indeed add to triethylvinyltin in the presence of benzoyl peroxide at about 90–95° to give moderate yields of adduct

$$(C_2H_5)_3SnCH{:}CH_2 + CCl_3Z \xrightarrow{Bz_2O_2} (C_2H_5)_3SnCHZCH_2CCl_3$$
$$(Z = H, Cl \text{ or } Br)$$

No proof was obtained that this is the structure of the addition product. However, in the case of vinylsilanes,[3a] it was shown by chemical means that addition of the trichloromethyl radical to the β-carbon atom of the vinyl group had occurred.

Triethylvinyltin was found to be considerably less reactive toward trichlorosilane than was trimethylvinylsilane. Thus only a 31% yield of adduct could be obtained in the case of the tin compound at 95° for 17 days. A yield of 71% was reported for the addition of trichlorosilane to trimethylvinylsilane.[4c] The adduct, β-trichlorosilylethyltriethyltin, could not be isolated in analytical purity, even after several fractional distillations. Pure β-trimethoxysilylethyltriethyltin was obtained, however, by treating the crude chlorosilane with a slurry of sodium methoxide in diethyl ether.[4c]

The platinum-on-charcoal–catalyzed addition of hydrogensilanes to olefins has been used extensively as a preparative method since its original disclosure by Wagner.[5] It was found that this catalyst system is not effective in promoting the reaction of triethylvinyltin with trichlorosilane or methyldichlorosilane. It is interesting to note that the attempted platinum-catalyzed hydrogenation of trialkylvinyltin compounds was also unsuccessful. It is thus possible that organotin compounds function as platinum catalyst poisons.

EXPERIMENTAL

Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Starting materials. Triethylvinyltin was prepared by the method described in Part I of this series.[6] The organic halides and hydrogensilanes were commercial materials.

Reaction of triethylvinyltin with polyhalomethanes. (*a*) *3,3,3-Trichloropropyltriethyltin.* A mixture of 23.4 g. (0.1 mole) of triethylvinyltin, 24 g. (0.2 mole) of $CHCl_3$, and 1.2 g. of benzoyl peroxide was sealed in a Carius tube and heated for 24 hr. in a steam bath. The tube was then cooled in liquid nitrogen and opened. Distillation of the contents gave 17.5 g. of unreacted $CHCl_3$, a small fraction apparently consisting of a mixture of triethylvinyltin and Et_3SnCl, and finally, 9.1 g. of $Et_3SnCH_2CH_2CCl_3$, b.p. 74° at 0.25 mm., n_D^{25} 1.5086, a yield of 25.8%.

Anal. Calcd. for $C_9H_{19}Cl_3Sn$: C, 30.68; H, 5.44; Cl, 30.19. Found: C, 30.70; H, 5.47; Cl, 30.05.

(*b*) *1,3,3,3-Tetrachloropropyltriethyltin.* A procedure similar to that described in (*a*) was used in the reaction of 22.4 g. (0.096 mole) of triethylvinyltin, 30.8 g. (0.2 mole) of CCl_4, and 1.2 g. of benzoyl peroxide. Fractional distillation gave a small forerun boiling from 35° at 2 mm. to 90° at 0.35 mm. and then 22.0 g. (59%) of $Et_3SnCHClCH_2CCl_3$, b.p. 100° at 0.3 mm., n_D^{25} 1.5230.

Anal. Calcd. for $C_9H_{18}Cl_4Sn$: C, 27.95; H, 4.69; Cl, 36.67. Found: C, 28.18; H, 4.40; Cl, 36.78.

(*c*) *1-Bromo-3,3,3-trichloropropyltriethyltin.* A mixture of 23.4 g. (0.1 mole) of triethylvinyltin and 20 g. of $CBrCl_3$ was heated to 90°, and then a solution of 1.2 g. of benzoyl peroxide in 20 g. of $CBrCl_3$ was added slowly in small portions. A very vigorous reaction commenced and the pot temperature quickly rose to 160°. After this initial exotherm, the pot temperature dropped to 120° during the addition of the remainder of the peroxide solution. Upon completion of the addition the reaction mixture was heated on the steam bath for 2 hr.

Distillation gave first a mixture of volatiles boiling from 32° at 1.3 mm. to 115° at 0.6 mm. This fraction smelled of trialkyltin halides, indicating some cleavage had taken place. The desired adduct, $Et_3SnCHBrCH_2CCl_3$, 15 g. (34.8%), b.p. 115° at 0.65 mm. to 119° at 0.9 mm., n_D^{25} 1.5425, followed.

Anal. Calcd. for $C_9H_{18}Cl_3BrSn$: C, 25.07; H, 4.21; Cl, 24.67; Br, 18.53. Found: C, 25.00; H, 4.08; Cl, 24.93; Br, 18.29.

Reaction of triethylvinyltin with trichlorosilane. A mixture of 23.4 g. (0.1 mole) of triethylvinyltin, 27 g. (0.2 mole) of $HSiCl_3$ and 2 g. of benzoyl peroxide was heated in a Carius tube in a steam bath for 17 days. Fractional distillation of the reaction mixture gave 14 g. of unreacted trichlorosilane, a forerun boiling from 25–72° at 0.6 mm., and 11.5 g. (31.2%) of crude $Et_3SnCH_2CH_2SiCl_3$, b.p. 85° at 0.6 mm.

Anal. Calcd. for $C_8H_{19}Cl_3SiSn$: C, 26.08; H, 5.20; Cl, 28.87. Found: C, 27.07; H, 5.70; Cl, 29.64.

Two further fractional distillations did not improve the analytical values.

β-Trimethoxysilylethyltriethyltin. A slurry of 7 g. (0.128 mole) of sodium methoxide in 100 ml. of diethyl ether was cooled to 0°. A solution of 15.6 g. (0.0424 mole) of crude $Et_3SnCH_2CH_2SiCl_3$ in an equal volume of ether was added slowly with vigorous stirring. The mixture then was refluxed for 2 hr., filtered, and the salts were washed with ether, the ether washings being added to the filtrate. Fractional distillation of the ether solution gave 9.9 g. (65.8%) of $Et_3SnCH_2CH_2Si(OMe)_3$, b.p. 78° at 0.4 mm., n_D^{25} 1.4638, d_4^{25} 1.209.

Anal. Calcd. for $C_{11}H_{28}O_3SiSn$: C, 37.20; H, 7.95; MR_D 80.0. Found: C, 37.37; H, 7.94; MR_D 81.0.

Acknowledgments. The author wishes to express his appreciation to the United States Office of Naval Research for support of this work, which may be reproduced in whole or in part for any purposes of the United States Government. It is also a pleasure to acknowledge a gift of trichlorosilane from Dow Corning Corporation, through the kind offices of Dr. W. Daudt. The author thanks also Helena A. Seyferth for carrying out the hydrogenation experiments mentioned in this note. Grateful acknowledgement is made of the advice and encouragement freely given throughout the course of this work by Professor E. G. Rochow.

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(5) G. H. Wagner, U. S. Patent 2,637,738 (May 1953).
(6) D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957).

Equilibration of Cryptone and Its β,γ-Unsaturated Isomer

MILTON D. SOFFER AND ANNE C. WILLISTON

Received April 28, 1957

One of the two recently reported[1] synthetic routes to *dl*-cryptone proceeds through the collidine dehydrobromination of 2-bromo-4-isopropylcyclohexanone, which gives a roughly equal mixture, separable by fractionation, of the α,β- and the β,γ-unsaturated ketones.

The formation of the β,γ-derivative under these conditions is of special interest since the method is in general use for the preparation of α,β-unsaturated ketones, and the apparent equilibration is an interesting example of favorable competition between conjugation and hyperconjugation effects.[2] That the ketones themselves form the same equilibrium mixture under the conditions of the dehydrohalogenation has now been demonstrated by treating the conjugated isomer with collidine and collidine hydrobromide. The distilled product appeared (λ_{max} 227 mμ, ε 7,620) to be a mixture comparable with that obtained from the collidine dehydrobromination (λ_{max} 227 mμ, ε 6,670) and this was confirmed by separating the pure isomers[1] (Δ^2 isomer, λ_{max} 227 mμ, ε 12,370; Δ^3isomer, no maximum at 210–360 mμ) which were converted in good yield to their characteristic dinitrophenylhydrazones.

We are indebted to the National Science Foundation for a grant in support of this work.

EXPERIMENTAL[3]

DL-*Cryptone* was regenerated[4] from a highly purified sample (9.50 g.) of the synthetic semicarbazone[1] (m.p. 194°).[5] Air was excluded with nitrogen, and an efficient steam distillation apparatus was used to effect a rapid continuous separation of the free ketone as it was formed in the acidic hydrolysis mixture. The colorless fragrant product was extracted with ether, dried over sodium sulfate, and distilled; 5.23 g. (78%), b.p. 76–80° (5 mm.), n_D^{20} 1.4815, λ_{max} 227 mμ, ε 11,100.

Equilibrium of DL-*cryptone.* Repeating as closely as possible the dehydrobromination conditions,[1] a mixture of 5.00 g. of cryptone, 7.3 g. of washed and dried collidine hydrobromide (from collidine in ether), and 18.9 g. of collidine, was refluxed under nitrogen for 20 min. The neutral fraction was extracted with ether, washed well in the cold with dilute hydrochloric acid, sodium bicarbonate solution, and water, dried over sodium sulfate, and distilled; 3.22 g. b.p. 60–68° (2 mm.), n_D^{20} 1.4776, λ_{max} 227 mμ, ε 7,620. Fractionation at 0.5 mm. through a sixty-plate Podbielniak Miniature Hypercal column[1] gave three fractions as follows: (I) 0.66 g. of *4-isopropyl-3-cyclohexenone,* b.p. 46–50°, n_D^{20} 1.4738, no maximum at 210–360 mμ (reported n_D^{20} 1.4710[1]). (II) 0.97 g. of an intermediate fraction, b.p. 51–55°, n_D^{20} 1.4824, λ_{max} 227 mμ, ε 9,540; and (III) 0.94 g. of *4-isopropyl-2-cyclohexenone,* b.p. 55–60°, n_D^{20} 1.4828, λ_{max} 227 mμ, ε 12,370 (reported for natural *l*-cryptone n_D^{20} 1.4810,[6] λ_{max} 226.3 mμ, ε 12,600[4]).

Treatment in the manner described previously[1] gave from fraction I the orange-yellow 4-isopropyl-3-cyclohexenone 2,4-dinitrophenylhydrazone, m.p. 105–106°.[1,7]

Similarly, from fraction III there was obtained[1] a 90% yield of the orange-red isopropyl-2-cyclohexenone 2,4-dinitrophenylhydrazone, m.p. 126–129°, which after recrystallization from ethanol had m.p. and mixed m.p. 134–135°.[1]

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(1) M. D. Soffer and M. A. Jevnik, *J. Am. Chem. Soc.*, **77**, 1003 (1955).

(2) *Cf.* W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1912 (1953).

(3) Melting points are corrected and boiling points uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol.

(4) R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, 1408 (1938).

(5) The reported melting points of the racemic product vary from 183° to 192° (*cf.* ref. 1), probably due to traces of the Δ^3 isomer.

(6) D. T. C. Gillespie and A. K. Macbeth, *J. Chem. Soc.*, 1531 (1939).

(7) This derivative tends to isomerize to the Δ^2 derivative and to decompose, if heated slowly, and it also shows a "double" melting point; the melt resolidifies and melts again at a temperature intermediate between the melting points of the derivatives of the two isomeric ketones. The temperature recorded represents the initial fusion.

Isolation of a Thiosulfonate from Reaction of Lithium Aluminum Hydride and a Sulfonyl Chloride

ERWIN A. LEHTO[1] AND DAVID A. SHIRLEY

Received April 26, 1957

Field and Grunwald[2] postulate that reduction of sulfonyl chlorides to mercaptans by lithium aluminum hydride may occur *via* two routes, one of which involves the reaction of a sulfinate salt with a sulfonyl chloride giving a disulfone, or with a metal mercaptide to give a thiosulfonate. Either of these intermediates then goes to the mercaptan *via* the disulfide. Apparently no one has isolated a thiosulfonate, although disulfides have been obtained.[2,3] The authors would like to report the isolation in 23% yield of *p-tert*-butylphenyl *p-tert*-butylbenzenethiosulfonate from the action of lithium aluminum hydride on *p-tert*-butylbenzenesulfonyl chloride. Structure of the thiosulfonate was indicated by its independent preparation from reduction of *p-tert*-butylbenzenesulfonyl chloride with zinc and hydrochloric acid by a procedure known to give the thiosulfonate.[4]

(1) Present address: The Koppers Co., Monaca, Pa.

(2) L. Field and F. A. Grunwald, *J. Org. Chem.*, 16, 949 (1951).

(3) J. Strating and H. J. Backer, *Rec. trav. chim.*, 69, 638 (1950).

(4) E. Vinkler and F. Klivenyi, *Acta Chim. Acad. Sci. Hung.*, 1, 319 (1951); *Chem. Abstr.*, 49, 2346 (1955).

EXPERIMENTAL

Reaction of lithium aluminum hydride and p-tert-butylbenzenesulfonyl chloride. Strating and Backer[3] have reported the formation of *p-tert*-butylthiophenol in 76% yield by the treatment of an ethereal solution of *p-tert*-butylbenzenesulfonyl chloride with an ethereal solution of lithium aluminum hydride. A reverse order of addition is used here.

p-tert-Butylbenzenesulfonyl chloride was prepared by the general procedure of Huntress and Carten.[5] A solution of 18.6 g. (0.08 mole) of the sulfonyl chloride in 75 ml. of ether was added slowly with stirring to a suspension of 4.56 g. (0.12 mole) of powdered lithium aluminum hydride in 225 ml. of ether. A nitrogen atmosphere was used. The mixture was stirred for 12 hr. and hydrolyzed with water, followed by dilute hydrochloric acid, and the mixture was then extracted with ether. The ethereal extract was dried and the ether evaporated. The solid residue was extracted with dilute aqueous sodium hydroxide solution and the residue from this recrystallized from absolute ethanol. There was obtained 7.0 g. of solid, m.p. 86–135°. This solid was washed thoroughly with petroleum ether and recrystallized once more from absolute ethanol to yield 3.3 g. (23%) of colorless crystals, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{26}O_2S_2$: C, 66.30; H, 7.18; S, 17.68. Found: C, 66.14; H, 7.19; S, 17.72.[6]

Preparation of p-tert-butylphenyl p-tert-butylbenzenethiosulfonate. A mixture of 11.6 g. (0.05 mole) of *p-tert*-butylbenzenesulfonyl chloride, 100 ml. of ether, and 4.9 g. of zinc dust was treated dropwise with 32 ml. of concentrated hydrochloric acid, according to the procedure described by Vinkler and Klivenyi[4] for the preparation of the phenyl ester of benzenethiosulfonic acid (thiosulfone) by reduction of benzenesulfonyl chloride. The reaction mixture was stirred at room temperature until all the zinc had dissolved. It was then poured into an excess of cold water and, after the removal of the ether, the precipitated solid was collected by filtration. The solid was washed thoroughly with petroleum ether and recrystallized twice from absolute ethanol, resulting in the isolation of a crystalline solid melting at 150–151°. A mixture melting point with the crystalline solid obtained from the lithium aluminum hydride reduction of *p-tert*-butylbenzenesulfonyl chloride, melting at 150–151°, was 150–151°.

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(5) E. H. Huntress and F. H. Carten, *J. Am. Chem. Soc.*, 62, 511 (1940).

(6) Galbraith Microanalytical Laboratories, Knoxville, Tenn.

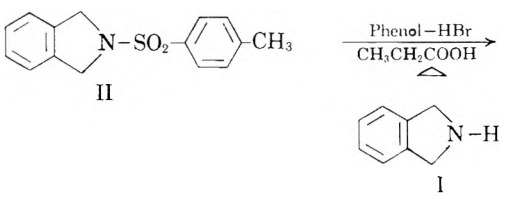
Facile Synthesis of Dihydroisoindole

JOSEPH BORNSTEIN, SHERMAN C. LASHUA, AND ARMAND P. BOISSELLE

Received April 8, 1957

In connection with the synthesis of compounds related to isoindole, it was necessary to prepare gram-quantities of dihydroisoindole (isoindoline) (I). In an effort to avoid the preparation of I by the electrolytic reduction of phthalimide,[1] because of the special apparatus and careful control required, we examined a number of the other methods[2] which have been described. All of them were found to be poor; particularly disappointing was the newest method involving the reduction of phthalimide with lithium aluminum hydride.[3] As a result, a new two-step synthesis of dihydroisoindole was devised, which is based on recent reports[4] that sulfonamides are cleaved rapidly to amines by treatment with hydrobromic acid in the presence of phenol.

When 2-(*p*-tolylsulfonyl)dihydroisoindole (II),[5] which is readily prepared from the easily obtainable substances *o*-xylylene dibromide and *p*-toluenesulfonamide, was heated with a mixture of phenol and hydrobromic acid in propionic acid, dihydroisoindole was obtained in a high state of purity and in yields of 70–78%. This method makes dihydroisoindole easily accessible and appears to be more convenient for small-scale preparations than the electrolytic reduction of phthalimide, which has been, heretofore, the only satisfactory source of dihydroisoindole.



II I

EXPERIMENTAL[6]

2-(p-Tolylsulfonyl)dihydroisoindole (II). This compound was obtained in slightly better yield and in a higher state of purity by modification of the procedure of Fenton and Ingold.[5] The solution, prepared by dissolving 17.0 g. (0.1 mole) of *p*-toluenesulfonamide in a solution of 5.0 g. (0.22 g.-atom) of sodium in 220 ml. of methanol, was added in the course of 40 min. to a stirred and refluxing solution of 26.4 g. (0.1 mole) of *o*-xylylene dibromide in 150 ml. of commercial ethanol. After completion of the addition, the reaction mixture was refluxed and stirred for 2 hr. The suspension was cooled, treated with 100 ml. of water, and neutralized with glacial acetic acid. Refrigeration overnight afforded white needles which, after recrystallization from 95% ethanol, weighed 13.0 g. (48%), and had m.p. 175–176° (dec.) (lit.[5] 176°).

Dihydroisoindole (I). A mixture of 12.0 g. (0.044 mole) of II, 12.0 g. (0.13 mole) of phenol, 90 ml. of 48% hydrobromic acid (freshly distilled from stannous chloride), and 15 ml. of propionic acid was heated under reflux for 2 hr.

(1) A. Dunet, J. Rollet, and A. Willemart, *Bull. soc. chim. France*, 877 (1950).

(2) S. Gabriel and A. Neumann, *Ber.*, 26, 521 (1893); R. E. Rose and W. Scott, *J. Am. Chem. Soc.*, 39, 273 (1917).

(3) A. Uffer and E. Schlittler, *Helv. Chim. Acta*, 31, 1397 (1948). The authors were able to obtain I in yields of only 3%; A. Dunet, J. Rollet, and A. Willemart (ref. 1) reported a 5% yield from this procedure.

(4) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, 74, 2006 (1952); H. R. Snyder and H. C. Geller, *J. Am. Chem. Soc.*, 74, 4864 (1952); D. I. Weisblat, B. J. Magerlein, and D. R. Myers, *J. Am. Chem. Soc.*, 75, 3630 (1953).

(5) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3295 (1928).

(6) Melting points are corrected and boiling points are uncorrected. Analyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass., and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

in an atmosphere of nitrogen. The wine-colored reaction mixture was cooled to room temperature and, after being washed twice with 200-ml. portions of ether, was added drop-wise to a stirred, ice-cold solution of 75 g. of sodium hydroxide in 200 ml. of water. The mixture was extracted with five 150-ml. portions of ether and the combined ethereal extract was dried over potassium carbonate, after being washed with water. Removal of the solvent *in vacuo* and distillation of the residue through a semimicro column afforded 3.8 g. (72%) of dihydroisoindole as a colorless oil, b.p. 115° at 30 mm., n_D^{24} 1.5698, d_4^{20} 1.081, which solidified in the refrigerator, m.p. 16.0–16.5°. The *picrate*, obtained as silky, yellow needles from ethanol, had m.p. 195–196° (reported[5] 196–197°).

The *2-trifluoroacetyl derivative* of I was prepared by treating an ethereal solution of dihydroisoindole with a slight excess of methyl trifluoroacetate and allowing the mixture to stand overnight at room temperature. Evaporation of the solvent *in vacuo* followed by recrystallization of the residue from 50% methanol yielded long, felted needles, m.p. 80.5–81.0° (with sublimation).

Anal. Calcd. for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; F, 26.49; N, 6.51. Found: C, 55.9; H, 3.7; F, 26.0; N, 6.6.

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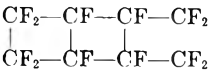
Thermal Reactions of Perfluorobutyne-2 and Perfluoropropene[1]

HENRY C. BROWN

Received April 2, 1957

The tendency toward formation of the cyclobutane ring and the thermal stability of this structural conformation has been noted in several instances in studies of reactions of fluorocarbons with C—C multiple bonds. For example, tetrafluoroethylene readily forms perfluorocyclobutane when heated under pressure.[2] Formation of a cyclobutane ring also occurs in the dimerization of trifluorochloroethylene to give 1,2 dichlorohexafluorocyclobutane.[3] Miller,[4] by heating the unsaturated dimer of perfluorobutadiene, produced a saturated dimer believed to have the fused tricyclic structure (I).

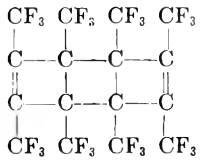


I

We have found that perfluorobutyne-2 and perfluoropropene undergo a cyclization reaction that appears to be similar to that of the previously studied fluorocarbon olefins.

Perfluorobutyne-2, $CF_3C{\equiv}CCF_3$, forms a white, crystalline tetramer when heated under autogenous pressure. The solubility properties of this product are interesting and somewhat unusual for fluorocarbons. It is slightly soluble in ethylene dichloride, carbon tetrachloride, ethyl alcohol, and benzene at room temperature. The solubility in each of these solvents increases markedly with increasing temperature. This compound is very soluble in acetone and in ethyl ether at room temperature. It does not show unsaturation by reaction with potassium permanganate in acetone but its infrared spectrum shows a weak absorption band at 5.72μ, which is in the region expected for C—C unsaturation in fluorocarbons.

A fused polycyclic structure (II) is proposed for this tetramer of perfluorobutyne-2 on the basis of data obtained to date. Its crystallinity and other



II

physical properties seem to favor this symmetrical type of structure. C—C double bonds in the position shown would not be expected to react readily with potassium permanganate under the mild conditions employed. The infrared absorption spectrum[5] shows the following peaks (microns): 5.72, weak; 6.75, weak; 7.15, moderate; 7.30, moderate; 7.47, moderate; 7.73, strong; 8.10–8.40, (unresolved) very strong; 8.52, very strong; 9.53, very strong; and 14.85, moderate.

The saturated cyclic dimer of perfluoropropene has not been described previously although Haszeldine[6] has reported formation of a trimer, tetramer, and pentamer from ultraviolet irradiation of perfluoropropene. We have found that perfluoropropene can be thermally dimerized by heating under autogenous pressure. The infrared spectrum of the saturated product, perfluorodimethylcyclobutane, shows the following peaks (microns): 7.22, moderate; 7.40, strong; 7.55, strong; 7.68, very strong; 7.95, very strong; 8.20, very strong; 9.38, weak; 9.58, weak; 11.00, strong; 11.35, strong; 13.45, weak, 13.63, moderate; and 13.82; moderate. This perfluoropropene dimer shows no unsaturation by infrared analysis, permanganate oxidation, or halogen addition. No higher boiling fractions that might indicate the presence of a linear dimer or higher polymers were found in the reaction product. Data is not yet available to show whether this compound as produced is a head-head dimer (III)

(1) This work was supported by the Office of Naval Research under Contract N-onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

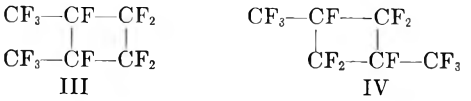
(2) A. F. Benning, F. B. Downing, and R. C. McHarness, U. S. Patent 2,384,821 (September 18, 1945).

(3) A. L. Henne and R. P. Ruh, *J. Am. Chem. Soc.*, 69, 279 (1947).

(4) W. T. Miller, *Preparation, Properties and Technology of Fluorine and Organic Fluoro Compounds;* McGraw-Hill Book Co., N. Y. (1951), p. 604.

(5) Infrared spectrum taken in carbon tetrachloride with a Perkin-Elmer Model 21 double beam spectrophotometer.

(6) R. N. Haszeldine, *J. Am. Chem. Soc.*, 75, 3559 (1953).



III IV

or head-tail dimer (IV). In general, unsymmetrical fluoroolefins tend to form head-head dimers and therefore (III) would be the expected form.

EXPERIMENTAL

Tetramer of perfluorobutyne-2. Perfluorobutyne-2 (30 g.) was placed in a previously evacuated 300-ml. stainless steel reaction vessel and heated at 320° for 31 hr. After cooling to room temperature, the reaction vessel was opened to the vacuum system and 23.8 g. of unreacted perfluorobutyne-2 recovered by transfer to a liquid-air cooled trap. The total solid material was removed by washing the reaction vessel with acetone. Subsequent removal of the acetone left a solid that was sublimed three times at atmospheric pressure, then recrystallized twice from benzene to produce 2.3 g. of white crystals, m.p. (sealed tube) 208–209°.

Anal.[7] Calcd. for $C_{16}F_{24}$: mol. wt. 648; C, 29.7; F, 70.3. Found: mol. wt. (ebullioscopic in benzene) 650; C, 29.9; F, 69.7.

Dimer of perfluoropropene. Perfluoropropene (150 g.) was condensed in a previously evacuated 300-ml. stainless steel reaction vessel and heated at 400° for 18 hr. Pressure in the vessel rose to a maximum of 2140 psi. and gradually decreased to 1100 psi. at the termination of the heating period. The vessel was cooled to room temperature, 73 g. of unreacted perfluoropropene recovered by transfer in the vacuum system, and the remaining higher boiling liquid fractionated in a column packed with nickel helices to give 72 g. of perfluorodimethylcyclobutane, b.p. 44.7–45.1°, d^{25} 1.667, n_D^{25} 1.2613.

Anal. Calcd. for C_6F_{12}: mol. wt., 300. Found: mol. wt. (Dumas), 300.

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(7) Analyses by Clark Microanalytical Laboratory, Urbana, Ill.

2-Pyrones. XXVII. 4-Methyl-6-alkyl-2-pyrones

RICHARD H. WILEY AND J. G. ESTERLE

Received April 1, 1957

It has been demonstrated previously[1] that the acylation and subsequent decarboxylation of β-methylglutaconic anhydride (I) offers a unique procedure for the preparation of 4-methyl-6-alkyl-2-pyrones (III). The utility of this procedure is, however, limited by the fact that conditions required for successful isolation of the intermediate 5-acyl-β-methylglutaconic anhydride (II) where the acyl group has more than four carbons have never been devised. Because of the interest in certain of the structures available by this synthesis as intermediates in the biosynthesis of cholesterol[2] we have reinvestigated the possibility of preparing 4-methyl-6-alkyl-2-pyrones with 6-alkyl groups of four or more carbons by this route.

The results of these studies have established that the intermediate acyl-β-methylglutaconic anhydrides need not be isolated and purified. The crude acylated anhydrides can be decarboxylated and rearranged to the 4-methyl-6-alkyl-2-pyrones in overall yields of 12–45% from the anhydride. Using this technique we have prepared and characterized the seven 4-methyl-6-alkyl-2-pyrones described in Table I. These illustrate preparations with 5 to 10 carbon acyl halides and establish a correspondingly broader utility for the reaction. Infrared absorption data, summarized in Table IV, establish the presence of characteristic absorption maxima in the 1730–1736 cm.$^{-1}$; 1634–1647 cm.$^{-1}$; 1560–1567 cm.$^{-1}$; 1140–1220 cm.$^{-1}$; and 840 cm.$^{-1}$ regions. The first of these is a carbonyl stretching frequency characteristic of the 2-pyrone carbonyl. The 1640 cm.$^{-1}$ and 1560 cm.$^{-1}$ maxima are carbon-carbon double bond stretching frequencies and again serve to characterize the 2-pyrone structure. In the 2′-methylpropenyl derivative, in which there is a double bond conjugated with the ring unsaturation, the 1560 cm.$^{-1}$ maximum is shifted to 1536 cm.$^{-1}$ Three maxima occur in the 1140–1220 cm.$^{-1}$ region where absorption characteristic of the C—O stretching frequency in esters is observed. It has been noted previously[3] that unsaturated esters have two absorption maxima in this region. In the 2-pyrones there are three bands which occur at about 1200 cm.$^{-1}$, 1140 cm.$^{-1}$, and 1120 cm.$^{-1}$ in this region. One of these is presumably the adsorption maximum associated with the C—O stretching frequency. The maxima in 840 cm.$^{-1}$ region are the most prominent in the spectra. This is assigned to the C—H out of plane deformation of one of the ring C—H groups. It occurs in approximately the same place as the maximum observed for the C—H deformation in 1,3,5-substituted benzenes (835 cm.$^{-1}$)[4]. The ring hydrogens are situated between two substituents in each case. The 3-bromo derivatives, listed in Table II, were observed to have infrared absorption characteristics, summarized in Table IV, similar to those of the unsubstituted pyrones. The carbonyl stretching frequency is shifted to slightly longer wave lengths (1712–1730 cm.$^{-1}$). The intensities of the maxima associated with the carbon-carbon double bond stretching frequencies are reversed. The 1640 cm.$^{-1}$ maxima is the more intense of the two in the bromo compounds. In the bromo compounds the 1560 cm.$^{-1}$ maxima is shifted to 1529–1536 cm.$^{-1}$ There is generally only

(1) Richard H. Wiley and N. R. Smith, *J. Am. Chem. Soc.*, **74**, 3893 (1952).

(2) Richard H. Wiley and J. G. Esterle, *J. Org. Chem.*, **21**, 1335 (1956).

(3) L. J. Bellamy, *Infra-Red Spectra of Complex Molecules*, John Wiley and Sons, N. Y., 1954, p. 163.

(4) L. J. Bellamy, *op. cit.*, p. 68.

TABLE I

4-METHYL-6-ALKYL-2-PYRONES

Alkyl	B.P. (°C./mm.)	n_D^{25}	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
n-Butyl	108/1	1.5040	23.8	72.26	72.21	8.49	8.48
Isobutyl	101/1	1.4999	45.0	72.26	72.12	8.49	8.33
2′-Methyl-1′-propenyl	[a]		12.0	73.14	73.08	7.37	7.37
n-Amyl	103/1	1.5035	27.8	73.29	73.43	8.95	9.04
Isoamyl	128/3	1.5004	17.4	73.29	73.07	8.95	9.16
n-Hexyl	109/1	1.5003	19.0	74.19	74.21	9.33	9.24
2′,6′-Dimethylheptyl	92/1	1.4936	17.0	76.22	76.05	10.24	10.20

[a] M.p. 46–47°.

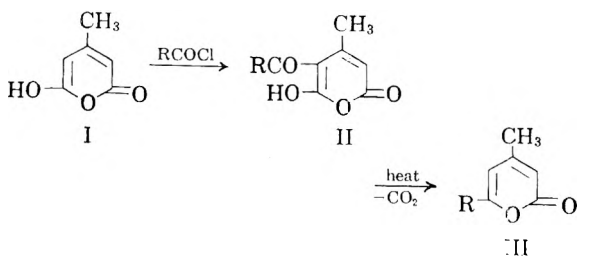
TABLE II

3-BROMO-4-METHYL-6-ALKYL-2-PYRONES

Alkyl	M.P. (°C.)	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
n-Butyl	35–36	50	49.00	49.08	5.35	5.49
n-Hexyl	49–49.5	45	52.76	52.55	6.27	6.36
1,2-Dibromo-2-methylpropyl	121–122	55	29.80	30.21	2.73	3.02

one absorption maximum, and this at about 1160 cm.$^{-1}$, in the C—O stretching region. The 840 cm.$^{-1}$ absorption maximum is modified or shifted in the 3-bromo compounds.

Several new tetrahydro 2-pyrones were prepared in 26–50% yields by catalytic reduction of the 2-pyrones. The infrared absorption of these compounds is characteristic of that of a saturated lactone structure. The carbon-carbon double bond absorption in the 1640 cm.$^{-1}$ and 1560 cm.$^{-1}$ region is lacking; the ester carbonyl absorption maximum is at 1733–1739 cm.$^{-1}$, the normal ester (δ-lactone) positions; and the C—O stretching frequency maximum is observed in the 1220–1240 cm.$^{-1}$ region. The last is much more intense than it is in the unsaturated 2-pyrones. Contamination of the tetrahydro compound with traces of the unsaturated derivative, insufficient to modify the refractive index, is readily detected by the appearance of absorption maxima at 1560 or 1640 cm.$^{-1}$



EXPERIMENTAL[5]

All of the 4-methyl-6-alkyl-2-pyrones were prepared in a similar manner. Details are given for a typical preparation. The yields, physical properties, and analytical data for the others are given in Table I.

(5) Analyses by Micro Tech Laboratories, Skokie, Ill.

4-Methyl-6-hexyl-2-pyrone. A slurry prepared from 30 ml. of dry ether and a solution of 5.0 g. (0.04 mole) of β-methylglutaconic anhydride in 10 ml. of dry pyridine was cooled to −5°. The stirrer was started, and a solution of 4.98 g. (0.04 mole) of heptoyl chloride in 20 ml. of dry ether was added with stirring to this slurry. After 0.5 hr. additional stirring 15 ml. of concentrated hydrochloric acid and 30 g. of ice were added. The mixture was stirred until all the solid material had dissolved. The ether layer was separated. The aqueous solution was extracted with two 100-ml. portions of ether. The ether extractions were combined and dried over sodium sulfate.

The ether solutions from three such runs were combined and the ether removed. The remaining 30 g. of red, viscous oil was flash-distilled at a temperature of 350°. The distillate was distilled from a Claisen flask (b.p. 100°/1 mm.) and fractionated through a spinning-band column to give 4.40 g. (19%) of the product, b.p. 109°/1 mm., n_D^{25} 1.5003.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.33. Found: C 74.21; H, 9.24.

The 3-bromo-4-methyl-6-alkyl-2-pyrones were prepared by dissolving the pyrone in carbon tetrachloride and adding an equivalent amount of bromine. After completion of the reaction, the solvent was evaporated and the residue crystallized from ligroin. The 3-bromo derivatives of 4-methyl-6-amyl, 4-methyl-6-isoamyl and 4-methyl-6-(2′,6′-dimethylheptyl)-2-pyrones were liquids at room temperature and were not characterized. Yields, physical properties, and analytical data for the solids are given in Table II.

The tetrahydro-4-methyl-6-alkyl-2-pyrones were prepared by catalytic hydrogenation. The 4-methyl-6-alkyl-2-pyrones were dissolved in ether and hydrogenated in a Parr hydrogenation apparatus over 5% palladium-on-carbon catalyst with an initial pressure of 50 lb./sq. in. The product were fractionated in a spinning-band column. The yields, physical properties, and analytical data are given in Table III.

The infrared absorption measurements were made with a Baird double beam recording spectrometer with sodium chloride optics. The pyrones and their tetrahydro derivatives were examined as carbon tetrachloride solutions. The bromo derivatives, except the *n*-butyl compound which was examined in carbon tetrachloride, were examined as potassium bromide pellets. All measurements are corrected against the 3.419 μ absorption maxima of polystyrene.

TABLE III

4-METHYL-6-ALKYLTETRAHYDRO-2-PYRONES

Alkyl	B.P. (°C./mm.)	n_D	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
n-Butyl[a]	114/4	1.4517					
Isobutyl	110/5	1.4484	40	70.55	70.22	10.67	10.73
Isoamyl	89/1	1.4509	26	71.69	71.66	10.94	10.76
n-Hexyl	89/1	1.4545	50	72.68	72.90	11.18	11.05

[a] See R. H. Wiley and H. G. Ellert, *J. Am. Chem. Soc.*, **79**, 2266 (1957).

TABLE IV

INFRARED ABSORPTION MAXIMA OF 4-METHYL-6-ALKYL-2-PYRONES AND THEIR 3-BROMO AND TETRAHYDRO DERIVATIVES[a]

6-Alkyl Group	C=O Stretching	C=C Stretching		C—O Stretching Region			C—H Out of Plane Deformation
2-Pyrones:							
Methyl	1736s	1645m	1565s	1227w	1147w	1130w	846m
n-Butyl	1730s	1637m	1567s	1222w	1142w	1125w	846m
Isobutyl	1736s	1639m	1562s	1225w	1145w		842m
2′-Methylpropenyl	1730s	1642m	1536s	1228w	1179w	1159w	840m
Amyl	1730s	1634m	1567s	1218w	1140w	1124w	845w
Isoamyl	1730s	1634m	1560s	1219w	1143w	1126w	846w
Hexyl	1736s	1647m	1567s	1222w	1147w	1130w	847m
2′,6′-Dimethyl-heptyl	1736s	1745m	1567s	1225w	1149w	1126w	844m
3-Bromo-2-pyrones:							
Methyl	1712s	1645m	1536w	—	1185m	—	846m
n-Butyl	1730s	1639m	1531w	—	1168w	—	—
1′,2′-Dibromo-2′-methyl	1724s	1631m	1531w	—	1186w	—	836w
n-Hexyl	1718s	1637m	1529w	—	1165w	—	—
Tetrahydro-2-pyrones:							
Methyl	1733s	—	—	1235s	1181m	1138w	—
n-Butyl	1736s	—	—	1236m	1170w		
Isobutyl	1739s	—	—	1235s	1168w	1147w	—
Isoamyl	1736s	—	—	1233s	1161w	—	—
n-Hexyl	1739s	—	—	1240s	1161w	—	—

[a] In cm.$^{-1}$ s, strong; m, medium; w, weak.

Acknowledgment: The authors wish to acknowledge partial support of this research through grants from the National Science Foundation and the United States Public Health Service.

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Cleavage of Trialkylamines by Chloroformates

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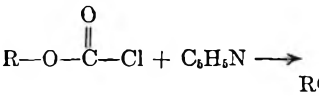
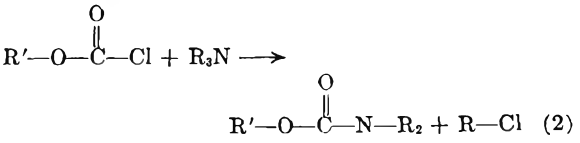
Received March 18, 1957

Girrard and Schild[1] have reported that chloroformates react with pyridine and quinoline to give an alkyl chloride, carbon dioxide, and the free base (Equation 1). It has been found in this laboratory that chloroformates will cleave trialkyl amines in boiling benzene to give the alkyl chloride and a carbamate (Equation 2). Both reactions take place



$$R{-}O{-}\overset{\overset{O}{\|}}{C}{-}Cl + C_6H_5N \longrightarrow RCl + CO_2 + C_5H_5N \quad (1)$$



$$R'{-}O{-}\overset{\overset{O}{\|}}{C}{-}Cl + R_3N \longrightarrow R'{-}O{-}\overset{\overset{O}{\|}}{C}{-}N{-}R_2 + R{-}Cl \quad (2)$$

with ethyl chloroformate and triethyl amine since carbon dioxide, ethyl chloride, and ethyl diethylcarbamate were produced. However, stigmasteryl chloroformate and triethyl amine react as in Equation 2 exclusively.

Stigmasteryl chloroformate cleaved both *N*-ethyl and *N*-methyl piperidine to give stigmasteryl *N*-piperidinylformate. These reactions are in

(1) W. Girrard and F. Schild, *Chemistry & Industry*, 1232 (1954).

contrast with the amine cleavages of the Hoffman and Von Braun reactions[2] in which the piperidine ring is opened.

Although some tertiary amines are cleaved by acid chlorides[3] at elevated temperatures[4] or when special favorable intramolecular conformations[5] are possible, triethyl amine was not affected by benzoyl chloride in boiling benzene. The cleavage of trialkyl amines by chloroformates may be a general reaction. However, further work is necessary to establish its limitations.

EXPERIMENTAL[6]

Stigmasteryl diethylcarbamate from diethyl amine and stigmasteryl chloroformate. Stigmasteryl chloroformate,[7] 5.0 g. (0.0105 mole) was dissolved in 100 ml. of benzene and 3 ml. of diethylamine was added. After standing a few minutes the mixture was warmed to about 50°, then allowed to stand at room temperature for 3 hr. The reaction mixture was extracted with 0.5*N* hydrochloric acid solution, and water, dried over magnesium sulfate, filtered, and concentrated to dryness, yield 5.0 g. Part of this material, 3.8 g., was dissolved in methylene chloride and filtered through a short column of Florisil. The solvent was removed from the filtrate and the residue (3.12 g.) was crystallized twice from acetone, yield 2.55 g., m.p. 146–148.5°, $[\alpha]_D$ −38° ($CHCl_3$).

Anal. Calcd. for $C_{34}H_{57}NO_2$: C, 79.78; H, 11.23. Found: C, 80.03; H, 11.09.

Stigmasteryl diethylcarbamate from stigmasteryl chloroformate and triethylamine. To a dry solution of 4.0 g. (0.0084 mole) of stigmasteryl chloroformate in 60 ml. of dry benzene was added 4 ml. of triethylamine (dried over CaH_2). After heating at reflux for 2 hr. the solution was cooled, extracted with water, dilute hydrochloric acid, and again with water, dried over magnesium sulfate, filtered, and concentrated to dryness. The residue, 3.85 g., was chromatographed through Florisil to give 3.45 g. (80% yield), m.p. 133–142° of stigmasteryl diethylcarbamate. One crystallization from acetone gave the pure carbamate identical in all respects to the material described above.

The gas produced from a similar run was collected and identified by its infrared absorption spectrum as ethyl chloride.

Ethyl diethylcarbamate.[8] A solution of 54 g. (0.5 mole) of ethyl chloroformate, 125 g. (1.25 moles) of triethylamine, and 200 ml. of dry benzene was heated at reflux for 24 hr. The gas was collected in a Dry Ice–acetone trap and identified as a mixture of carbon dioxide and ethyl chloride by infrared analysis. The ethyl chloride was purified by passing the vapors through a tube of Ascarite. The reaction solution was washed with water, dilute hydrochloric acid, and again with water, dried over magnesium sulfate, and filtered. The filtrate was distilled at atmospheric pressure until the boiling point reached about 165°. Vacuum was applied and the distillate collected was the ethyl diethylcarbamate n_D^{25} 1.4188. Infrared analysis supports the proposed structure with bands at 1692 cm.$^{-1}$, 1270 cm.$^{-1}$, and 1172 cm.$^{-1}$

Stigmasteryl piperidinylformate from stigmasteryl chloroformate and N-ethyl piperidine. This product was prepared following the second procedure described for the diethylcarbamate. From 1.0 g. (0.00211 mole) of stigmasteryl chloroformate, 1.0 g. of stigmasteryl *N*-piperidinylformate, m.p. 125–135° was obtained. It was crystallized from acetone–ethylacetate, then from isopropyl alcohol, yield 0.65 g., m.p. 137–140°, $[\alpha]_D$ −33° ($CHCl_3$).

Anal. Calcd. for $C_{35}H_{57}NO_2$: C, 80.25; H, 10.97; N, 2.67. Found: C, 80.54; H, 10.89; N, 2.69.

From N-methylpiperidine. Following the same procedure 1.0 g. of stigmasteryl chloroformate gave 1.0 g. of crude carbamate, m.p. 134–136°. One recrystallization from isopropyl alcohol gave material, m.p. 136–137°. This product is identical in all respects to the stigmasteryl piperidinylcarbamate prepared as described above.

Acknowledgment. The author is indebted to Drs. D. A. Shepherd and J. C. Babcock for their many suggestions and encouragement, to Dr. J. L. Johnson and Mrs. G. S. Fonken for determination and interpretation of the infrared spectra, and to W. A. Struck and associates for rotations and analyses.

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(2) J. Schmidt and H. G. Rule, *A Text Book of Organic Chemistry*, Revised by N. Campbell, 5th Edition, Gurney and Jackson, London, 1947, p. 703.

(3) H. Gilman, *Organic Chemistry*, 2nd Edition, John Wiley and Sons, 1942, p. 1172.

(4) O. Hess, *Ber.*, **18**, 685 (1885).

(5) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, **71**, 2821 (1949); F. F. Blicke and A. J. Zambito, Abst. of 111st American Chemical Society Meeting, p. 3K (1947); J. H. Gardner, N. R. Easton, and J. R. Stevens, *J. Am. Chem. Soc.*, **70**, 2906 (1948).

(6) M.p.'s were taken on a Kofler micro melting point hot stage. $[\alpha]_D$'s were determined at 22–26° at concentrations of 1–1.5 g. per 100 ml. in a 2-cm. tube.

(7) J. A. Campbell, D. A. Shepherd, B. A. Johnson, and A. C. Ott., *J. Am. Chem. Soc.*, **79**, 1127 (1957).

(8) J. v. Braun, *Ber.*, **36**, 2286 (1903).

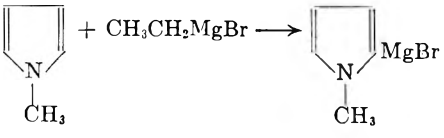
Nature of the So-Called Grignard Reagent Formed from *N*-Methylpyrrole[1]

WERNER HERZ

Received March 18, 1957

The formation of the pyrrole Grignard reagent from pyrrole and alkylmagnesium halides is well-known.[2] It might be expected that *N*-alkylpyrroles, having no—NH—group, would be inactive toward alkylmagnesium halides. However, in 1914, Hess and Wissing[3] reported the formation of 2-acyl-1-methylpyrroles on treatment of *N*-methylpyrrole with ethylmagnesium bromide and subsequent addition of an acid chloride.

Hess and Wissing[3] assumed originally that *N*-methylpyrrole formed a true Grignard reagent, as indicated in equation 1, but following a challenge



(1) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-436.

(2) B. Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909).

(3) K. Hess and F. Wissing, *Ber.*, **47**, 1416 (1914).

by Oddo[4] they were forced to revise their conclusions. Hess observed that no ethane was evolved until the reaction mixture (which consisted of *N*-methylpyrrole, ethylmagnesium bromide, and acid halide) was decomposed with water.[5] To explain this phenomenon and the acylation which took place, Hess invoked the existence of an unstable tertiary amine-Grignard reagent complex which somehow reacts with the acid chloride only in the presence of water to form the 2-acyl-1-methylpyrrole and ethane.[5]

Our interest in pyrrole chemistry attracted our attention to the somewhat labored interpretation of this reaction.[5,6] The fact that carbonation[3,5] of the mixture of *N*-methylpyrrole and ethylmagnesium bromide does not result in the formation of *N*-methylpyrrole carboxylic acid[7] and the observation[5] that *ethane is not evolved until the mixture is decomposed with water* suggested that the reaction was not due to interaction of *N*-methylpyrrole with the Grignard reagent but that the 2-acyl-*N*-methylpyrrole was formed as the result of a Friedel-Crafts type acylation catalyzed by magnesium bromide, the latter arising out of equilibrium (2).[8]

$$2CH_3CH_2MgBr \rightleftharpoons (CH_3CH_2)_2Mg + MgBr_2 \quad (2)$$

Indeed, when a mixture of *N*-methylpyrrole and magnesium bromide in ether was treated with acetyl chloride a vigorous reaction ensued and 2-acetyl-*N*-methylpyrrole was isolated in about the same yield as when acetyl chloride was added to a mixture of *N*-methylpyrrole and ethylmagnesium bromide under the conditions of Hess and Wissing.[3] No acylation was observed when ether solutions of *N*-methylpyrrole and acetyl chloride were mixed in the absence of magnesium bromide or Grignard reagent.

It is considered that these experiments fully substantiate the hypothesis that the reaction of the so-called *N*-methylpyrrole Grignard reagent with acid chlorides is in reality an acylation of *N*-methylpyrrole catalyzed by magnesium bromide.[9]

(4) B. Oddo, *Ber.*, **47**, (1914). See also F. Runge, *Organometallverbindungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1932, p. 223.

(5) K. Hess, *Ber.*, **48**, 1969 (1915).

(6) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., N. Y., 1954, p. 80.

(7) Two of the illustrations given on p. 80 of ref. 6 (the reaction of the so-called *N*-methylpyrrole Grignard reagent with ethyl chloroformate and halogen) represent work not actually recorded in the literature.

(8) The author is indebted to Professor A. C. Cope who pointed out this possibility at a symposium "The Chemistry of High Nitrogen Compounds," sponsored by the Office of Ordnance Research, U. S. Army, and held at Duke University, March 28–29, 1956.

(9) A recent paper by H. J. Anderson, *Can. J. Chem.*, **35**, 20 (1957), has demonstrated that boron trifluoride etherate is also a useful acylating catalyst for *N*-methylpyrrole.

EXPERIMENTAL

To a solution of 8 g. (0.1 mole) of *N*-methylpyrrole in 25 ml. of anhydrous ether was added 10 ml. of a solution of magnesium bromide in ether.[10] There was no evidence of a reaction. Addition of 8 g. of acetyl chloride in 20 ml. of chilled ether to the ice-cold mixture resulted in a vigorous reaction and immediate separation of a yellow precipitate. The product was decomposed with ice water and steam-distilled. The distillate was neutralized with sodium carbonate and extracted thoroughly with ether. The ether was dried and distilled giving 3.8 g. (31%) of a fraction boiling at 85–95° (22 mm.). Redistillation gave 3.2 g. of 2-acetyl-1-methylpyrrole, b.p. 88–93° (22 mm.), lit. 75–76° (15 mm.),[3] 88–91° (21 mm.).[9]

Reaction of *N*-methylpyrrole with ethylmagnesium bromide and acetyl chloride[3] gave a 25% yield of redistilled 2-acetyl-1-methylpyrrole.

A solution of 4 g. of *N*-methylpyrrole in 15 ml. of cold anhydrous ether was mixed with 4 g. of acetyl chloride in 15 ml. of cold anhydrous ether. There was no evidence of a reaction. Upon decomposition with ice water and working up in the usual manner, there was recovered 3.3 g. of *N*-methylpyrrole.

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(10) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

Preparation of 3-Dehydroreserpic Acid Lactone and Its Conversion to Reserpic Acid Lactone

EUGENE FARKAS, EDWARD R. LAVAGNINO, AND RICHARD T. RAPALA

Received March 15, 1957

The reaction of the yohimbine alkaloids with mercuric acetate has been summarized recently by Weisenborn[1] and Wenkert.[2] Concurrently the authors had also studied and utilized this reaction to obtain compounds of this class with a double bond in the 3:4 position. It was hoped that reduction of such dehydro derivatives would afford the naturally occurring epiallo bases. The present paper describes the results of this study.

The dehydrogenation proceeded normally by removal of two hydrogens in the case of yohimbane, yohimbine, and isoreserpine, giving good agreement with published results.[1,2] Similarly, dehydrogenation occurred with reserpine, deserpidine, reserpic acid lactone, and isoreserpic acid lactone while heating at reflux in 10% acetic acid. Contrary to the published work,[1] compounds in the epiallo series were dehydrogenated under these slightly more vigorous conditions. A possible explanation for this discrepancy can be found in the

(1) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).

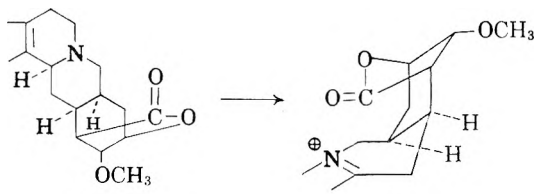
(2) E. Wenkert and D. K. Roychaudhuri, *J. Org. Chem.*, **21**, 1315 (1956).

observed partial epimerization at C_3 of isoreserpic acid lactone while heating in the same solvent.

Hydrogenation of $\Delta^{3(4)}$-dehydroyohimbine and reserpine using Adams' catalyst in either neutral or acetic acid solution furnished yohimbine and isoreserpine, respectively, under all conditions. Furthermore, reduction with sodium borohydride readily gave the same products.

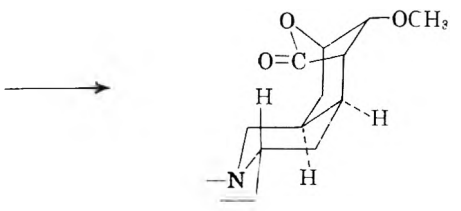
The dehydrogenation of the 3-iso and 3-normal reserpic acid lactones never went to completion, and although the salts obtained in these studies were consistently gelatinous, a flavianate salt was finally crystallized and characterized. The gelatinous chloride salt of the dehydrolactone, however, upon reduction with sodium borohydride, gave as the sole product reserpic acid lactone.[3] Thus, another route was available for proceeding from the isoreserpine series to the normal series. A small amount of the reserpic acid lactone could also be obtained by liberating the free base from the impure dehydro salt. This material was present because of the difficulty of purification of the gelatinous chloride salt. The purity of the dehydro-11-methoxy indole compounds was determined by measurement of the intense ultraviolet absorption near 285 mμ.

A possible reason for the hydrogen addition from the more hindered top side of the molecule (II) can be attributed to coordination of the borohydride anion with the carbonyl oxygen of the lactone and subsequent attack of the hydride anion from the top.[4] Molecular models confirm the possibility for this complex formation. Another explanation would necessitate a ready epimerization at C_3 of the hydrogenation product under the slight alkaline conditions of the reduction. The latter possibility was eliminated by recovery of the starting isoreserpic acid lactone (I) after treatment under the same reaction conditions.



I

II



III

(3) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead. *J. Am. Chem. Soc.*, 78, 2023 (1956).

(4) This possibility was first suggested by Dr. R. B. Turner of The Rice Institute during a discussion of this problem.

EXPERIMENTAL[5]

Mercuric acetate dehydrogenation. Using a modification of Leonard's procedure[6] in a small flask equipped with a condenser and nitrogen inlet tube was placed 0.5 g. of isoreserpic acid lactone, 0.5 g. of mercuric acetate, and 30 ml. of 10% acetic acid solution. The solution was heated at reflux at about 95° for 14 hr. at which time some solid had separated, and the solution had darkened. Hydrogen sulfide was bubbled through the solution to remove any starting reagent, and the mixture was filtered. The filtrate was treated in several ways depending on the purpose of the succeeding experiments.

A. When further synthetic work was contemplated, the chloride was prepared by adding 5 ml. of concentrated hydrochloric acid and evaporating to dryness under vacuum. The residue containing some sulfide salts was recrystallized to give the gelatinous dehydrolactone chloride in 70% yield as determined by ultraviolet measurements. Similar results were obtained using reserpic acid lactone as the starting material.

B. The same flavianate was obtained from both reserpic acid and isoreserpic acid lactone after dehydrogenating by the above procedure. The filtrate, after removing the sulfide salts, was concentrated to about 15 ml. under vacuum, and there was added 10 ml. of a 5% solution of flavianic acid in methanol. Several crops of material were obtained by concentration of the solution to give 0.41 g. of the yellow-orange dehydrolactone flavianate, m.p. 220–223° dec., λ_{max}^{EtOH} 384 mμ, log ϵ 4.45, λ_{max}^{Nujol} 5.66 μ.

Anal. Calcd. for $C_{32}H_{30}N_4SO_{12}$: C, 55.30; H, 4.37; N, 8.1. Found: C, 55.07, 55.04; H, 4.58, 4.60; N, 8.22.

Reserpic acid lactone flavianate. The lactone, 0.10 g., was dissolved in 4 ml. of reagent methanol, and 4 ml. of a 5% solution of flavianic acid in methanol was added. After standing for 2 hr. the solution was concentrated to effect crystallization, giving on cooling 0.04 g. which on recrystallization had m.p. 230–232° dec. The ultraviolet spectrum did not show the same intense absorption as the dehydro compound.

Anal. Calcd. for $C_{32}H_{32}N_4SO_{12}$: C, 55.17; H, 4.63. Found: C, 54.72; H, 4.95.

Reduction of dehydroreserpic acid lactone with sodium borohydride. Because of the difficulty encountered in obtaining an anhydrous crystalline salt of the dehydro compound (which would not give a complex reaction with the borohydride reagent) the amorphous vacuum-dried chloride salt was used. The crude material, 0.25 g., which by ultraviolet measurements was at least 34% dehydrolactone and 10–15% starting lactone was dissolved in 30 ml. of reagent methanol.

A. To one half of the solution was added an excess of reagent sodium borohydride (0.1 g.) and the solution was kept at room temperature for 1 hr. After the usual work-up, the residue was recrystallized from acetone to give 0.034 g. of reserpic acid lactone, m.p. 285–288°, identical in every respect with an authentic sample. During a large number of reductions of the dehydrolactone in various degrees of purity no isoreserpic acid lactone could be found, thus indicating the stereospecificity of the method.

B. In contrast, direct liberation of the material was undertaken by basifying the remaining 15 ml. of solution with dilute ammonium hydroxide. After extraction with chloroform and the usual work-up the material was recrystallized from acetone to give only 0.014 g. of the lactone, m.p. 282–285°, once again identical in all respects with an authentic sample.

(5) Melting points were determined on the Fisher-Johns block.

(6) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, 77, 442 (1955).

Acknowledgment. The authors are grateful to Dr. H. Boaz, P. Landis, and L. Howard for the physical chemical data and G. M. Maciak, W. L. Brown, H. L. Hunter, and Gloria Beckmann for the microanalyses.

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Pyridineamidoximes

EDWARD BERNASEK

Received March 8, 1957

In a recent publication,[1] Buu-Hoï, *et al.* reported that the 5-chloro-, 3,5-dichloro-, 5-bromo- and 5-iodo-salicylamidoximes inhibited the *in vitro* growth of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of the order of one microgram per milliliter. In view of the above findings, an investigation of the amidoximes derived from the pyridine monocarboxylic acids was undertaken.

The pyridineamidoximes were prepared according to the procedure of Tiemann and Krüger,[2] which involves the heating of the appropriate cyanopyridine at 80–85° with an aqueous solution of hydroxylamine. In the case of 3-pyridineamidoxime, the reaction was carried out in a sealed tube at 70°.[3] If the cyanopyridine was not soluble in water, as was the case with 2-cyanopyridine, sufficient ethyl alcohol was added to effect solution.

The pyridineamidoximes reported here were tested for *in vitro* tuberculostatic activity but were found to be inactive.

EXPERIMENTAL[4,5]

2-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 2-cyanopyridine was added in one portion, followed by sufficient ethyl alcohol (approximately 7 ml.) to dissolve the 2-cyanopyridine. The temperature of the mixture was raised to 85° and maintained for 2 hr. The alcohol was removed under reduced pressure and a tan oil separated from solution. On cooling to 0°, the oil solidified. The crystalline solid was filtered, washed twice with 10 ml. of ice-cold water, and dried in a vacuum desiccator over calcium chloride. The crude product (3.9 g.; 98%) melted at 114–116°. A sample recrystallized from water and dried *in vacuo* at 110° melted at 115.5–116°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.0; N, 30.4.

3-Pyridineamidoxime. Prepared according to the procedure of Michaelis[3] in 70% yield, m.p. 127.5–128°.

4-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 4-cyanopyridine was added in one portion. An exothermic reaction took place causing the temperature to rise to 75°. Almost immediately a mass of colorless crystals separated from solution. Heating was continued at 80° for 0.5 hr. to complete the reaction. The suspension was cooled to 0°, filtered and dried in a vacuum desiccator over calcium chloride. The crude product (3.6. g.; 90%) melted at 175–177°. Recrystallization from ethyl alcohol gave colorless needles, m.p. 178–179°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.1; N, 30.4.

Acknowledgment. The author wishes to thank Irene Melvin for performing the *in vitro* testing of compounds reported in this paper.

RESEARCH LABORATORIES
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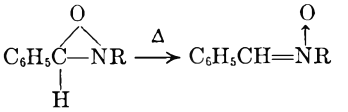
(1) N. P. Buu-Hoï, M. Welsch, N. D. Xuong, and K. V. Thang, *Experientia*, **10**, 169 (1954).
(2) F. Tiemann and P. Krüger, *Ber.*, **17**, 1685 (1884).
(3) L. Michaelis, *Ber.*, **24**, 3439 (1891).
(4) All melting points are uncorrected.
(5) Carbon and hydrogen analyses by Schwarzkopf Microanalytical Laboratory.

Kinetics of the Thermal Isomerization of 2-*tert*-Butyl-3-Phenyloxazirane

M. FREDERICK HAWTHORNE AND
R. DONALD STRAHM

Received March 6, 1957

The observation[1] that 2-*tert.*-alkyl-3-phenyloxaziranes (I) isomerize on heating to the corresponding nitrones (II) and the novelty of the oxazirane ring system prompted the immediate investigation



I II

R = *tert*-alkyl

of the kinetices of this reaction. This kinetic study was primarily designed to determine the enthalpy and entropy of activation for the rearrangement of 2-*tert.*-butyl-3-phenyloxazirane, III, in diethyleneglycol diethyl ether (diethyl carbitol) solvent over a 40° temperature range.

Preliminary experiments showed that the rearrangement of III to *N-tert.*-butyl benzaldoxime, IV, proceeded quantitatively in the 60–100° temperature range and that the ultraviolet absorption spectra of these two materials were sufficiently different in acetonitrile to afford an analytical method for IV in the presence of III. The nitrone (IV) has an extinction coefficient of 1.68×10^4 at λ_{max} 298 mμ while III has an extinction coefficient of only 92 at this same wave length.

The isomerization of III to IV was carried out in diethyl carbitol solvent at 60, 85, and 100° and the

(1) W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956).

initial concentration of III was varied from 0.1 to 0.44*M*. In each case the kinetic experiments were followed to at least 75% completion and then allowed to proceed for infinite time. Final values of conversion always corresponded to from 95 to 100% isomerization to IV. Graphical treatment of the rate data afforded very clean first-order plots. Table I records the first-order rate constants which were obtained.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE THERMAL ISOMERIZATION OF 2-*tert.*-BUTYL-3-PHENYLOXAZIRANE TO *N-tert.*-BUTYL BENZALDOXIME

Temp., °C. ± 0.05°	Initial Oxazirane Concentration, (mole/l.)	k_1,[a] (sec.$^{-1}$) × 10^7
100.0	0.437	545
	0.252	537
85.0	0.116	530
	0.241	119
	0.229	113
	0.120	113
	0.115	117
	0.233	5.40
60.0	0.127	5.40

[a] Average k_1 values are 5.37×10^{-5} at 100.0°, 1.16×10^{-5} at 85.0° and 5.40×10^{-7} (sec.$^{-1}$) at 60.0°.

A plot of reciprocal temperature *versus* log k_1 produced a good straight line from which $\Delta H^{\ddagger}$ was found to be 28 kcal. per mole between 60 and 100°. The entropy of activation, $\Delta S^{\ddagger}$ was found to be -3 ± 1 entropy units, a value which indicates that the structures of oxazirane reactant and nitrone product are equally rigid. The slight negative value may indicate increased solvation of the transition state due to the development of a strong N → O dipole.

EXPERIMENTAL

Materials. Acetonitrile was Eastman Spectrograde. Diethyl carbitol was technical grade which had been rigorously purified according to the procedure given by Brown, Meade, and Subba Rao[2] for the purification of diglyme. The material so obtained boiled at 94–96° at 33 mm., n_D^{20} 1.4115. 2-*tert.*-Butyl-3-phenyloxazirane (III) was generously supplied by W. D. Emmons (ref. 1) and was further purified by chromatography on silica gel using methylene chloride solvent followed by vacuum distillation. The pure material boiled at 63° at 0.8 mm., $n^{24}D$ 1.5081. The ultraviolet spectrum of the compound in acetonitrile solvent showed only end absorption.

Pure N-*tert.*-butylbenzaldoxime (IV) was obtained from the same source, m.p. 75–77°. The ultraviolet spectrum of this compound in acetonitrile solvent gave λ_{max} 289 mμ with an extinction coefficient of 1.68×10^4.

Kinetic procedure. Solutions of 2-*tert.*-butyl-3-phenyloxazirane (0.1 to 0.44*M*) in pure diethyl carbitol were prepared in 10-ml. volumetric flasks. The flasks were placed in the appropriate thermostat at zero time. At intervals small aliquots were removed and delivered to a volume of acetonitrile which was subsequently made up to 10 ml. with the same solvent. Optical density readings were made at 298 mμ with a Model DK-1 Beckman spectrophotometer and the concentration of nitrone (IV) was computed. Points were taken until the reaction had progressed to 75% completion. After several days (or weeks at lower temperatures) the rearrangement of III to IV was found to be essentially complete as determined by the ultraviolet absorption spectrum of the reaction mixture.

First-order plots were prepared by plotting log (oxazirane) *vs.* time. The first-order constants obtained are shown in Table I.

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(2) H. C. Brown, E. J. Meade, and B. C. Subba Rao, *J. Am. Chem. Soc.*, 77, 6209 (1955).

Cyanoethylation of Phenol; Isolation of an *ortho*- Addition Product[1]

H. W. JOHNSTON[2] AND F. J. GROSS[3]

Received May 23, 1957

The carbon-carbon cyanoethylation of the more active phenols, such as resorcinol, to give *beta*-substituted propionitriles in the presence of anhydrous zinc chloride and anhydrous hydrogen chloride is well known.[4] Phenol itself does not react under these conditions, but if a more active catalyst, anhydrous aluminum chloride, is used, a good yield of β-(*p*-hydroxyphenyl)propionitrile is obtained.[5] Recently Westfahl and Gresham reported the addition of vinylidene cyanide to phenol in the presence of anhydrous aluminum chloride at 30–35° to give β-(*p*-hydroxyphenyl)α-cyanopropionitrile in 45% yield.[6] A trace of the δ-lactone of β-(*o*-hydroxyphenyl)propionic acid (melilotol), I, was tentatively identified by means of its infrared spectrum. This compound was formed, presumably, by hydrolysis and decarboxylation of the parent cyano compound during isolation of the products of the Friedel-Crafts reaction.

The authors have noted a result similar to that of Westfahl and Gresham. Phenol was cyanoethylated in the presence of anhydrous aluminum chloride and dry hydrogen chloride. (It was noted that the use of hydrogen chloride considerably lowered the viscosity of the reaction mixture, presumably by minimizing the formation of the insoluble salt, $C_6H_5OAlCl_2$.) The expected β-(*p*-

(1) In part, an undergraduate senior research project by F. J. Gross.

(2) Present address: Whitworth College, Spokane 53, Wash.

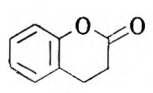
(3) Present address: Swift and Co., Newark, N. J.

(4) W. D. Langley and R. Adams, *J. Am. Chem. Soc.*, 44, 2326 (1922); L. C. Behr, J. E. Kirby, R. N. MacDonald, and C. W. Todd, *J. Am. Chem. Soc.*, 68, 1296 (1946).

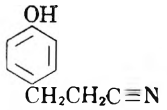
(5) R. Schnabel, German Patent 870,273, March 12, 1953.

(6) J. C. Westfahl and T. L. Gresham, *J. Am. Chem. Soc.*, 76, 1076 (1954).

hydroxyphenyl)propionitrile, II, was obtained in 72% yield. In addition, a careful fractional distillation of the products of the reaction gave the δ-lactone of β-(*o*-hydroxyphenyl)propionic acid, I, in 3% yield.



I



II

Although several experiments were made, at no time under the reaction conditions used, was any trace of the *ortho*-cyanoethylphenol observed. It is reasonable to expect that this compound or its tautomeric imine was attacked by the neighboring *ortho*-phenolate ion in the aluminum chloride complex or during the subsequent hydrolysis of the complex ions. The relatively low yield of this *ortho* addition compound suggests steric hindrance.

EXPERIMENTAL

Four hundred grams (3 moles) of anhydrous C.P. aluminum chloride was added slowly with rapid mechanical stirring at 15° to 564 g. (6 moles) of freshly distilled phenol and 387 g. (6 moles) of freshly distilled acrylonitrile. Dry hydrogen chloride was passed into the rose-colored viscous slurry over a period of about 1.5 hr. during which time there was a pronounced decrease in viscosity of the mixture.

The slurry was heated to 80° whereupon it dissolved to a dark red fluid solution. Although further external heating was discontinued the reaction was strongly exothermic and refluxed at 105°. Addition of dry gas was continued over a period of 1.5 hr. after which the mixture was allowed to cool.

The contents of the reaction vessel were poured over 2 kg. of cracked ice and stirred until the precipitated salts redissolved. The dark red phenolic layer was removed by means of a separatory funnel and the aqueous portion was extracted with two 250-ml. portions of toluene which were combined with the phenolic material. The organic mixture was washed several times with 10% potassium chloride solution and stripped of solvent at reduced pressure.

Vacuum distillation of the residue through a 24-in. helix-packed column connected to a distillation head equipped for partial take-off gave 374 g. of phenol, b.p. 69° at 7 mm.; 15 g. of melilotol (containing phenol as a contaminant), b.p. 84–109° at 1 mm.; and 317 g. of β-(*p*-hydroxyphenyl)-propionitrile, b.p. 157–163° at 1 mm., m.p. 58–59°, which is in agreement with that recorded in the literature.[7] Alkaline hydrolysis of this nitrile gave phloretinic acid, m.p. 127–129°.[8]

Redistillation of the second fraction gave melitolol, b.p. 111–112° at 2.5 mm., identified by comparison of its infrared spectrum with that of an authentic sample prepared by an independent method.[9,10]

Strong bands in the infrared spectrum of the lactone were noted at 1775, 1242, 1227, 1140, and 760 cm.$^{-1}$ Hydrolysis of the lactone with aqueous KOH followed by acidification gave melilotic acid, m.p. 81–83°. A mixed melting point with an authentic sample[9] showed no depression.

(7) G. Zemplen, Z. Csuros, A. Gerecs, and S. Aczel, *Ber.*, 61, 2486 (1928).

(8) T. C. Bruice, *J. Org. Chem.*, 19, 333 (1954).

(9) T. Nakabayaski, *J. Pharm. Soc. Japan*, 74, 23 (1954); *Chem. Abstr.*, 47, 1257.

(10) R. Pschorr and H. Einbeck, *Ber.*, 38, 2067 (1905).

Acknowledgment. The authors wish to express their appreciation to the Research Council of Rutgers University for support of this work.

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α-Phenylcycloalkylideneacetic Acids

F. F. BLICKE AND R. H. COX

Received May 22, 1957

α-Phenyl-3-methylcyclohexylidenaecetic, α-phenyl-4-methylcyclohexylideneacetic and α-phenylcycloöctylideneacetic acids have been prepared by dehydration of the required α-phenyl-α-(1-hydroxycycloalkyl)acetic acids[1] with acetic anhydride according to the procedure described for α-phenylcyclohexylideneacetic acid.[2] The ultraviolet absorption spectra of the new acids were compared with those of α-phenylcyclohexylideneacetic acid[2,3] and α-phenyl-1-cyclohexenylacetic acid.[3] The spectrum of each new acid was essentially coincident with that of α-phenylcyclohexylideneacetic acid,[4] which indicated that each possessed the α-phenylcycloalkylideneacetic acid structure rather than that of the corresponding α-phenyl-1-cycloalkenylacetic acid. The much lower adsorption above 220 mμ shown by α-phenyl-1-cyclohexenylacetic acid was expected, since the ethylenic bond in this compound is not in conjugation with the benzene nucleus.

EXPERIMENTAL

α-Phenyl-3-methylcyclohexylideneacetic acid. This acid, obtained in 22% yield after recrystallization from petroleum ether (90–100°), melted at 142–148°; it was undoubtedly a mixture of geometric isomers.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.24; H, 7.86: neut. equiv., 230.3. Found: C, 78.20; H, 8.10; neut. equiv., 230.1.

α-Phenyl-4-methylcyclohexylideneacetic acid. This acid melted at 122–124° after recrystallization from absolute ethanol; yield 36%.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.24; H, 7.86: neut. equiv., 230.3. Found: C, 78.28; H, 8.19; neut. equiv., 229.3.

α-Phenylcycloöctylideneacetic acid. This acid, obtained in 11% yield, melted at 139–141° after recrystallization from absolute ethanol.

(1) F. F. Blicke and R. H. Cox, *J. Am. Chem. Soc.*, 77, 5401 (1955).

(2) N. L. Phalnikar and K. S. Nargund, *J. Indian Chem. Soc.*, 14, 736 (1937).

(3) α-Phenylcyclohexylideneacetic acid and α-phenyl-1-cyclohexenylacetic acid, which are structural isomers, were prepared and characterized by oxidative degradation by Phalnikar and Nargund.[2]

(4) The ultraviolet absorption spectrum determined by us for α-phenylcyclohexylideneacetic acid was in agreement with that reported by K. Scholz, M. Spillman, E. Tagmann, and K. Hoffman [*Helv. Chim. Acta*, 35, 2016 (1952)] for a basic ester of this acid.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25; neut. equiv., 244.3. Found: C, 78.17; H, 8.34; neut. equiv., 245.4.

The ultraviolet absorption spectra were determined between 220 and 300 mμ with a Beckman DU spectrophotometer. A concentration of 0.01% in absolute ethanol was employed in each case.

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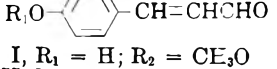
Reactions of Vanillin and Its Derived Compounds. XXVIII.[1] Coniferaldehyde and *p*-Coumaraldehyde

IRWIN A. PEARL AND STEPHEN F. DARLING[2]

Received May 13, 1957

In connection with other studies in these laboratories on reactions of lignin, wood, and wood extractives, it was necessary to prepare substantial quantities of coniferyl aldehyde (I) and *p*-coumaraldehyde (II). These aldehydes had been prepared recently by Freudenberg and co-workers[3,4] by the stannous chloride reduction of the phenylimidochlorides of the corresponding acetylated acids, but the procedures involved did not lend themselves to quantity production. Attempts to adapt the Rosenmund procedure as used by Freudenberg and Hübner[5] for the preparation of the closely related sinapyl aldehyde resulted only in the recovery of the acid chlorides as their parent acids. The elegant method of Brown and McFarlin[6] for the production of aldehydes by the reduction of acid chlorides with lithium tri-*t*-butoxyaluminohydride was tried on acetylferulic and acetyl *p*-coumaric acid chlorides. These acid chlorides gave good yields of acetylconiferyl aldehyde (III) and acetyl *p*-coumaraldehyde (IV), respectively, and the acetylated aldehydes yielded the desired coniferyl aldehyde and *p*-coumaraldehyde upon hydrolysis with sodium methylate in chloroform solution.



I, $R_1 = H$; $R_2 = CH_3O$
II, $R_1 = R_2 = H$
III, $R_1 = CH_3CO$; $R_2 = CH_3O$
IV, $R_1 = CH_3CO$; $R_2 = H$

(1) For paper XXVII of this series, see *J. Org. Chem.*, 22, 1229 (1957).

(2) Lawrence College, Appleton, Wis.

(3) K. Freudenberg and R. Dillenburg, *Chem. Ber.*, 84, 67 (1951).

(4) K. Freudenberg and G. Gehrke, *Chem. Ber.*, 84, 443 (1951).

(5) K. Freudenberg and H. H. Hübner, *Chem. Ber.*, 85, 1181 (1952).

(6) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, 78, 252 (1956).

EXPERIMENTAL

All melting points are uncorrected, and ultraviolet spectral data are for solution in 95% ethanol (concentration, 0.02 g. per liter).

Lithium tri-t-butoxyaluminohydride. The reagent was prepared by treating a filtered solution of lithium aluminum hydride in absolute ether with dry *t*-butyl alcohol with stirring. The white precipitate was filtered, washed with anhydrous ether, and dried at 60°.

Acetylconiferylaldehyde (III). A solution of 12.2 g. (0.05 mole) of acetylferuoyl chloride[3] in 75 ml. of dry tetrahydrofuran was placed in a 250-ml. 3-neck flask fitted with a dropping funnel, thermometer, and mercury-sealed stirrer, and immersed in a Dry Ice–acetone bath. The solution was cooled to −65° and treated dropwise with stirring with a solution of 12.7 g. (0.05 mole) of lithium tri-*t*-butoxyaluminohydride in 50 ml of dry tetrahydrofuran while maintaining the temperature at −65°. After addition was complete the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature with stirring. With rise in temperature, the turbid mixture became clear. When the temperature reached 20° the mixture was poured onto a mixture of crushed ice and water. The precipitate was filtered, and the filtrate deposited colorless platelets upon standing. These were collected, and the filtrate was concentrated and cooled to give more platelets. The total yield of platelets melting at 95–96° was 1.2 g. The original aluminum hydroxide precipitate was extracted with boiling ethanol, and the ethanol was concentrated in a rotating evaporator to yield 5.0 g. of product melting at 81–97°. Both of these products, when adsorbed on aluminum oxide and eluted with ether, yielded pure pale yellow crystals of III melting at 97–98° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 240 mμ, ε 11800; λ_{max} 290 mμ, ε 19440.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.67; H, 5.49.

Freudenberg and Dillenburg[3] reported a melting point of 102–103° for III prepared by acetylation of isolated I, but repetition of their work in this laboratory confirmed the 97–98° melting point.

This experiment was repeated with diglyme as the solvent with essentially the same results.

Coniferaldehyde (I). A solution of 2 g. of III in 50 ml. of chloroform was treated with cooling with a solution of 0.5 g. of sodium in 10 ml. of anhydrous methanol. The mixture was allowed to stand at 20° for 30 min., and then treated with 50 ml. of water. The mixture was shaken, and the aqueous layer was separated and acidified with dilute sulfuric acid. The acidified mixture was extracted with chloroform, and the chloroform was dried and concentrated to dryness. The residual sirup was covered with a little benzene and scratched to induce crystallization. The crude crystals melted at 70–72°, and the material obtained upon recrystallization from benzene melted at 80–81° and did not depress the melting point of authentic coniferaldehyde.[3] The yield was 75%.

Acetyl p-coumaraldehyde (IV). Similar reduction of 11.2 g. of acetyl *p*-coumaroyl chloride (m.p. 119–121° from benzene–petroleum ether) in diglyme or tetrahydrofuran as a solvent yielded 7 g. of crude IV melting at 70–75° which, upon recrystallization from ether–petroleum ether, yielded colorless crystals of IV melting at 77–78° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 223 mμ, ε 14800; λ_{max} 293 mμ, ε 24750.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.32; H, 5.17.

The *semicarbazone*, after crystallization from ethanol, melted at 213–215°.

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.29; H, 5.30. Found: C, 58.46; H, 5.26.

p-Coumaraldehyde (II). Reduction of IV with a solution of sodium methylate in methanol-chloroform as described

above gave an almost quantitative yield of II which was recrystallized from benzene to yield slightly yellow crystals melting at 138–140°, which was the melting point recorded for II prepared by reduction of acetyl *p*-coumaric acid phenylimidochloride with stannous chloride.[4]

Acknowledgment. The authors wish to thank the Analytical Department of The Institute of Paper Chemistry for the analyses and spectra reported in this paper.

THE INSTITUTE OF PAPER CHEMISTRY
APPLETON, WIS.

Urethanes of Tropine and Phenylmethylpyrazolone

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Received April 1, 1957

Some years ago, when these laboratories were engaged in the synthesis of cholinergic drugs, it became desirable to prepare the dimethylurethanes of tropine and of phenylmethylpyrazolone and to study pharmacologically these substances and some of their quaternary salts.

EXPERIMENTAL

Tropine, m.p. 63–64°, could be obtained from atropine in 85–95% yield by refluxing 20–25 min. with alcoholic potassium hydroxide, followed by rapid ethereal extraction of the cooled diluted solution (Tropic acid, m.p. 105–106°, could be isolated from the acidified alkaline solution).

Dimethylcarbamoyltropine. Equal weights of tropine and dimethylcarbamoyl chloride were rapidly heated to 150–160°. The color of the mixture changed to reddish brown and on cooling the mixture solidified. The pulverized solid was extracted with benzene and then dissolved in water. The aqueous solution was made basic with sodium carbonate, extracted with chloroform, and the solvent stripped from the extract to leave the crude product. This could be purified *via* the picrate (chromatographed on alumina) but this procedure offered little advantage over direct distillation. The pure product distilled at 105–120° (1 mm.) without decomposition and was obtained in 38 to 46% yield. It was a colorless liquid, soluble in water, benzene, alcohol, and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.26; H, 9.43; N, 13.20. Found: C, 62.52; H, 9.62; N, 12.89.

The *picrate* was prepared in the usual manner and melted at 210–212° after recrystallization from alcohol.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot C_6H_3N_3O_7$: C, 46.26; H, 5.25; N, 15.80. Found: C, 46.09; H, 4.88; N, 16.33.

The methiodide was prepared by interaction of the urethane and methyl iodide in methanol. It melted at 250–252° after recrystallization from methanol and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot CH_3I$: C, 40.67; H, 6.49; N, 7.90. Found: C, 40.86; H, 6.77; N, 7.74.

The *methobromide* was prepared by the addition of a dry benzene solution of the urethane to a solution of an excess of methyl bromide in benzene. It melted at 280–283° after recrystallization from methanol and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot CH_3Br$: C, 46.89; H, 7.55; N, 9.11. Found: C, 46.61; H, 7.58; N, 9.13.

The *benzochloride* was so hygroscopic that it could not be obtained pure. The *benzobromide* was prepared by the interaction of the urethane and benzyl bromide in boiling benzene. It melted at 250–252° after recrystallization from ethanol and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot C_7H_7Br$: C, 56.39; H, 7.10; N, 7.31. Found: C, 55.61; H, 7.28; N, 7.01.

1-Phenyl-3-methyl-5-dimethylcarbamoyloxypyrazole. Equal weights of the dry potassium salt of 1-phenyl-3-methyl-5-pyrazolone and dimethylcarbamoyl chloride were heated on the steam bath for 15 min. and the mixture was then leached with chloroform. The chloroform solution was washed with aqueous sodium carbonate, dried, and distilled to give 45–50% yields of product, b.p. 167–172° (2–3 mm.).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.67; H, 6.12. Found: C, 63.98; H, 6.40.

This material did not give a picrate, methiodide, or benzochloride (no picrate or quaternary salts of phenylmethylpyrazolone are reported in the literature).

The methiodide and benzobromide of dimethylcarbamoyltropine showed no cholinergic effect on isolated guinea pig intestine at a concentration of 100 γ/cc. (determined by Dr. R. J. Schachter).

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Reaction of NBS with Allylic Alcohols

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Received April 1, 1957

In connection with previous studies[2] on selective oxidations of secondary alcohols with *N*-bromosuccinimide, the oxidation of the steroid allylic alcohols was investigated. Δ^4-Cholestene-3β,6β-diol was oxidized mainly to 3,6-cholestanedione (42% yield), presumably through the intermediate formation of Δ^4-cholestene-6β-ol-3-one, which was indeed isolated also but in low yield (17%). The results contrast with those obtained with the corresponding saturated 3β,6β-diol,[2] where only the 6β-hydroxyl group is affected, but are understandable in terms of a half-chair conformation for Ring A in the unsaturated diol.[3]

In the reaction of *N*-bromosuccinimide with 7β-hydroxycholesterol, neither of the hydroxyl groups is oxidized; instead a bromohydrin is obtained (57% yield). This is converted into an oxide when treated with base. This oxide and the isomeric oxide were both obtained by oxidation of Δ^5-cholestene-3β,7β-diol with perphthalic acid. The

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(2) L. F. Fieser, H. Heymann, and S. Rajagopalan, *J. Am. Chem. Soc.*, **72**, 2306 (1950); L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3935 (1949); **71**, 3938 (1950); **72**, 5530 (1950).

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configuration of the two oxides can be assigned by molecular rotation differences as compared with α- and β-cholesteryl oxides. The oxide obtained through the bromohydrin is evidently the β-oxide and therefore the bromohydrin from which it is formed is 5α-bromocholestane-3β,6β,7β-triol. The addition of hypobromous acid to the 5,6-double bond therefore is contrary to Markownikoff's rule, as has been observed in the addition of halogens[4] and hypochlorous acid,[5] and is controlled by steric factors.[6]

EXPERIMENTAL[7]

Oxidation of Δ^4*-cholestene-3*β*,6*β*-diol.* Δ^4-Cholestene-3β,6β-diol (430 mg.) in hot dioxane (75 ml.) containing 2 ml. of water was treated with *N*-bromosuccinimide (400 mg.) and the mixture was warmed on the steam bath until complete solution was effected. The solution turned yellow and then colorless. At this stage the reaction mixture was poured into water and the precipitate collected by suction. A first crystallization from benzene–petroleum ether gave 80 mg. (17% yield) of colorless needles m.p. 191–193° identified as Δ^4*-cholestene-6*β*-ol-3-one* by direct comparison with an authentic sample of this compound. From a second crop of the initial solution a crystalline product, m.p. 169–170°, α_D +3.2, was obtained, which was not depressed on admixture with a pure sample of *3,6-cholestandione*. Yield, 200 mg. (42%).

5α*-Bromocholestane-3*β*,6*β*,7*β*-triol* was obtained from the reaction of Δ^5-cholestene-3β,7β-diol (450 mg.) with NBS (280 mg.) in dioxane-water (6 ml., 0.8 ml.), 6 hr., 25°. It forms small prisms when crystallized from petroleum ether, m.p. 179–180°, α_D +28.6°.

Anal. Calcd. for $C_{27}H_{47}O_3Br$: C, 64.91; H, 9.48; Br, 15.99. Found: C, 64.99; H, 9.53; Br, 15.93.

The 3,7-dibenzoate was obtained by a similar reaction from Δ^5-cholestene-3β,7β-diol dibenzoate; 89% yield, m.p. 142–143°, α_D −60.6°.

Anal. Calcd. for $C_{41}H_{55}O_5Br$: C, 69.57; H, 7.83. Found: C, 69.93; H, 7.56.

When refluxed with 2% potassium hydroxide for 1 hr. the bromohydrin is converted into the β-oxide of 7β-hydroxycholesterol in 92% yield; plates from petroleum ether, m.p. 166–167°, α_D +50°. The oxide is reconverted into the bromohydrin by the action of hydrogen bromide.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.45; H, 11.07. Found: C, 77.12; H, 10.99.

The 3,7-dibenzoate of the β-oxide was obtained from the corresponding bromohydrin; 64% yield, m.p. 151–153°, α_D +86°.

7β*-Hydroxycholesteryl* α*-oxide* was obtained by refluxing Δ^5-cholestene-3β,7β-diol (800 mg.) for 6 hr. with a solution of perphthalic acid (800 mg.) in ether (40 ml.). After the usual work-up, chromatography afforded some starting material (60 mg.); the α-oxide, 250 mg., 30% yield, m.p. 153–155°, α_D +12°; intermediate nonhomogeneous fractions; and finally the β-oxide, 12% yield, m.p. 166–167° α_D +50° (no melting point depression on admixture with the oxide from the bromohydrin).

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.45; H, 11.07. Found: C, 76.86; H, 11.22.

Acknowledgement. I am indebted to Professor and Mrs. L.F. Fieser for their help and suggestions in connection with this work.

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Reaction of Ethyl Acrylate with Methyl *n*-Hexyl Ketone

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Received March 25, 1957

It has been reported that the reaction of ethyl acrylate with methyl *n*-hexyl ketone in the presence of an excess of sodium ethoxide gives 1-hendecene-3,5-dione.[2] When this reaction was repeated, a product (I) with the reported melting point 69–70° and composition (corresponding to $C_{11}H_{18}O_2$) was obtained. Although examination of the infrared spectrum confirmed the presence of a 1,3-diketone by a very broad band[3] at about 1600 cm.$^{-1}$, there was no indication of the presence of a double bond. The compound did not absorb hydrogen in the presence of either Pt or Pd catalyst. The diketone had a neutralization equivalent of 178 and molecular weight (ebulliometric) of 182. It did not give a color in the ferric chloride test.

Two possible structures for the product were 2-pentyl-1,3-cyclohexanedione (II) and 4-pentyl-1,3-cyclohexanedione (III), which could be formed, respectively, by an initial Michael condensation of the two reactants at the methyl or the methylene carbon atom, followed by a cyclization reaction. Whereas II would give only one product on basic hydrolysis, 5-ketohendecanoic acid, III would give a mixture of 2-pentyl-5-ketohexanoic acid and 4-pentyl-5-ketohexanoic acid. Hydrolysis of I with barium hydroxide solution[4] gave after acidification a clear oil which resisted attempts at crystallization. This oil had a neutralization equivalent of 205 (calcd. for $C_{11}H_{20}O_3$, 200). The infrared spectrum was consistent with the keto acid structure, the carbonyl groups absorbing in a single band at about 1715 cm.$^{-1}$ A weak iodoform test was obtained, showing the presence of some material containing the CH_3CO- group. The resistance of the keto acid to crystallization and this iodoform test indicated that the original product was III, and that hydrolysis had given the mixed keto acids.

III has been prepared by the hydrogenation of 4-pentylresorcinol, in alkaline solution and in the presence of Raney nickel catalyst.[5] Repetition of

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this synthesis gave a product, m.p. 68.5–70° (reported m.p. 67°), which when mixed with I showed no depression of melting point. The infrared spectrum of the substance was identical with that of I.

I is therefore properly formulated as 4-pentyl-1,3-cyclohexanedione.

EXPERIMENTAL

Ethyl acrylate was commercial grade used without purification. Methyl *n*-hexyl ketone was freed of capryl alcohol by refluxing for 28 hr. with 1.5% of its weight of boric acid and removing the water produced. It was then carefully distilled, b.p. 85° at 30 mm.

Product I from ethyl acrylate and methyl hexyl ketone. To a suspension of sodium ethoxide in xylene, prepared by addition of absolute ethanol (17.4 g.) to a suspension of sodium (6.90 g., 0.3 g. atom) in xylene (200 cc.) was added ethyl acrylate (40 g., 0.4 mole). The mixture was cooled in an ice bath and methyl *n*-hexyl ketone (20 g., 0.15 mole) was added dropwise. Heat was evolved and the mixture became viscous. As the mixture was stirred at 0° for 0.5 hr., the solution became less viscous. Stirring was continued overnight (17 hr.) at room temperature and 100 cc. of water was introduced. After the mixture had been stirred for another hour, the aqueous and xylene layers were separated and the aqueous layer was acidified with glacial acetic acid. The oil which separated on acidification crystallized while standing in the refrigerator. Recrystallization of the gummy yellow solid from ethyl acetate gave 8 g. (27%) I, colorless crystals, m.p. 69–70°.

Anal., Calcd. for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0. Found: C, 72.6; H, 10.1.

Hydrolysis of I. A suspension of $Ba(OH)_2 \cdot 8H_2O$ (34.7 g., 0.11 mole) and I, (5 g., 0.022 mole) in 100 ml. of water was heated at reflux for 28 hr. Solid carbon dioxide was introduced until the mixture was neutral to *p*H paper. The precipitated barium carbonate was removed by filtration. The mixture was heated to reflux again and the hot solution was filtered. When the filtrate was treated with 20 ml. of 2*N* hydrochloric acid, a clear oil separated. The oil was extracted with ether and the ethereal solution was dried over magnesium sulfate. Evaporation of the ether left an oil which resisted attempts at crystallization. Some iodoform was obtained in the iodoform test on this oil. Treatment of it with 2,4-dinitrophenylhydrazine gave an oil which could not be crystallized.

4-n-amyl-1,3-cyclohexanedione (III). 4-Pentylresorcinol was prepared by the method of Dohme, Cox, and Miller.[6] The procedure of Adams and Baker[5] was followed in the reduction to III. The product was obtained in 88% yield, m.p. after recrystallization from pentane, 68.5–70°, mixture m.p. with I, 68.5–70°.

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Formylation of Furans

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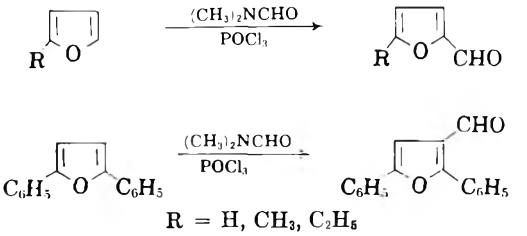
Received March 25, 1957

In recent years the use of dimethylformamide and phosphorus oxychloride as a formylating agent has found many applications in the heterocyclic series. The systems studied contained sulfur[1] and nitrogen[2] heteroatoms. In this report the authors wish to extend the scope of this reaction to the oxygen systems, namely furan and its derivatives.



R = H, CH_3, C_2H_5

The formylation of furan, 2-methylfuran, and 2-ethylfuran proceeded under mild conditions and gave furfural (64%), 5-methyl-2-furaldehyde (76%) and 5-ethyl-2-furaldehyde (80%), respectively. These aldehydes were identified by physical constants, solid derivatives, and, in the case of furfural, by comparison of the infrared spectrum with that of an authentic sample (experimental section).

Conversion of the above furans to the corresponding aldehydes by the Gatterman reaction has been reported by Reichstein;[3] however, the dimethylformamide-phosphorus oxychloride method gives better yields by 15 to 30%. In view of the commercial availability of 2-methylfuran, this reaction presents an excellent procedure for the preparation of 5-methyl-2-furaldehyde.

When two substituents are introduced into the α positions of the furan nucleus, the formylation with dimethylformamide and phosphorus oxychloride becomes more difficult. In the case of 2,5-dimethylfuran resinification took place; however, 2,5-diphenylfuran gave 2,5-diphenyl-3-furaldehyde (40%) m.p. 89–90°, oxime, m.p. 170–171° (reported[4] m.p. of aldehyde 90–92°, m.p. of oxime 171–173°) and starting material (39%). This reaction presents an example of direct formylation in the β-position of the furan ring. Generally these aldehydes are prepared by conversion of some functional group in the β-position to an aldehyde.

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EXPERIMENTAL

2-Ethylfuran. 2-Acetylfuran, b.p. 70° (14 mm.), prepared in 65% yield using the procedure of Hartough and Kosak,[5] was converted to 2-ethylfuran, b.p. 90–91°, n_D^{20} 1.4400, in 17% yield by a Wolf-Kishner reduction according to the directions of Reichstein.[3]

2,5-Diphenylfuran. The procedure of Lutz and Rowlett[6] was used to prepare 2,5-diphenylfuran, m.p. 88–89°, in 84% yield from dibenzoylethylene.

Furfural. Phosphorus oxychloride (115 g., 0.75 mole) was added with constant stirring to dimethylformamide (54.8 g., 0.75 mole) in a flask fitted with a thermometer, dropping funnel, condenser, and stirrer. The addition, carried out at ice bath temperatures, required 30 min. and the reaction mixture was then kept at 0–5° for 40 min. Freshly distilled furan, b.p. 31–32°, n_D^{20} 1.4211 (45 g., 0.66 mole) was added with stirring over a period of 15 min. The ice bath was removed and the mixture heated. At 30° an exothermic reaction commenced with the evolution of hydrogen chloride. The ice bath was returned and after the reaction subsided, the mixture was heated at approximately 100° for 0.5 hr., cooled, and poured into ice water. A solution of potassium carbonate (132 g., 0.80 mole) in 200 ml. of water was added slowly and the mixture was steam distilled. The distillate was saturated with potassium carbonate and extracted with ether. After the extract was dried over sodium sulfate and ether was removed and the residue was distilled. The yield of pure furfural, b.p. 62–63° (19 mm.), n_D^{20} 1.5252 (lit.,[7] b.p. 63° (19 mm.), n_D^{20} 1.52608), was 40.3 g. (34%). The infrared spectra of the above and an authentic sample were identical.

The *oxime* was prepared in the usual way and after recrystallization from water melted at 89–90° (lit.,[8] m.p. 91–92°).

The *semicarbazone* was prepared and after recrystallization from 50% aqueous ethanol melted at 201–202° (lit.,[9] m.p. 202–203°).

5-Methyl-2-furaldehyde.[10] The above procedure was followed with some minor modifications. To a mixture of dimethylformamide (51 g., 0.70 mole) and phosphorus oxychloride (107 g., 0.70 mole) which was kept at 0.5° for 20 min. was added freshly distilled 2-methylfuran, b.p. 64°, n_D^{20} 1.4338 (50.5 g., 0.70 mole) at a rate such that the temperature of the reaction mixture did not rise above 20°. After the addition was completed, the mixture was kept at 0.5° for 1 hr. and then at room temperature for 1 hr. The mixture was poured into 600 ml. of cracked ice and water, neutralized with sodium carbonate (185 g., 1.75 mole) and allowed to stand overnight. The organic layer was separated and the aqueous phase extracted 3 times with 200-ml. portions of ether. The extracts and organic liquid were combined and dried over sodium sulfate, and the ether was removed. Distillation gave 41.7 g. (76%) of 5-methyl-2-furaldehyde, b.p. 72–73° (11 mm.), n_D^{20} 1.5283 [lit.,[11] b.p. 75–76° (13 mm.), n_D^{20} 1.53049].

The product was fractionated through 0.8 × 25 cm. electrically heated column packed with 1/16-in. glass helices and equipped with a variable take-off head. Five center-cut fractions were collected, combined weight 34.6 g. (63%), b.p. 79° (15 mm.), which had a constant refractive index n_D^{20} 1.5310–1.5312.

The *oxime* was prepared and after recrystallization from water melted at 112–113° (lit.,[12] m.p. 110–112°).

The *semicarbazone* was prepared and after recrystallization from 50% ethanol melted at 197° (lit.,[3] m.p. 197°).

In another experiment the mixture of phosphorus oxychloride (123 g., 0.80 mole), dimethylformamide (58.5 g., 0.80 mole), and methylfuran (50.5 g., 0.70 mole) as prepared above was heated to 130° over a 2-hr. period. Evolution of hydrogen chloride was observed. The product was isolated by steam distillation and after distillation gave 51.8 g. (67%) of pure 5-methyl-2-furaldehyde, b.p. 82–84° (17 mm.), n_D^{20} 1.5312.

5-Ethyl-2-furaldehyde. The procedure described for 5-methyl-2-furaldehyde was employed to convert 2-ethylfuran (6.2 g., 0.065 mole) to 6.4 g. (80%) 5-ethyl-2-furaldehyde, b.p. 99° (24 mm.), n_D^{20} 1.5201 [lit.,[3] b.p. 79–81° (12 mm.)]. Fractionation through a Vigreux column gave the following constants, b.p. 82–83° (11 mm.), n_D^{20} 1.5220.

A *semicarbazone* was prepared and after recrystallization from 50% aqueous ethanol melted at 167–168° (lit.,[3] 176–177°).

5-Ethyl-2-furoic acid[13] was prepared by oxidation with silver oxide. Recrystallization from benzene gave the pure acid m.p. 93.5–94.5° (lit.,[3] 93–94°).

2,5-Diphenyl-3-furaldehyde. A mixture of 2,5-diphenylfuran (2.2 g., 0.010 mole), dimethylformamide (1.1 g., 0.015 mole), and phosphorus oxychloride (2.3 g., 0.015 mole) was heated on a steam bath for 3 hr. The reaction mixture was dissolved in 25 ml. of dimethylformamide and poured into 100 ml. of water. An oil separated, which solidified and gave 2.36 g. of a tan solid m.p. 54–64°.

This substance was heated on a steam bath with 100 ml. of 40% sodium bisulfite solution for 1 hr., cooled, filtered, and dried. The resulting solid was triturated with ether and filtered. Evaporation of the ether gave 1.08 g. of a pale yellow solid, m.p. 77–85°. This crude material was purified by chromatography on 75 g. of Merck acid-washed alumina. The fraction eluted with 20% benzene in pentane was 0.86 g. (39%) of 2,5-diphenylfuran m.p. 88–89°. It gave no depression in melting point when mixed with starting material.

The bisulfite addition product was decomposed with hydrochloric acid to give 1.20 g. of a brown solid, m.p. 85–87°. Recrystallization from ethanol after a charcoal treatment gave 1.0 g. (40%) of 2,5-diphenyl-3-furaldehyde m.p. 89–90° (lit.,[4] m.p. 90–92°).

The *oxime* was prepared and after recrystallization from ethanol melted at 170–171° (lit.,[4] 171–173°).

Attempts to formylate 2,5-dimethylfuran by the above procedures lead to resinification.

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Synthesis of Quercetin-2-C^{14}

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Received March 7, 1957

For use in biological tracer studies, the preparation of quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavone) specifically labeled at the number 2 position has become of value. Although syntheses of quercetin have been previously described,[1] no published synthesis could be used unmodified for the authors' purpose. The usual starting materials cannot be readily obtained radioactive, and the methods were not designed to give the required purity of product. This paper describes a synthesis of chromatographically pure quercetin-2-C^{14} on a semimicro scale, using the readily available potassium cyanide-C^{14} as starting radioactive compound. Some steps of the synthesis have been adapted, though with significant improvements from Kostanecki *et al.*[2] All the steps of the labeled synthesis were first worked out in trial runs, using nonlabeled materials.

EXPERIMENTAL[3]

4-Iodoveratrole (I). This required intermediate was prepared by a method similar to that of Minnis.[4] A solution of 28 ml. (0.2 mole) of redistilled veratrole in 75 ml. of 95% ethanol was heated to 60° and, while stirring, was treated with 50 g. of iodine and 30 g. of mercuric oxide. The iodine, in 5-g. portions, and the mercuric oxide, in 3-g. portions, were added alternately over a period of 1 hr. After the addition was complete, the solution was filtered, and the alcohol was distilled from the filtrate. The residue, a dark red oil, was dissolved in ethyl ether and washed with solutions of sodium thiosulfate and sodium hydroxide, and finally with water.

After drying over anhydrous magnesium sulfate, the ether was evaporated and the residue distilled under reduced pressure. This gave 25 g. of a heavy pale yellow oil; b.p. 80–85° at 1 mm. A portion of this oil crystallized after a month in the ice box. Subsequent oils were seeded with these crystals.

Veratronitrile–(nitrile-C^{14}) (II). In an oil bath at 250°, with stirring, 2.4 g. (0.027 mole) of cuprous cyanide–C^{14}, specific activity 0.033 mc./mM obtained from commercially available, radioactive potassium cyanide by the method of Barber,[5] was heated for 2 hr. with 7.5 g. (0.028 mole) of I. The cooled, hard reaction mixture was extracted with several portions of anhydrous ether by rubbing, under ether, with a stirring rod.

A chromatographic column containing Magnesol brand magnesium silicate (Food Machinery and Chemical Corp., N. Y.) as adsorbent was prepared with anhydrous ethyl ether. After passage through the column of the ethereal solution of II, the eluant, light tan in color, was transferred to a flask of Corning No. 7280 glass. After removing the ether under reduced pressure, the residue, still containing some I, weighed 4.5 g.

Veratric acid–(carboxyl-C^{14}) (III). To the residue containing II were added 120 ml. of a 15% potassium hydroxide solution and 40 ml. of methanol. After boiling under reflux for a total of 30 hr., the methanol was distilled and the resulting aqueous solution was extracted twice with 15-ml. portions of ethyl ether to remove I and II. About 0.3 g. of these radioactive impurities were removed.

The veratric acid was precipitated by adding concentrated hydrochloric acid to the aqueous solution at 75°. Purification was accomplished by dissolving III in 25 ml. of dilute sodium hydroxide solution and heating with activated charcoal at 100°. After filtering, the filtrate was acidified with concentrated hydrochloric acid at 75°. The resulting white crystals were collected by filtration, washed with a small amount of dilute acid, and dried in a desiccator (yield, 4.0 g.; m.p. 181°; specific activity 0.034 mc./mM). Upon working up the mother liquors and washings, an additional 0.3 g. of III was obtained.

Decarboxylation of a small aliquot of the radioactive III yielded radioactive carbon dioxide and a residue with no detectable radioactivity.

Veratroyl chloride–(carbonyl-C^{14}) (IV). Four grams (0.022 mole) of III was heated with 25 ml. of purified thionyl chloride under reflux on a water bath for 2 hr. After removal, *in vacuo*, of excess thionyl chloride, the pale amber liquid solidified on cooling.

Veratraldehyde–(carbonyl-C^{14}) (V). The veratroyl chloride was reduced to the corresponding aldehyde by the Rosenmund reaction, using procedures similar to those of Hershberg and Cason.[6] Dry hydrogen, 0.022 mole of IV (based on the veratric acid), 30 ml. of purified xylene, 5 microliters of the quinoline-sulfur regulator, and 0.5 g. of the palladium–barium sulfate catalyst were used in the conversion. At the end of the reaction the solvents were removed under reduced pressure. The pale yellow residue, weighing 3.6 g., contained approximately 2.2 g. of the aldehyde. The product was carried on to the next step without purification.

2,4-Dimethylphloroacetophenone (VI). White crystals of VI, m.p. 81°, were obtained by a procedure involving the partial methylation of phloroacetophenone.[7]

In a dry flask, 12.6 g. of phloroacetophenone (dried at 120°) was dissolved in 45 ml. of anhydrous acetone. Then 225 ml. of anhydrous benzene, 45 g. of anhydrous potassium carbonate, and 14.5 ml. of dimethyl sulfate were added to this solution. The mixture was refluxed on a water bath for 12 hr. After filtration and washing of the residue with hot benzene, the filtrate and benzene solution were then washed with water and extracted with 5% aqueous sodium hydroxide. The extract was poured into cold, 25% hydrochloric acid which caused the dimethylphloroacetophenone to separate as white crystals. These crystals were filtered and washed with 5% aqueous sodium carbonate and then with water. After drying in a vacuum desiccator, the product weighed 12 g.; m.p. 81°. This product was purified by passage in anhydrous ether through a column containing Magnesol. The compound passed through the column with the solvent front; m.p. 83°.

Chalcone (VII) *of 3′,4′,5,7-tetramethyleriodictyol-2-C^{14}*. A mixture of 3 g. (0.015 mole) of VI, the residue containing V in 200 ml. of 95% ethanol, and 6 ml. of 50% aqueous potassium hydroxide was shaken at frequent intervals over a 30-min. period. After 48 hr. at 40°, the deep red solution was diluted with 400 ml. of distilled water. Concentrated hydrochloric acid was added dropwise to the solution until it showed an acid reaction to Congo Red paper. The floc-

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culent yellow precipitate was filtered off. The filtrate was extracted with four 50-ml. portions of benzene until no more color was removed. The benzene extract was then used to dissolve the precipitate, and the resulting solution was dehydrated by azeotropic distillation.

The crude chalcone solution in dry benzene was passed onto a column of Magnesol, prewashed with anhydrous benzene. The chalcone developed as a bright yellow zone near the top of the column. Under ultraviolet light, this zone exhibited dark brown fluorescence. The first 125 ml. of eluant was colorless, and, after evaporation of the benzene, yielded 1.6 g. of unreacted VI. A sharp, distinct separation between this ketone and the unreacted V which followed in the next 75 ml. of eluant was not accomplished. The unreacted, radioactive veratraldehyde was recovered from the eluant.

The chalcone, by this time, had developed as a zone below the dark impurities at the top of the column and also below a narrow pale yellow zone just under the dark impurities. After washing with a total of two columns of anhydrous benzene, the Magnesol was extruded from the top of the column, and then cut with a stainless steel spatula into the three zones. The top zone contained unknown impurities. The second zone contained tetramethyleriodictyol. It was eluted with anhydrous acetone and combined with the crude tetramethyleriodictyol obtained in a later reaction. The third zone contained the purified chalcone and was eluted with the anhydrous acetone. After removal of the solvent, VII weighed 2.3 g. (30%).

3′,4′,5,7-Tetramethyleriodictyol-2-C^{14} (VIII). A mixture of 2.3 g. of VII dissolved in 300 ml. of 95% ethanol, and 11 ml. of concentrated hydrochloric acid in 30 ml. of distilled water was refluxed for 20 hr. Then 500 ml. of distilled water was added. The resulting bright yellow precipitate was filtered off without suction, and the filtrate was extracted three times with a total of 150 ml. of benzene. This benzene was then used to dissolve the precipitate. The solution was filtered to remove the drops of water present and dried by azeotropic distillation.

The flavanone solution was then passed onto a column of Magnesol, prewashed with anhydrous benzene. The flavanone was adsorbed tightly onto the adsorbent and appeared as an ivory-colored zone in visible light and as a dull gray in ultraviolet light. The chalcone developed just below VIII. About 250 ml. of anhydrous benzene was needed to wash the unreacted VII from the column. The chalcone was recovered from this eluate and twice recycled through the same ring-closure reaction and chromatographic separation. The Magnesol, which now contained only the desired flavanone and a small amount of impurities on the top surface, was washed with 300 ml. of anhydrous acetone. This removed VIII very readily. The flavanone solution was combined with additional fractions of VIII from subsequent runs. The solvent was removed from the combined solutions and VIII was obtained as a pale yellow solid which weighed 1.5 g., a 66% yield of the chalcone.

3′,4′,5,7-Tetramethylquercetin-2-C^{14} (IX). The methylated eriodictyol was converted by means of *n*-butyl nitrite and hydrolysis, adapted from a procedure by Row and Seshadri,[8] into the corresponding tetramethylquercetin. A total of 0.45 g. of IX was obtained.

Quercetin-2-C^{14} (X). The tetramethylquercetin was dried, made into a paste with acetic anhydride, and demethylated, using hydriodic acid, sp. gr. 1.70. The yield of X was 0.3 g. The over-all conversion of labeled potassium cyanide into quercetin was 3.5%. Previous runs with unlabeled material had given an 8% yield. In the C-14 synthesis, however, a 29% recovery of intermediates, based on the labeled potassium cyanide, was obtained.

The labeled quercetin was compared on paper chromatograms with authentic synthetic quercetin and with natural quercetin obtained by hydrolysis of buckwheat rutin. The labeled product showed only one spot and gave the same R_f value as the two standards in every solvent system tried. The R_f values obtained in *n*-butyl alcohol–acetic acid-water (6:1:2, by vol.) and in 60% aqueous acetic acid with S&S #589, red ribbon paper, were 0.72 and 0.34, respectively.

In order to show the position of the labeled carbon atom, 1.3 mg. of X was diluted with 68.5 mg. of unlabeled quercetin for various analyses. The diluted quercetin had a calculated specific activity of 0.00055 mc./mM. The diluted quercetin was completely methylated with dimethyl sulfate to produce white-needle crystals of pentamethylquercetin (XI), m.p. 147°. This melting point was not depressed when a mixed melting point was taken with an authentic sample of unlabeled pentamethylquercetin. The sample of XI had a specific activity of 0.0005 mc./mM.

Seventy milligrams of XI was degraded, using 15 ml. of a solution containing 4 g. of potassium hydroxide in 45 ml. of absolute ethanol, and refluxing for 8 hr. After the ethanol was distilled off, the resulting solid was dissolved in 10 ml. of water, and concentrated hydrochloric acid was added to make the solution acid. The acidic solution was extracted with three 10-ml. portions of ethyl ether. The ether solution was extracted with two 10-ml. portions of 5% sodium bicarbonate solution. The ketone fragment, which remained in the ether, was obtained as an oil which did not contain any detectable radioactivity. The bicarbonate solution, containing III, was acidified. About 10 mg. of III was collected; m.p. 179°; specific activity 0.0005 mc./mM.

The sample of veratric acid obtained by degradation was then decarboxylated to produce radioactive carbon dioxide and a residue containing no detectable radioactivity.

Acknowledgment. This work was supported in part by grants, at various stages, from Research Corporation, Eli Lilly and Co., National Institutes of Health, and the National Vitamin Foundation. The authors also thank Dr. O. K. Neville, Technical Director, Nuclear-Chicago, for his helpful suggestions in the original planning of this synthesis.

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Two New Flavonol Glycosides in Commercial Xanthorhamnin

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Received March 7, 1957

Commercially available xanthorhamnin (rhamnetin-3-rhamninoside), supposedly pure, has been separated by mass paper chromatography into pure xanthorhamnin plus two other flavonol glycosides apparently new to the literature. All three of these glycosides contain 2 moles of rhamnose to 1 mole of galactose to 1 mole of flavonol aglycone. The carbohydrate attachment is through the number three position on each flavonol. The aglycones have been identified as rhamnazin (3′,7-dimethyl ether of quercetin), rhamnetin (7-methyl ether of

quercetin), and quercetin (3,3′,4′,5,7-pentahydroxyflavone).

Xanthorhamnin commonly is isolated from Persian or Avignon berries. Previous workers[1] have reported the presence of quercetin, rhamnazin, and rhamnetin in a hydrolyzate of the flavonoid portion of these berries, but have been unable to separate in pure form and identify the glycosides of quercetin and rhamnazin present in the berries before hydrolysis.

The anomalous behavior of xanthorhamnin in the determination of its acid dissociation constants has been reported earlier.[2] This behavior has now been accounted for by the discovery that this material was a mixture of the three closely related flavonol glycosides above, even though the commercially available xanthorhamnin had been recrystallized several times and had the expected neutralization equivalent within experimental error. Using the procedure of the previous paper[2] and the method of Simms[3] to interpret the data, the apparent acid dissociation constants of the pure xanthorhamnin have been determined to be pK'_1 8.69, pK'_2 11.28, and pK'_3 12.22.

EXPERIMENTAL

Paper chromatographic separation of the commercial xanthorhamnin. A methyl alcohol solution containing 300 mg. of commercial xanthorhamnin (S. B. Penick and Co., N. Y.) was applied as bands to 36 sheets of Whatman 3MM chromatography paper, 18 1/4 × 22 1/2 in., prewashed with a 2% hydrochloric acid solution and then with distilled water. The chromatography chamber was first allowed to equilibrate for 10 hr. in the presence of 2 l. of distilled water and of 200 ml. of the organic layer of the solvent system *n*-butyl alcohol-chloroform-acetic acid-water (4:4:1:1, by vol.). The solvent trays were then filled with the organic layer of the solvent system; the sheets were next allowed to develop for approximately 10 hr., then removed and allowed to air dry. Three major zones resulted and could be detected by ultraviolet "black-light": Fraction I (R_f 0.68); Fraction II (R_f 0.55); and Fraction III (R_f 0.37). Each zone was cut out separately and eluted with methyl alcohol. The eluates were concentrated to 100 ml., and a large quantity of ethyl ether was added. Fractions I and II each yielded an amorphous yellow precipitate. Each was recrystallized as a yellow crystalline compound from 50% ethyl alcohol - 50% isopropyl alcohol. Fraction III did not crystallize under these conditions, but remained as a brownish oil. The 300-mg. sample yielded 20 mg. of Fraction I, 80 mg. of Fraction II, and about 10 mg. of Fraction III.

Fraction I. Hydrolysis with 2% sulfuric acid yielded the aglycone rhamnazin, and the sugars rhamnose and galactose. The aglycone had m.p. 214°, and its acetyl derivative, m.p. 154°, which check well with the literature.[4] All melting points were determined on a Fisher-Johns melting point block. This aglycone co-chromatographed with authentic rhamnazin in all four different solvent systems tried, and no lowering of the melting point was observed on mixing the aglycone from Fraction I with authentic rhamnazin. Demethylation of the aglycone with hydriodic acid produced quercetin.

The sugars rhamnose and galactose were identified by means of paper chromatography, using known standards for comparison on Whatman No. 1 paper in the solvent system *n*-butyl alcohol-pyridine-water (2:1:1.5, by vol.). Spray reagents consisted of solutions of aniline hydrogen oxalate and of naphthoresorcinol. Co-chromatography of each sugar with an authentic sample of L-rhamnose and D-galactose was carried out in the system above as well as in *n*-butyl alcohol–acetic acid–water (4:1:5, by vol.) and phenol-saturated with water solvent systems.

For determination of moles of sugar to moles of aglycone in the rhamnazin glycoside, 10 mg. of Fraction I, m.p. 187°, was completely hydrolyzed in 2% sulfuric acid for 2 hr. After cooling the mixture, the aglycone was collected on a weighed sintered glass filter and dried *in vacuo* over phosphorus pentoxide at 80° to constant weight. Three moles of sugar to 1 mole of rhamnazin were found.

For determination of the ratio of rhamnose to galactose in the glycoside, 1.5 mg. of the glycoside was hydrolyzed, and the sugar solution was separated from the aglycone, as described above. The sugar solution was then streak chromatographed on Whatman 3MM chromatography paper in the *n*-butyl alcohol-pyridine-water system, cut out, and eluted with distilled water into a 5-ml. volumetric flask and made up to volume. Each of these steps was performed as quantitatively as possible. A 1-ml. aliquot was then reacted with the anthrone reagent according to the method of Yemm and Willis,[5] with the exception that the anthrone reagent was made by dissolving the crystalline anthrone in 85% sulfuric acid instead of in 70% sulfuric acid. The optical density was determined at 625 mμ on the Beckman spectrophotometer. Simultaneously with the unknown, samples containing known microgram amounts of the authentic sugars were carried through each step of the procedure. Standard curves, one for each sugar, were obtained by plotting optical density against sugar concentration. Both rhamnose and galactose yielded a straight line relationship at concentrations from 0–80 micrograms. The sugars were found to be present in the ratio of 2 moles of rhamnose to 1 mole of galactose.

Methylation of the rhamnazin glycoside with dimethyl sulfate, followed by hydrolysis, and subsequent recrystallization from ethyl alcohol according to the method of Shimokoriyama[6] yielded the tetramethoxy quercetin, m.p. 195–196°, indicating that sugar is attached only to the number three position in the glycoside.

Thus, the new glycoside has a trisaccharide containing 2 moles of rhamnose and 1 mole of galactose attached to the number three position of rhamnazin.

Fraction II (*pure xanthorhamnin*). Hydrolysis yielded the aglycone rhamnetin, m.p. 293°; acetyl derivative 187°,[4] and the sugars rhamnose and galactose. Studies similar to those on Fraction I above confirmed these identities of the aglycone and sugars. There were 2 moles of rhamnose to 1 mole of galactose to 1 mole of rhamnetin, and the sugar was attached at the number three position.

This glycoside appears to be pure xanthorhamnin, corresponding qualitatively and quantitatively in aglycone and sugar content to the flavonoid in the literature by that name, although the m.p. 195° of the pure xanthorhamnin is higher than the previously reported value, 160°.[7]

Fraction III. Hydrolysis yielded the sugars rhamnose and

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galactose and an aglycone identified as quercetin by previously described procedures.[8]

This flavonol glycoside, probably new to the literature, has a trisaccharide containing 2 moles of rhamnose and 1 mole of galactose attached to the number three position of the aglycone quercetin (1 mole).

TABLE I

R_f VALUES OF FLAVONOL GLYCOSIDES AND AGLYCONES

Compound	Solvent System: *n*-Butyl Alcohol–Acetic Acid–Water, 4:1:5, by vol.	Acetic Acid–Water 15:85, by vol.	Acetic Acid–Water 2:3, by vol.
Fraction I	0.54	0.70	0.86
Fraction II	0.51	0.68	0.84
Fraction III	0.45	0.62	0.78
Aglycone from I	0.82	0.10	0.60
Aglycone from II	0.80	0.10	0.52
Aglycone from III	0.77	0.10	0.41

TABLE II

COLOR REACTIONS OF FLAVONOL GLYCOSIDES AND AGLYCONES[a]

Compound	Spray Reagents: Benedict's Solution V.	Benedict's Solution U.V.	1% Alcoholic Aluminum Chloride V.	1% Alcoholic Aluminum Chloride U.V.	Basic Lead Acetate V.	Basic Lead Acetate U.V.
Fraction I	Y	Y	Y	Y	Y	YGr
Fraction II	Y	OBr	Y	Y	Y	OBr
Fraction III	Y	OBr	Y	Y	Y	OBr
Aglycone from I	Y	YBr	Y	YGr	Y	Y
Aglycone from II	Y	O	Y	YGr	Y	O
Aglycone from III	Y	O	Y	YGr	Y	O

[a] V. = Visible light, U.V. = Ultraviolet light, Y = Yellow, Br = Brown, Gr = Green, O = Orange.

Materials and apparatus for acid dissociation constant determination. The purified xanthorhamnin prepared as described above, was dried for several weeks at *ca.* 1 mm. in a vacuum desiccator containing separate vessels of phosphorus pentoxide and potassium hydroxide pellets. A sample of 59.19 mg. of the xanthorhamnin required 0.0180 ml. of 3.8472*N* sodium hydroxide (corrected for blank) to attain the first end point in the titration curve, giving an observed molecular weight of 855. The pentahydrate, $C_{34}H_{42}O_{20}\cdot 5H_2O$ would require 860.76.

Carbonate-free sodium hydroxide solutions were standardized against potassium hydrogen phthalate. Oxygen-free nitrogen passed through suitable traps to remove acidic and basic gases was swept over the titration solutions. Beckman *p*H 7.00 buffer was used to standardize the *p*H meter, and the glass electrode system was calibrated with Sörenson glycine-sodium hydroxide buffer standards.[9] Meter readings agreed with the buffer values within 0.05 *p*H unit.

The titrations were performed in 10-ml. beakers fitted with covers having holes for admitting the electrodes, buret, and nitrogen, and were placed on the door of a Beckman model G *p*H meter. The meter was operated with the door open, using Beckman 290-E and 270 electrodes, and shielding was provided by surrounding the electrode system with aluminum foil. The solutions were stirred magnetically with a borosilicate glass-encased stirring bar, except while readings were being taken The standard base was measured with a calibrated Gilmont micro buret-pipet. The experiments were performed in an air-conditioned room at 24° ± 0.5°; no other temperature control was attempted.

Procedure for pK′ determination. Using a microbalance, 59.19 mg. of the xanthorhamnin was weighed out. This was dissolved in 4.00 ml. of water. The solution was placed on the *p*H meter and swept with nitrogen, with stirring, until the meter reading was constant. The buret was then inserted, and increments of 3.8472*N* sodium hydroxide were added so as to produce *p*H increments of about 0.1. A blank of 4.00 ml. of water was titrated in the same way. Meter readings were corrected to the Sörenson buffer values. The *p*H range studied was 7 to 12, with the results shown by representative data in Table III.

TABLE III

XANTHORHAMNIN *p*K′ DETERMINATION USING 3.8472*N* SODIUM HYDROXIDE

Base, ml.	*p*H	Base, ml.	*p*H	Water: Base, ml.	Water: *p*H
0.0012	7.49	0.0201	10.43	0.0001	9.83
0.0025	7.80	0.0217	10.67	0.0002	10.18
0.0042	8.09	0.0235	10.85	0.0003	10.38
0.0065	8.39	0.0248	10.95	0.0004	10.50
0.0095	8.74	0.0280	11.16	0.0006	10.71
0.0125	9.10	0.0300	11.26	0.0008	10.85
0.0152	9.47	0.0325	11.40	0.0010	10.96
0.0165	9.70	0.0350	11.51	0.0013	11.07
0.0174	9.87	0.0380	11.64	0.0017	11.19
0.0183	10.08	0.0410	11.72	0.0022	11.30
0.0192	10.25			0.0028	11.40
				0.0035	11.50
				0.0045	11.62
				0.0057	11.72
				0.0070	11.82

Acknowledgment. The authors sincerely thank Prof. Dr. L. Hörhammer, Director, Institut für Pharmazeut. Arzneimittellehre, University of Munich, Germany, for writing us of his isolation of rhammazin from the hydrolyzate of commercial xanthorhamnin and sending us authentic samples of methylated quercetin for comparisons. We also thank Dr. B. O. Heston, University of Oklahoma for his advice on the *p*K′ determinations. This research was supported in part by a grant from the U. S. Atomic Energy Commission.

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Synthesis of DL-S-Trifluoromethylhomocysteine (Trifluoromethylmethionine)

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Received February 22, 1957

The successful use of compounds such as 6-mercaptopurine in the treatment of cancer has given impetus to the search for other antimetabolites. The preparation of analogs of methionine offers promise because of the general metabolic significance of the parent compound. The role of methionine as a methyl donor suggests that substitution of the trifluoromethyl group for the essential methyl unit might be of particular value. Such an analog, in addition to being a possible antimetabolite, conceivably might serve as an intermediate in the biosynthesis of other compounds of physiological interest.

Haszeldine[2] has reported the synthesis of mercuric trifluoromethylmercaptide in small quantities from the reaction of mercury with bis(trifluoromethyl) disulfide. In the present work, however, adequate quantities of the mercaptide were obtained more readily from mercuric fluoride and carbon disulfide by the method of Muetterties.[3] This product was conveniently converted to the mercaptan in essentially quantitative yield by treatment with a dioxane solution of hydrogen chloride.

Initial attempts to add trifluoromethyl mercaptan to acrolein in the presence of cupric acetate gave low yields, apparently due to a competing polymerization which produced an adduct of one molecule of the mercaptan to three of the aldehyde. By the reverse addition of acrolein to the mercaptan, the side reaction was minimized and 61% yields of the desired β-trifluoromethylmercaptopropionaldehyde were obtained. The competing polymerization reaction is not unique, for Gilbert and Donleavy[4] have reported analogous adducts of one molecule of water to several molecules of acrolein in the base-catalyzed hydration of the aldehyde. Although in the present work the type of catalyst and the highly acidic nature of the trifluoromethyl mercaptan are conducive to ionic reaction, it is interesting to note that in the addition of simple mercaptans to unsaturated esters,[5] the polymerization reaction becomes predominant only under free radical conditions and ionic catalysis gives almost exclusively simple addition.

The β-trifluoromethylmercaptopropionaldehyde was smoothly converted to *S*-trifluoromethylhomocysteine by the method of Tishler, Giella, and Pierson.[6] An over-all yield of 11% was obtained, based on the mercaptan used.

The *S*-trifluoromethylhomocysteine will be tested physiologically by Dr. Arnold Welch of the Department of Pharmacology, Yale University School of Medicine.

EXPERIMENTAL

Mercuric trifluoromethyl mercaptide.[3] A mixture of 50.0 g. (0.66 mole) of carbon disulfide and 140 g. (0.59 mole) of technical mercuric fluoride (Harshaw Chemical Co.) was heated to 150° for 6 hr. in a pressure vessel and then extracted with 200 ml. of ether. The ether extract, after filtration, was evaporated to give 61.4 g. (0.15 mole) of crude mercuric trifluoromethylmercaptide. The crude mercaptide (used without purification in the present work) when allowed to stand, formed white crystals, m.p. 37.5–39° (lit.[3] m.p. 37–38°), together with a very small quantity of dark supernatant liquid.

Trifluoromethyl mercaptan. Hydrogen chloride was passed into anhydrous dioxane and the resultant solution weighed to determine the acid content (24%). To 30.0 g. (0.075 mole) of crude mercuric trifluoromethyl mercaptide, cooled with ice, was added 22.8 g. (0.15 mole hydrogen chloride content) of the dioxane–hydrogen chloride mixture. An exothermic reaction resulted, accompanied by a copious precipitation of mercuric chloride. The trifluoromethyl mercaptan was quite soluble in dioxane and no product was collected in an attached trap, cooled with Dry Ice, during the addition. After diluting with 15 ml. of anhydrous dioxane and refluxing for 2 hr., however, 14.3 g. (0.14 mole, 94% yield) of the mercaptan condensed in the trap. A quantitative yield was obtained using an excess of hydrogen chloride, but in the present work a stoichiometric quantity was employed to avoid the presence of hydrogen chloride, as a contaminant, in the product.

The mercaptan has been previously prepared in small quantity by Haszeldine and Kidd,[2] using hydrogen chloride gas, instead of the dioxane solution. The method herein described is more readily carried out in common laboratory equipment upon a macro scale.

β-Trifluoromethylmercaptopropionaldehyde. To a mixture of 45.5 g. (0.543 mole) of trifluoromethyl mercaptan and 0.3 g. of cupric acetate in 700 ml. of chloroform was added 36.6 g. (0.651 mole) of acrolein. After the addition was complete, stirring was continued for 2 hr. The chloroform and excess acrolein were removed at room temperature, under reduced pressure. The residue was distilled at 20 mm. pressure to give 38.7 g. of β-trifluoromethylmercaptopropionaldehyde (b.p. 44–48°). Additional product (13.4 g.) was recovered by fractionation of the chloroform distillate through a helices-packed column and vacuum distillation of the residue thus obtained. The total yield was 52.1 g. (61%). The procedure just described was found necessary, because the β-trifluoromethylmercaptopropionaldehyde undergoes appreciable decomposition if heated for an extended period of time. A portion of the aldehyde was fractionated through a multiplate column to give an analytical sample, b.p. 46.5° at 20 mm., n_D^{23} 1.4120, d_4^{25} 1.3713.

Anal. Calcd. for $C_4H_5F_3OS$: C, 30.4; H, 3.18 F, 36.1. Found: C, 31.01; H, 3.60 F, 35.7.

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In a preliminary experiment, the mercaptan was added to the acrolein. From this reaction, in addition to the desired product, a fraction, b.p. 112° at 1 mm. ($n_D^{25.5}$ 1.4490) was obtained, which corresponded roughly in analysis to the addition product of one mole of the mercaptan to three moles of acrolein.

Anal. Calcd. for $C_{10}H_{13}F_3O_3S$: C, 44.5; H, 4.73; S, 11.8. Found: C, 43.56; H, 5.65; S, 10.26.

5-(β-Trifluoromethylmercaptoethyl)hydantoin. A mixture of 20.0 g. (0.127 mole) of β-trifluoromethylmercaptopropionaldehyde, 90.5 g. (0.79 mole) of finely powdered ammonium carbonate, 10.6 g. (0.40 mole) of sodium cyanide, 270 ml. of ethanol, and 270 ml. of water was stirred and heated to 50–55° for 16 hr. The mixture was concentrated to about 200 ml. at room temperature under reduced pressure, made slightly acid with concentrated hydrochloric acid, and heated to 90° for 5 min. to cyclize any of the hydantoic acid which might be present. After cooling the mixture to 0° overnight, the yellow crystals which deposited were removed by filtration. After drying, the compound was recrystallized from boiling chloroform to give 8.7 g., (30.0% yield) of 5-(β-trifluoromethylmercaptoethyl)hydantoin, m.p. 128–128.5°.

Anal. Calcd. for $C_6H_7F_3O_2N_2S$: C, 31.60; H, 3.09; F, 25.0. Found: C, 31.76; H, 3.19; F, 25.7.

S-Trifluoromethylhomocysteine. A solution of 17.0 g. (0.074 mole) of 5(β-trifluoromethylmercaptoethyl)hydantoin, 68.0 ml. of water, and 7.5 g. (0.19 mole) of sodium hydroxide were refluxed for 6 hr. An additional 3.7 g. (0.09 mole) of sodium hydroxide was then added and refluxing continued for 18 hr. The solution was cooled and neutralized with concentrated hydrochloric acid to a *p*H of 6. Cooling to 0° for 1 hr. produced a cream colored solid which was washed twice with water and twice with acetone, dried, and extracted with 560 ml. of boiling methanol. Cooling the methanol solution to 0° overnight gave 4.4 g. of *S*-trifluoromethylhomocysteine, m.p. 229° dec. Reduction of the volume of the methanol mother liquor and cooling produced an additional 4.5 g. of product. The total (8.9 g.) represented a 60% yield. Recrystallization from methanol gave an analytical sample, m.p. 230° with decomposition.

Anal. Calcd. for $C_5H_8F_3O_2NS$: C, 29.60; H, 3.97; N, 6.94; F, 28.2. Found: C, 29.65; H, 3.95; N, 6.52; F, 26.6.

Acknowledgment. The authors would like to express their appreciation to the Anne Fuller Fund for a grant which made this work possible.

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16-Ketoyohimbane

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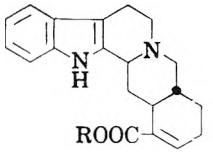
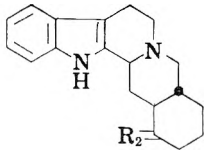
Received December 26, 1956

Because of its α,β-unsaturated ester grouping, apoyohimbine (I) should be convertible, by methods which transform a carboxyl group into an amino group, into 16-ketoyohimbane (III), a compound of interest in connection with stereochemical studies of the yohimbine alkaloids. An attempt to apply the Curtius reaction failed when apoyohimbine was recovered unchanged from treatment with hydrazine,[2] and apoyohimbic acid (II) was decomposed by thionyl chloride.

This transformation, however, was realized by means of the Schmidt reaction[3] on apoyohimbic acid, giving 16-ketoyohimbane in low yield. Evidence for the ketonic nature of the product was provided by the elementary analysis, a sharp carbonyl band in the infrared at 5.87 μ,[4] and the formation of an oxime.

The ketone could be reduced by the Huang-Minlon procedure to yohimbane[5,6] (IV), identical with the reduction product of 17-ketoyohimbane (yohimbone). Since the skeleton of yohimbine is in its most stable stereochemical configuration,[7–9] no isomerization takes place during this rather drastic reduction.





I. R = CH_3 III. R_2 = O
II. R = H IV. R_2 = H_2

EXPERIMENTAL

16-Ketoyohimbane. Apoyohimbic acid hydrochloride[10] (6.7 g.) was dissolved in 30 ml. of concentrated sulfuric acid and stirred to drive off hydrogen chloride fumes. While stirring at room temperature, 40 ml. of a 0.6*N* chloroform solution of hydrazoic acid was added dropwise. Stirring was continued for 20 min., and 20 ml. more of the hydrazoic acid solution added. When gas evolution had ceased (about 30 min.), the mixture was poured into ice water, separated, and the aqueous layer filtered. The filtrate was made alkaline with ammonia, extracted with chloroform, and the extracts washed with saturated salt solution. Drying over sodium sulfate and evaporation left a tan solid which was recrystallized from ethanol. The yield was 1.1 g. (20%) of colorless needles; after two further recrystallizations from ethanol they melted at 283–285° (capillary inserted at 250°). Drying overnight at 100° *in vacuo* over P_2O_5 did not remove all the water of crystallization.

Anal. Calcd. for $C_{19}H_{22}N_2O \cdot {}^1/_2H_2O$: C, 75.21; H, 7.64; N, 9.23. Found: C, 74.88, 74.74; H, 8.03, 7.87; N, 9.00.

$[\alpha]_D^{21}$ −89° (*c*, 1.46 in pyridine).

An anhydrous sample could be prepared by two further recrystallizations from xylene, distilling half the xylene at each step to azeotrope the water. M.p. 274–276° dec.

(1) Taken in part from the B.A. thesis of Karl H. Muench, Princeton University, 1956.

(2) Compare the difficulty found in preparing the hydrazide and amide of yohimbine, by C. F. Huebner, R. Lucas, H. B. MacPhillamy, and H. A. Troxell, *J. Am. Chem. Soc.*, **77**, 469 (1955).

(3) H. Wolff, *Org. Reactions*, **III**, 1946.

(4) Yohimbone absorbs at the same frequency, somewhat shifted from the normal ketone position.

(5) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

(6) B. Witkop and S. Goodwin, *J. Am. Chem. Soc.*, **75**, 3371 (1953).

(7) G. Stork, quoted in ref. 6.

(8) R. C. Cookson, *Chemistry & Industry*, **1953**, 337.

(9) M. M. Janot, R. Goutarel, A. Le Hir, M. Amin, and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

(10) G. Barger and E. Field, *J. Chem. Soc.*, **123**, 1038 (1923).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52, H, 7.53; N, 9.52. Found: C, 77.37 H, 7.62 N, 9.36.

The *oxime*, prepared by refluxing the ketone with hydroxylamine hydrochloride and pyridine in ethanol, was recrystallized from methanol, in which it is barely soluble. M.p. 316–319° dec.

Anal. Calcd. for $C_{19}H_{23}N_3O$: N, 13.6. Found: N, 13.9.

Yohimbane. 16-Ketoyohimbane (0.46 g.), 0.2 g of sodium hydroxide, and 3.0 ml. of 85% hydrazine hydrate were refluxed for 70 min. in 8.0 ml. of diethylene glycol. The condenser was removed, and water and hydrazine allowed to distill until the temperature reached 197°. The solution was refluxed at this temperature for 4 hr., diluted with water, and extracted with chloroform. The extracts were washed with water, dried over magnesium sulfate, and evaporated. Sublimation of the residue at 150° and 0.01 mm. gave 0.33 g (75%) of light yellow crystals. Recrystallization from ethanol yielded colorless needles, m.p. 204–206° alone, or mixed with an authentic sample of yohimbane.[6]

The authors express their thanks to Dr. Glenn Arth of Merck and Co. for a generous gift of yohimbine.

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Ozonization of Methylene Chloride and Chloroform[1]

GEORGE SLOMP, JR.

Received May 7, 1957

In studying the preparation of 3-ketobisnor-4-cholen-22-al by the selective ozonolysis of 4,22-stigmastadien-3-one[2] and 4,22-ergostadien-3-one[3] at −78° important new observations were made concerning the behavior of the solvents, methylene chloride and chloroform, towards ozone. This information should be useful to others who are planning to use ozonolysis as a preparative reaction for aldehydes.

As solvents for the above reaction acetic acid, formic acid, methanol, carbon tetrachloride, and ethyl acetate[4] were eliminated for various reasons and the choice was between methylene chloride and chloroform. Furthermore, since selective ozonolysis of the side-chain double bond was desired, it was important to know how much of the ozone was reacting with the solvent.

These solvents were studied by a method somewhat different from that employed by Greenwood,[5] and designed to show how much ozone dissolved in the solvent as well as the amount which reacted with it. The solvents were ozonized at a constant, known rate. The dissolved ozone which imparted an intense blue color was then swept out by a stream of nitrogen and the amount of ozone which had reacted with the solvent was determined by difference. These results are recorded graphically in Fig. 1.

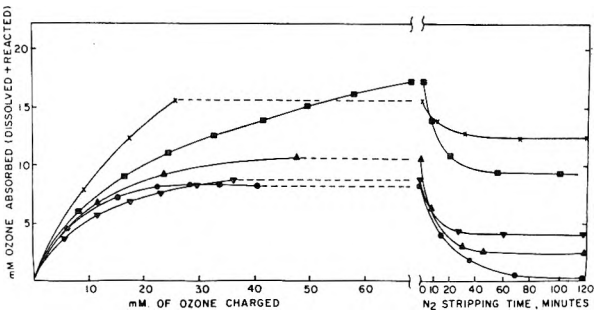


FIG. 1. OZONE ABSORBED BY SOLVENTS AND THE AMOUNT RECOVERABLE BY NITROGEN SPARGING. (⊙–Methylene chloride; △–methylene chloride + pyridine, ⊡–methylene chloride + diphenyl sulfoxide; x–methylene chloride + pyridine 1-oxide, ▽–chloroform.)

The curve obtained from the treatment of stabilized chloroform at −60° with ozone shows that this solvent underwent some attack by ozone. This attack was probably on the ethanol, which was present as the stabilizer, and could account for the acidity observed earlier in these laboratories[6] when chloroform was used as a solvent for ozonolysis of various steroidal olefins and enol acetates.

Ozone attack on methylene chloride at −78° was negligible, a saturated solution about 0.033*M* in ozone being formed from which all of the ozone could be recovered.

The inclusion of an organic base in the ozonolysis solvent for its acid-binding ability has been described[2,6,7] to be beneficial, resulting in higher yields.[8] Solutions of methylene chloride containing about 1% of the Lewis bases pyridine, diphenyl sulfoxide, and pyridine oxide were investigated in a similar manner. All of them consumed some ozone, the amount increasing in the order mentioned. Further investigation showed that the bases were not destroyed but probably only formed salt-like compounds (I) or complexes (II) with the ozone

(1) Included in part in a paper presented before the First International Ozone Conference, Chicago, Ill., Nov. 28–30, 1956.

(2) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **72**, 2617 (1950).

(3) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(4) In ethyl acetate the yield of aldehyde was greatly lowered and large amounts of the corresponding acid were formed.

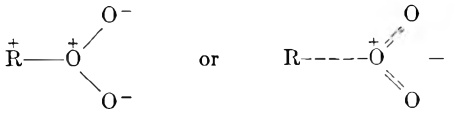
(5) F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945).

(6) (a) F. W. Heyl, A. P. Centolella, and M. E. Herr, *J. Am. Chem. Soc.*, **69**, 1957 (1947); (b) F. W. Heyl and M. E. Herr, U.S. Patent 2,554,986 and U.S. Patent 2,601,287; (c) F. W. Heyl and A. P. Centolella, U.S. Patent 2,623,052.

(7) (a) W. Logemann and H. Dannenbaum, U.S. Patent 2,344,992; (b) W. L. Ruigh, U.S. Patent 2,413,000.

(8) The yield of 3-ketobisnor-4-chloenaldehyde from the ozonolysis of 4,22-ergostadien-3-one was 70% in chloroform. [A. F. Daglish, J. Green, and V. D. Poole, *J. Chem. Soc.*, 2627 (1954).] compared with 94.5%[3] in methylene chloride-pyridine.

which were dissociated on warming to room temperature.



I or II

R = C_5H_5N-, $(C_6H_5)_2SO$- or C_5H_5NO-

An unstable white crystalline material was isolated from the pyridine oxide solution which was believed to be one of the above-mentioned products.

These results show that methylene chloride has an advantage over stabilized chloroform as an ozonolysis solvent. The latter solvent undergoes irreversible attack by the ozone. Methylene chloride alone is stable to ozone, but in the mixed solvents which were studied some ozone consumption was observed. The salt-like complex which is postulated for the products will be discussed in a later paper.

EXPERIMENTAL

Ozone. The ozone for this work was generated from oxygen in an apparatus built in our department of physics and quite similar to that described by Henne and Perilstein.[9] The 25-kilovolt ozonizer, operated at 93–95 v. input and oxygen flow rate of 0.3 l. per min. at 12 cm. gauge pressure, generated 0.376 millimole of ozone per min. (2.7 mole % ozone in oxygen).

Ozone assays. The ozone-rich oxygen stream was assayed by means of a concentration meter.[10] The gas stream was passed through a 1-mm. thick cell and the % transmission at 253.7 mμ was read from the dial. A calibration curve at the desired pressure, temperature, and flow enabled a rapid conversion to millimoles of ozone per min. being charged. The % transmission was maintained at a constant value by manipulation of the input voltage.

Several iodometric methods[11] were also investigated for assaying the concentration of ozone in the stream. The reaction of ozone with potassium iodide is quantitative only in neutral solution but as the reaction progresses hydroxyl ions are accumulated which cause erroneously low results. The reaction of ozone with acidified potassium iodide, on the other hand, gave results which were too high. The chosen method involved passing the stream into 75 ml. of 5% solution of potassium iodide for 2 min. adding 1 to 2 ml. of 3*N* hydrochloric acid, and then titrating with 0.1000*N* sodium thiosulfate in the usual manner. The amount of acid added was shown to be unimportant as long as the solution was acidic. At this low ozone concentration the formation of some hydroxyl ions[11] was apparently not critical, *i.e.*, use of aluminum chloride[12] in the potassium iodide solution to remove hydroxyl ions as they were formed afforded the same titration results.

Noninterference of phosgene.[13] A solution of 21.35 g. of phosgene in 250 ml. of methylene chloride was prepared. The solution was sparged at −78° with nitrogen for 1 hr. and the effluent gases were bubbled through a 5% aqueous solution of potassium iodide. No iodine could be detected in the solution.

Absence of chlorine.[13] The effluent gases from the ozonization of methylene chloride at −78° were passed into a 10% solution of sodium carbonate in water for 55 min. A portion of the solution was acidified with nitric acid and showed a negative halide-ion test with silver nitrate.

Ozonization of methylene chloride. A 250 ml. solution of methylene chloride (Du Pont) was ozonized in a tubular reactor equipped with a magnetic stirrer and cooled in a Dry Ice-acetone bath. (The new volume at this temperature was about 220 ml.) The ozone was admitted to the reactor at the bottom through a sparger consisting of a bulb with ten small holes in it. The effluent gas was passed by means of a similar distributor through 500 ml. of 5% solution of potassium iodide. The latter was changed and titrated often enough so that the iodine concentration did not become more than about 16 mmole per liter. The amount of ozone absorbed (dissolved plus reacted) by the solution was determined by difference. The solution began to turn blue immediately and was observed to become saturated at about 0.033 molar in ozone. (This concentration was dependent, of course, on the concentration of ozone in the gas admitted to the reactor.) When a total of 40.23 mmole. of ozone had been charged, as determined from the concentration meter readings, the ozonization was interrupted and the deep blue solution was swept with nitrogen at about the same flow rate to free the dissolved ozone until no more could be detected in the effluent. In this way 99% of it was recovered. The results are indicated in Fig. 1. Potentiometric titration of the reaction mixture showed it contained 0.62 m. equiv. of acid.

Ozonization of chloroform. The ozonization was repated on 250 ml. of chloroform (containing 0.75% ethanol as preservative) at −60° using 35.70 mmole of ozone. A lower solubility of ozone in this solvent than in methylene chloride was indicated by a slower rising curve. All of the ozone could not be recovered by sparging, 4.19 mmole. or 11.7% of it was lost. Apparently the solvent had been attacked by the ozone.

Ozonization of methylene chloride-pyridine. A solution[14] of 250 ml. of methylene chloride and 2.37 ml. of pyridine (29.4 mmole) (0.94 vol. %) was ozonized in a similar manner with 47.58 mmole. of ozone. These results are also shown in Fig. 1. The dissolved ozone was not all recoverable. There was 2.5 mmole. or 5.2% of it lost presumably by reaction with the solvent. Ultraviolet analysis on both cold and warmed samples of the reaction mixture showed 2.37 g. and 2.41 g. of pyridine,[15] respectively. Iodimetric titration showed 0.25 mmole of oxidant and potentiometric titration showed 2.7 m. equiv. of acid present. The solution gave a positive test for chloride ions with silver nitrate.

Ozonization of methylene chloride-diphenyl sulfoxide. The determination was repeated on a solution of 7.0 g. (34.6 mmole.) of diphenyl sulfoxide (B and A plasticizer No. 239, m.p. 62–72°) in 250 ml. of methylene chloride using 67.75 mmole. of ozone. The results are summarized in Fig. 1. There was 91.5 mmole. or 13.5% of the ozone lost. When the outgassing was completed, an aliquot of the solution was evaporated to dryness. There was obtained 6.5 g. (32.2 mmole.) (93% recovery) of white needles of diphenyl sulfoxide of slightly improved purity, m.p. 60–62°. There was no sulfone[16] detectable in the product by infrared analysis.

(9) A. L. Henne and W. L. Perilstein, *J. Am. Chem. Soc.*, 65, 2183 (1943).

(10) C. D. Alway and G. Slomp, *Advances in Chemistry Series*, in press.

(11) See Clark E. Thorp, *Bibliography of Ozone Technology*, Vol. 1, Armour Research Foundation, Chicago, Ill., 1954.

(12) C. E. Throp, *Ind. Eng. Chem., Anal. Ed.*, 12, 209 (1940).

(13) Greenwood[6] found that at higher temperatures phosgene and halogen were liberated by the treatment of chlorinated solvents with ozone.

(14) This solution should be freshly prepared just before use. On storing, white crystals of methylenebispyridinium chloride monohydrate [E. Schmidt, *Arch. Pharm.* 251, 186 (1913)] are deposited.

(15) F. L. J. Sixma, [*Rec. trav. chim.*, 71, 1124 (1952)] has already shown that the ozonolysis of pyridine is extremely slow at −78°C.

(16) A. Maggiolo and E. Allan Blair, Abstracts, First International Ozone Conference, Chicago, Ill., Nov. 28–30, 1956, p. 20, have shown that the oxidation of sulfoxides to sulfones with ozone is slow even at room temperature.

Ozonization of methylene chloride-pyridine 1-oxide. A solution of 250 ml. of methylene chloride and 2.87 g. (30.2 mmole.) of pyridine-1-oxide (Reilly Tar) was ozonized at −78°. The ozone was absorbed very rapidly but the blue color of dissolved ozone was only very faint. After outgassing, there was 12.45 mmole. of ozone (or 48.6% of the amount charged) missing and the solution contained a white crystalline material which was presumed to be a pyridine oxide-ozone complex. The solution was difficult to sample, but approximately 4 mmole. of oxidant was found by iodimetric titration and 2.8 g. of pyridine oxide[17] was still present, by ultraviolet analysis.

Some of the white crystalline material was collected on a sintered glass funnel. It melted and then decomposed rapidly at room temperature yielding a brown residue. In one instance air was allowed to suck through the material on the funnel and it decomposed violently. The cold crystalline material liberated iodine from potassium iodide rapidly and when dissolved in methanol showed only a strong absorption in the ultraviolet spectrum corresponding with that of pyridine oxide.[17]

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(17) M. Colonna and A. Risaliti, *Boll. sci. fac. chim. ind., Bologna*, **10**, 157 (1952). H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan*, **72**, 1025 (1952).

Communications TO THE EDITOR

Conformational Study of 1,2,2,6,6-Pentamethyl-4-Phenyl-4-Piperidinol[1,2]

Sir:

Compounds having three opposing axial substituents are unknown with cyclohexane derivatives[3]; however, several substituted piperidines having this structural feature have been prepared. Prominent among these are the 1,2,2,6,6,-pentamethyl-4,4-disubstituted-piperidines[4] which, assuming the piperidine ring to be in the chair form, must have three opposing axial substituents due to the geminal substitution on the 2, 4, and 6 positions.

The consequence of this three-way axial interference in the chair form should be a lowering of the energy barrier between the chair and boat forms. The major steric interaction in the boat form of a cyclohexane derivative, *i.e.*, the 1-"flagpole" substituent with the 4-"flagpole" substituent, is missing in the piperidine ring provided the "second substituent" on the nitrogen, the free pair of electrons, interacts with the "flagpole" substituent on the 4-position of the piperidine.

A piperidine derivative having the favorable requirements for the boat form mentioned above is 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (I). The preparation of I hydrochloride has been reported[4b]; however, the reactions of the compound did not indicate any unusual properties of the hydroxyl group. Thus I was reported to be acylated to 1,2,2,6,6-pentamethyl-4-acetoxy-4-phenylpiperidine (II) using conditions no more vigorous than those required for the acylation of 1-methyl-4-phenyl-4-piperidinol (III). This reaction may be contrasted with the unsuccessful attempts to acylate 1,2,2,6-tetramethyl-4-phenyl-4-piperidinol (IV)[5].

A reinvestigation of the properties of I has led to several interesting observations. The reactions of phenyl lithium with 1,2,2,6,6-pentamethyl-4-piperidone gave I, b.p. 130–133° at 0.5 mm., $n_D^{25.5}$ 1.5339 (Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19. Found: C, 77.43; 9.99) which had not been isolated previously. The ultraviolet and infrared absorption spectra were consistent with this structure and definitely eliminated any possibility that I had undergone dehydration. Unlike III and IV, 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (I) was a thick oil which defied all attempts at crystallization (even standing for periods of greater than one year). The hydrochloride of I was prepared, m.p. 235–236°, lit.[4b] m.p. 234–236°, but analysis did not indicate the six molecules of water of hydration previously reported (Calcd. for $C_{16}H_{26}ClNO$: Cl, 12.5; calcd. for $C_{16}H_{26}ClNO \cdot H_2O$: Cl, 11.8; calcd. for $C_{16}H_{26}ClNO \cdot 6H_2O$: Cl, 9.07. Found: Cl, 11.7). All attempts to form the acetate ester of I failed and only starting material could be isolated. Although the melting point 242–244°, of the hydrochloride from this reaction was higher than that obtained for I hydrochloride, the infrared and ultraviolet absorption spectra of the reaction product were identical with those of I hydrochloride. The higher melting hydrochloride melted with decomposition, perhaps indicating a difference in degree of hydration; however, neither halogen analysis nor infrared absorption spectra show any difference in composition. *Anal.* Calcd. for $C_{16}H_{26}ClNO$: Cl, 12.5. Found: Cl, 11.8

The physical state of I and the reduced reactivity of the hydroxyl of I suggested the possibility of intramolecular hydrogen bonding between the 1-nitrogen and the 4-hydroxyl group of the boat form of I. This hypothesis was confirmed by the infrared absorption spectra of I in carbon disulfide and carbon tetrachloride solutions at low concentrations (2.20×10^{-2} *M* in 1 mm. path; 1.10×10^{-2} *M* in 2 mm. path; and 5.5×10^{-3} *M* in 4 mm. path). There was no change in the spectrum on dilution: a sharp band at 3555 cm.$^{-1}$ (unbonded) and a broad band at 3350 cm.$^{-1}$ (bonded). For comparison a similar study of 1-methyl-4-phenyl-4-piperidinol (III) was made. At comparable concentrations (1.47×10^{-2} *M* in 2 mm. path and 7.3×10^{-3} *M* in 4 mm. path) the infrared absorption spectra of III showed little or no bonded hydroxyl for it gave only a sharp band at 3565 cm.$^{-1}$ (unbonded). More concentrated solutions of III showed intermolecular hydrogen bonding with a sharp band at 3565 cm.$^{-1}$ (unbonded) and a broad band at 3130 cm.$^{-1}$ (bonded). The 3130-cm.$^{-1}$ band disappears on dilution of the solution.

These data indicate the presence of significant

(1) This investigation was supported in part by a research grant, H-1713, from the National Heart Institute of the National Institutes of Health, Public Health Service.

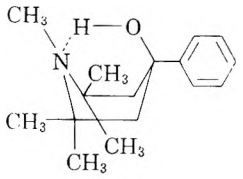
(2) This paper was presented before the Division of Organic Chemistry at the 132nd Meeting of the AMERICAN CHEMICAL SOCIETY at New York, N. Y., September 8–13, 1957.

(3) W. Klyne, *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. I, p. 51.

(4) (a) G. Merling, *Ber. deut. pharm. Ges.*, **6**, 173 (1896); *J. Chem. Soc.*, **72**, 499 (1897). (b) G. M. Badger, *et al.*, Brit. Patent **576,962**, April 29, 1946; *Chem. Abstr.*, **24**, 3782 (1948). (c) Robert R. Chauvette, thesis, University of New Hampshire (1954). (d) W. Steinkopf and W. Ohse, *Ann.*, **448**, 205 (1926). (e) L. Orthner, *Ann.*, **459**, 217 (1927).

(5) G. Badger, J. Cook, and G. Donald, *J. Chem. Soc.*, 197 (1950).

amounts of the boat form of I in the pure state and in solution. This is unique with the monocyclic piperidine derivatives and undoubtedly results from the combination of three factors: (1) extreme steric strain of three opposing axial groups in the chair form, (2) lack of interference between the two "flagpole" substituents in the boat form, but rather (3) stabilization of the boat form by hydrogen bond formation between the two "flagpole" substituents.[6]



I

(6) Added in proof: Barton [*J. Chem. Soc.*, 2907 (1957)] recently reported similar conclusions concerning the conformation of the A ring of 2-β-bromolanostan-3-one.

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ROBERT E. LYLE

Received June 20, 1957

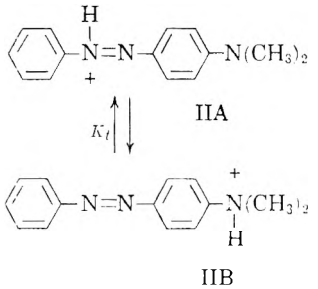
Tautomeric Equilibria. III. The Structure of the Conjugate Acid of *p*-Dimethylaminoazobenzene

Sir:

The structure of the conjugate acid of *p*-dimethylaminoazobenzene has been the subject of considerable discussion and controversy in recent years.[1] We are currently engaged in an extensive program having for one of its aims the unequivocal determination of this structure by a variety of methods. One of the lines of attack has given such a clear-cut decision that we believe preliminary publication in this form is indicated.

We have now determined the pK_a of the conjugate acid of *p*-phenylazo-*N,N,N*-trimethylanilinium methyl sulfate and of the second conjugate acid of *p*-dimethylaminoazobenzene by a spectrophotometric technique. In the process the spectra of *p*-phenylazo-*N,N,N*-trimethylanilinium ion (I) and of the first conjugate acid of *p*-dimethylaminoazobenzene (II) were needed. The spectra, in 5% sulfuric acid as solvent, are given in Fig. 1. The spectra are readily explained by the assumption, proposed by earlier workers[1b] that II is an equilibrium mixture of II A and II B.

(1) (a) M. T. Rogers, T. W. Campbell, and R. W. Maatman, *J. Am. Chem. Soc.*, **73**, 5122 (1951); H. H. Jaffé, *J. Chem. Phys.*, 21, 415 (1953); I. M. Klotz, H. A. Fiess, J. Y. Chen Ho, and M. Mellody, *J. Am. Chem. Soc.*, **76**, 5136 (1954); (b) W. S. McGuire, I. F. Izzo, and S. Zuffanti, *J. Org. Chem.*, 21, 632 (1956); G. Cilento, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956); E. Sawicki, *J. Org. Chem.*, **22**, 365 (1957).



IIB

The band at 316 mμ, due to II B, occurs at a lower intensity than the same band in I. The 516 mμ band, then, must be ascribed to II A. The equilibrium appears to shift slightly with solvent composition; with increasing sulfuric acid concentration in the range from 5–30%, the height of the 516 mμ peak increases, and simultaneously the height of the 316 mμ peak decreases. Making the perfectly reasonable assumption that the spectra of I and II B agree exactly, not only in wave length but also in intensity, we calculate an equilibrium constant $K_t = [\text{IIA}]/[\text{IIB}] = 1.2$ in 5% sulfuric acid, and $K_t = 2.2$ in 20% sulfuric acid.

The pK_a measurements confirm the above conclusions. Since no H_+-Scale is available the calculations were based on Hammett's H_0-Scale.[2] Although this procedure may partially invalidate the absolute values found, it is unlikely to have a profound effect on the difference between the pK_a's of the two compounds, which is the only quantity of importance for the present argument. The pK_a values found in this way were: IH^+, -3.65 ± 0.03; IIH^+, -3.04 ± 0.06.

Since

$$pK_a(IH^+) = -\log [I][H^+]/[IH^+]$$

$$pK_a(IIH^+) = -\log [IIA + IIB][H^+]/[IIH^+]$$

$$= -\log [IIB](1 + K_t)[H^+]/[IIH^+]$$

and assuming that the basicities of I and IIB are identical, *i.e.* that the effect of the groups $-\overset{+}{N}(CH_3)_3$ and $-\overset{+}{N}H(CH_3)_2$ on the basicity of azobenzene is the same, it follows that

$$pK_a(IIH^+) = pK_a(IH^+) - \log(1 + K_t)$$

hence $K_t = 3.0$. Since this value applies to a solution approximately 50% in sulfuric acid, the agreement with the spectroscopic values is excellent.

Thus it appears unequivocally established that the first conjugate acid of *p*-dimethylaminoazobenzene is an equilibrium mixture of IIA and IIB and the value of the equilibrium constant, although solvent dependent, in moderately concentrated sulfuric acid solution is about 1–3. The implications of this finding relating to substituted dimethylaminoazobenzenes will be examined in a later paper.

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 267.

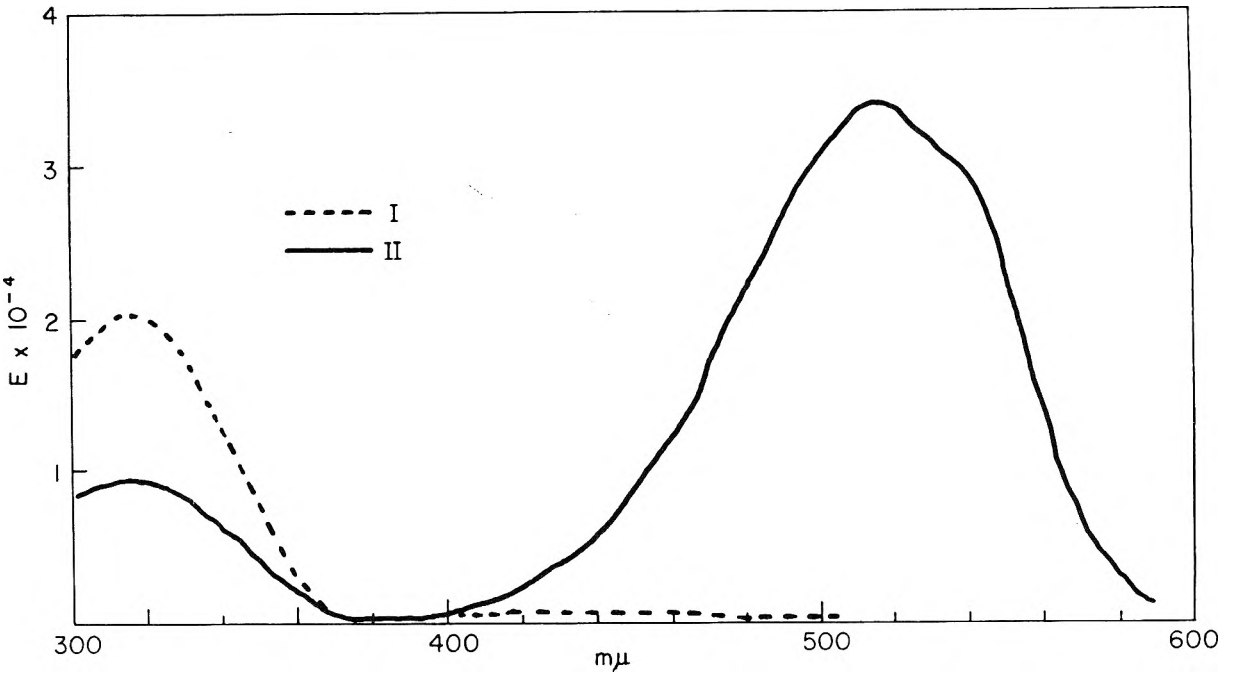


FIG. 1. SPECTRA OF *p*-PHENYLAZO-*N*,*N*,*N*-TRIMETHYLAMMONIUM METHYL SULFATE AND OF THE FIRST CONJUGATE ACID OF *p*-DIMETHYLAMINOAZOBENZENE.

Acknowledgments. A grant in aid from the American Cancer Society, which made this work possible, is gratefully acknowledged. Preliminary experiments leading to this work were performed by Messrs. J. Smith, R. Eibeck, A. Bunk, and L. Jones.

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Received July 15, 1957

Reaction of Dialkyl Phosphites with Quinones[1]

Sir:

Dialkyl phosphites $(RO)_2P(O)H$ are known to add to unconjugated *olefins* in the presence of peroxides[2]. These have been regarded as radical chain processes propagated by the radical $(RO)_2P(O)$. Benzaldehyde and *chloranil* combine photochemically with formation of the monobenzoate of tetrachlorohydroquinone[3]. For this reaction, Moore and Waters[3] postulated: (1) a photo-activation of the quinone to a diradical (or triplet state), $\cdot O\text{-}C_6Cl_4\text{-}O\text{-}O\cdot$, (2) a chain initiation step involving hydrogen abstraction from the aldehyde by the diradical and (3) a chain propagation sequence in which (a) the benzoyl radical added to unactivated quinone molecules giving aryloxy-radicals, $\cdot O\text{-}C_6Cl_4\text{-}O\text{-}COC_6H_5$ and (b) the latter reacted with benzaldehyde forming the product and regenerating benzoyl radicals.

During our studies on the mechanism of action of oxidizing agents on organophosphorus compounds,[4] we have related the two sets of observations described above. It was found that dialkyl phosphites and chloranil reacted smoothly with formation of the mono-dialkoxyphosphinyl derivatives of tetrachlorohydroquinone, I and II. The results obtained under several conditions are summarized in Table I.

TABLE I

REACTION OF DIALKYL PHOSPHITES, $(RO)_2P(O)H$ WITH CHLORANIL[a]

Temp., °C.	Conditions	Time	Yield,[b] % R=CH_3	Yield,[b] % R=C_2H_5
25	Dark	4.5 hr.	26(I)	24(II)
25	360–370 mμ[c]	4.5 hr.	64(I)[d]	66(II)[d]
25	Dark	3 days	100(I)	97(II)
100	Dark	1 hr.	95(I)	91(II)

[a] All reactions were carried out in an excess of freshly distilled dialkyl phosphites, in a nitrogen atmosphere. [b] Of dialkoxyphosphinyl derivatives of tetrachlorohydroquinone (I and II), based on chloranil. The material balance was unreacted chloranil. [c] Irradiation in quartz flask with a Hanovia 100-w Utility Model ultraviolet lamp and filter. [d] Quantitative yield in about 15–20 hr.

(1) This work was carried out under Public Health Service Grant CY-3250.

(2) (a) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, 79, 1961 (1957); (b) W. E. Hanford and R. M. Joyce, U.S. Patent 2,478,390; (c) J. A. Bittles, Jr. and R. M. Joyce, U.S. Patent 2,559,754; (d) E. C. Ladd and M. P. Harvey, U.S. Patent 2,664,438; (e) N.V. de Bataafsche Petroleum Maatschappij, Brit. Patent 660,918; (f) A. R. Stiles and F. F. Rust, U.S. Patent, 2,724,718.

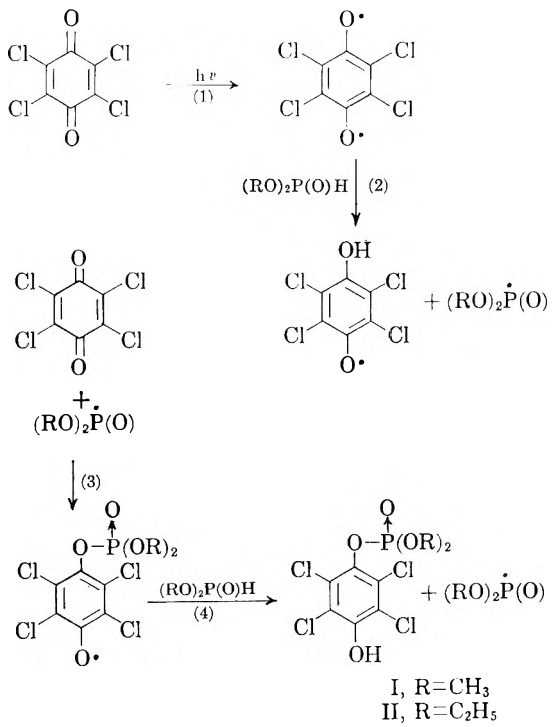
(3) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953).

(4) (a) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, 78, 5614 (1956); (b) F. Ramirez and S. Dershowitz *J. Org. Chem.* (in press).

The reactions were significantly accelerated by light of the wave-length range 360–370 mμ. In this wave-length range, the dialkyl phosphites are transparent while chloranil exhibits an absorption band. Hence, if the reactions are regarded as radical chain processes,[2,3] it seems likely that the photochemical effect is due to the excitation of the chloranil to its diradical, as shown in the following sequence. The photodissociation $(RO)_2P(O)H \rightarrow (RO)_2\dot{P}(O) + H\cdot$ cannot provide the required radicals at 360–370 mμ.

Logical extensions of this simple and practical method for the preparation of hydroxyarylalkyl phosphates, and the significance of the "dark" reactions, are under investigation.

Dimethyl-(4-hydroxy-2,3,5,6-tetrachlorophenyl) phosphate (I), m.p. 236–238° (from methanol) was soluble in aqueous sodium hydroxide solution and had a strong band at 7.98 μ (bonded phosphate P→O)[4b]; calcd. for $C_8H_7O_5PCl_4$: C, 27.0; H, 2.0; found: C, 27.2; H, 2.2. Diethyl-(4-hydroxy-2,3,5,6-tetrachlorophenyl) phosphate (I), m.p. 180–181° (from cyclohexane) had a band at 7.92 μ; calcd. for $C_{10}H_{11}O_5PCl_4$: C, 31.3; H, 2.9; found: C, 31.5; H, 3.1. The phenolic phosphates I and II could also be made, but in low yields, by the rather complex reaction of tetrachlorohydroquinone and one equivalent of the dialkyl phosphorochloridate, in the presence of one equivalent of sodium alkoxide.



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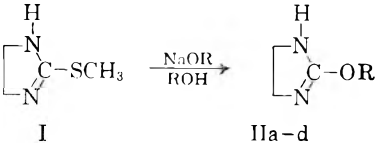
2-Alkoxyimidazolines

Sir:

We wish to report the conversion of 2-methylmercapto-2-imidazoline, "S-methylethylenethiourea," I, to 2-alkoxy-2-imidazolines II by treatment with sodium alkoxides in the corresponding alkanol. Although compound I and many related



I IIa–d

a. R=CH_3
b. R=C_2H_5
c. R=i-C_3H_7
d. R=n-C_4H_9

structures react with amines to give products in which the methylmercapto group has been replaced by an amino group,[1–3] no example could be found in the literature of the conversion of an alkylisothiourea such as I to an alkylisourea although this displacement reaction is of a type that might be anticipated.

Equimolar quantities of I and sodium methoxide after 18 hr. heating under reflux in methanol provided, along with 20% of ethyleneurea, 20–25% of 2-methoxy-2-imidazoline (IIa) as somewhat volatile, water-soluble, colorless crystals, m.p. 70–72°; λ_{max}^{Nujol} 3.15, 6.11, 6.59 μ; no selective absorption from 210–350 mμ in methanol and acid solution; pK_a 5.8, neut. equiv. 101; acid fumarate m.p. 136–139°.

Anal. Calcd. for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.60; N, 12.96. Found: C, 44.70; H, 5.52; N, 13.27.

Picrate m.p. 168–170°.

Anal. Calcd. for $C_{10}H_{11}N_5O_8$: C, 36.48; H, 3.37; N, 21.27. Found: C, 36.53; H, 3.23; N, 20.86.

The free base IIa tended to become oily on standing; when it was pressed in potassium bromide disks for infrared study, extensive alterations in structure occurred as judged by the appearance of new bands at 5.8 and 5.9 μ. However, 2-methoxyimidazoline was recovered essentially unchanged after standing overnight both in normal sodium hydroxide and normal hydrochloric acid solution.

In a similar fashion I and sodium ethoxide led to 2-ethoxy-2-imidazoline (IIb, 13%), m.p. 48–50°; λ_{max}^{Nujol} 3.23, 6.14, 6.59, 6.73 μ; acid fumarate m.p. 123–125°.

Anal. Calcd. for $C_9H_{14}N_2O_5$: N, 12.17. Found: N (Kjeldahl), 12.16.

Prolonged heating of I with sodium isopropoxide gave IIc (11%), m.p. 65–67°, λ_{max}^{Nujol} 3.16, 6.16, 6.63, 6.74 μ; picrate m.p. 127–128°.

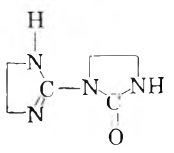
(1) S. R. Aspinall and E. J. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).
(2) C. K. Cain, U. S. Patent 2,742,481 (1956).
(3) A. F. McKay and D. L. Garmaise, *Can. J. Chem.*, **35**, 8 (1957.)

Anal. Calcd. for $C_{12}H_{15}N_5O_8$: C, 40.34; H, 4.23; N, 19.60. Found: C, 40.62; H, 4.23; N, 19.36.

A major portion (66%) of unchanged I was recovered in this case. The n-butoxy derivative IId was obtained in 47% yield; m.p. 55–58°; λ_{max}^{Nujol} 3.15, 6.14, 6.58, 6.71 μ; acid fumarate m.p. 126–128°.

Anal. Calcd. for $C_{11}H_{18}N_2O_5$: N, 10.85. Found: N (Kjeldahl), 10.82.

From the preparations of IIb and IId, another product was isolated in low (10–15%) yield. A consideration of the analysis (Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.77; H, 6.51; N, 36.31), infrared spectrum (λ_{max}^{Nujol} 3.00, 3.18, 5.82, 6.22, 6.64, 6.70 μ) and other properties of this relatively high melting (210°) monoacidic base (pK_a 6.0; neut. equiv. 160) has led to assignment of the 1-(2-imidazolin-2-yl)-2-imidazolidinone structure (III) to this compound.



III

Further studies on imidazolines II and III and related compounds are in progress.

Acknowledgments. The authors are indebted to Dr. Leon Mandell for helpful suggestions in connection with this work.

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Concerning the Structure of C_{27}-Phthienoic Acid

Sir:

The physiologically active C_{27}-phthienoic acid, isolated[1] from tubercle bacillus, has previously been reported[2] to have the partial structure, 2-methyl-4,x-dialkyl-2-alkenoic acid. Investigators at Oxford[3] have degraded by oxidation the mixture of acids with more than twenty carbons from tubercle bacillus, and on this basis assigned the structure, 2,4,6-trimethyl-2-tetracosenoic acid, to a component of this mixture termed "mycolipenic acid," although there had not been presented evidence of isolation of any pure component from the mixture. More recently, there has been reported[4] synthesis of optically active 2,4,6-trimethyl-2-tetracosenoic acid and comparison with an acid isolated from tubercle bacillus, but limited data were included. Although we have shown[5] that the mixture of higher acids from tubercle bacillus contains thirteen or more components, of which at least nine are unsaturated, it has nevertheless been stated by Bailey, Polgar, and Robinson[6] that "there can be very little doubt but that C_{27}-phthienoic and mycolipenic acid are identical." We are aware of no experimental evidence in support of this idea and much to the contrary[5]; however, it has been accepted to the point that there has appeared a paper[7] entitled "Synthesis of Racemic Methyl Phthienoate." Since we now have evidence, which appears firm, that C_{27}-phthienoic acid is *not* 2,4,6-trimethyl-2-tetracosenoic acid, this preliminary report is submitted in the hope of preventing additional confusion in the literature.

Ozonolysis at −14° in chloroform solution, followed by oxidation with silver oxide, of 2,4-dimethyl-2-docosenoic acid gave 2-methyleicosanoic acid in 60% yield and a 40% yield of neutral material which was shown to be about 3 parts 2-eicosanone and 1 part 2-eicosanol. Similar ozonolysis, in two lots, of a total of 743 mg. of pure C_{27}-phthienoic acid yielded 282 mg. of a crystalline C_{24} acid[8], m.p. 39–43°, $[\alpha]_D^{21}$ +4.96°, eq. wt. 364. In gas phase chromatography on silicone grease at 245° of the methyl ester of this acid, retention time was 6 min. 15 sec. Retention time of 6 min. 18 sec. for methyl 2,4-dimethyldocosanoate confirms the C_{27} formula for C_{27}-phthienoic acid. Chromatography on alumina of the neutral material from ozonolysis (total 302 mg.) yielded three crystalline ketone fractions and one alcohol fraction (infrared characterization), eluted in that order and weighing respectively 63, 28, 21 and 59 mg. Gas phase chromatography of the ketone fractions (numbered in order of elution from alumina), and of certain synthetic ketones, yielded retention times recorded in Table I.

Retention times in Table I, coupled with analyses for C, H, and O, show that "ketone-1" is a dioxygen

(1) J. Cason and G. Sumrell, *J. Biol. Chem.*, 192, 405 (1951).

(2) (a) J. Cason, N. K. Freeman, and G. Sumrell, *J. Biol. Chem.*, 192, 415 (1951); (b) J. Cason and C. F. Allen, *J. Biol. Chem.*, 205, 449 (1953).

(3) N. Polgar, *J. Chem. Soc.*, 1008 (1954).

(4) D. J. Millin and N. Polgar, *Proc. Chem. Soc.*, 122 (1957).

(5) J. Cason and G. J. Fonken, *J. Biol. Chem.*, 220, 391 (1956); C. F. Allen and J. Cason, *J. Biol. Chem.*, 220, 407 (1956).

(6) A. S. Bailey, N. Polgar, and R. Robinson, *J. Chem. Soc.*, 3031 (1953).

(7) C. Collin-Asselineau, J. Asselineau, S. Ställberg-Stenhagen, and E. Stenhagen, *Acta Chem. Scand.* 10, 478 (1956).

(8) Polgar[3] reported data only for the crude acid from permanganate oxidation, m.p. 34–35°, $[\alpha]_D^{16}$ +7.1°; for synthetic (+)-2,4-dimethyldocosanoic acid, after purification *via* the quinine salt, $[\alpha]_D^{22}$ +7.4°, no m.p. reported [G. I. Fray and N. Polgar, *J. Chem. Soc.*, 2036 (1956)].

TABLE I

RETENTION TIMES OF KETONES

Ketone	Retention Time (min., sec.) at 180°	220°
6-Hexadecanone	6′15″	
6-Heptadecanone	8′34″	2′46″
2-Heptadecanone	9′32″	
2-Octadecanone	12′53″	
2-Eicosanone		5′06″
6-Tricosanone		9′49″
5,11-Pentadecanedione	7′44″	
Pentadecan-5-ol-11-one	9′12″	
5,12-Hexadecanedione	10′50″	
5,14-Octadecanedione	20′35″	4′36″
"Ketone-1"		13′48″
"Ketone-2"		9′00″[a]
"Ketone-3"	10′44″	3′14″[b]

[a] Minor bands at 5′11″ (6% of total area) and 3′14″ ("ketone-3," 1% of total). [b] Minor band at 6′23″ (13% of total), no band at 9′.

compound (probably a C_{23} keto alcohol) and that "ketone-2" is a mono-oxygen compound (probably a C_{23} ketone with one branch in chain). Of most interest is "ketone-3," whose properties are those of a C_{16} diketone. *Anal.* Calcd. for $C_{16}H_{30}O_2$: C, 75.5; H, 11.9. Found: C, 75.8; H, 11.5. A C_{16} diketone cannot be obtained by oxidation of 2,4,6-trimethyl-2-tetracosenoic acid; and 2-eicosanone, which would be expected and should be isolated by our procedure, has not been found among our degradation products.

The x-ray diffraction pattern[9] of C_{27}-phthienoic acid gives good, but not entirely rigorous, evidence that the longest chain in the substance contains 20 carbons. Infrared evidence[10] suggests that the substituent in the 4-position is methyl, and shows the absence[2a] of ethyl or propyl groups. If these data and other firm evidence[2] be combined with the C_{16} formula for the diketone, the structure for C_{27}-phthienoic acid may be deduced to be *trans*-2,4-dimethyl-13-*n*-amyl-2-eicosenoic acid; however, this structure must be regarded as tentative until more rigorous evidence is secured.

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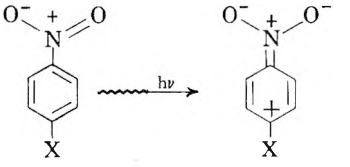
(9) Dr. E. S. Lutton of the Miami Valley Laboratories, Procter and Gamble Co., carried out x-ray diffraction on a sample of phthienoic acid isolated by one of us (C.F.A.), and advised us on June 7, 1956, that the unstable polymorph of this acid melting at about 21° appears to crystallize in an "alpha" form, which allows direct calculation of the chain length.

(10) J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, 20, 1591 (1955).

Example of Net Electron Release by Formyl, Nitro, Cyano, and Carbomethoxy Groups

Sir:

We have found that normally electron accepting substituents such as formyl can give a net *release*, relative to hydrogen, in the "principal" ultraviolet transition of *para* substituted nitrobenzenes. This transition involves excitation to a highly dipolar state, with the transition moment lying in the long axis of the molecule toward the nitro group.[1] It is approximately described by equation 1.[2] The energy of the excited state should be lowered, relative to that of nitrobenzene, whenever X is able to release electrons and absorb some of the electron deficiency created in the neighborhood of the *para* position to a greater extent than does a *para* hydrogen. If this stabilization is greater than that of the ground state, the transition energy would be expected to be lowered. Presumably this accounts for the fact that *p*-alkylnitrobenzenes absorb at a lower energy (*i.e.* lower frequency, higher wave length) than nitrobenzene (*cf.* ref. 2).



(1)

The results for the *para* halonitrobenzenes (Table I) show that stabilization of excited relative to the ground state is in the order I > Br > Cl > F, indicating a net electron release, on excitation, in the same order. This order is opposite to the accepted normal order of electromeric release, but corresponds to the polarizability order.[3,4] The *p*-halonitrobenzene results prompted the authors to study nitrobenzene substituted in the *para* position with CHO, NO_2, CN and $COOCH_3$. These substituents are considered to be electron acceptors, by both the inductomeric and electromeric mechanisms.[3] The gas phase results of Table I indicate that, on excitation, there is a greater net electron *release* by these substituents than by hydrogen. The authors interpret this as meaning that the formal aromatic (*p*-nitrophenyl) moiety in the excited state is more electronegative than the

(1) A. C. Albrecht and W. T. Simpson, *J. Chem. Phys.*, 23, 1480 (1955); *J. Am. Chem. Soc.*, 77, 4454 (1955).

(2) W. M. Schubert, J. Robins, and J. L. Haun, *J. Am. Chem. Soc.*, 79, 910 (1957).

(3) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, 1953, Chapters II and III.

(4) While this work was in progress, A. Burawoy and A. R. Thompson, *J. Chem. Soc.*, 4314 (1956) published results on *p*-halonitrobenzene spectra in hexane that parallel the authors' observations in heptane. An explanation in terms of polarizability, similar to that of the authors, was advanced to account for the order of excitation energy observed.

TABLE I

VALUES OF ν_{max} (CM.$^{-1}$) FOR *para* SUBSTITUTED NITROBENZENES[a]

Substituent	Gas Phase $\nu \times 10^{-1}$	Gas Phase $\epsilon_{max} \times 10^{-2}$	95% EtOH $\nu \times 10^{-1}$	H_2O $\nu \times 10^{-1}$	20.6% $HClO_4$ $\nu \times 10^{-1}$
H	4182[b]	96	3850	3739	3722
F	4080	84	3786	3667	3651
Cl	3979	118	3686	3583	3564
Br	3928	137	3625	3524	3516
I	3786[c]	129	3394	33.6	3303
CHO	4058	150	...	3736	3724
CN	4114	143	3896	3836	3820
NO_2	4102	155	3848	3755	3747
$COOCH_3$	4120	138	3867	3785	3771

[a] Determined by methods previously described;[2] the ν_{max} values are averages of at least two determinations and were duplicated to ±20 cm.$^{-1}$ [b] Erroneously reported previously.[2] [c] The same order of ν_{max} was observed for *p*-haloacetophenones.

substituent and consider the amount of electron release by the substituent to be a function of both the electronegativity difference between the aromatic moiety and the substituent *and* the polarizability of the Ar-X bond. The electronegativity difference between the excited *p*-nitrophenyl moiety and the substituent would be greatest for hydrogen, but the polarizability of the Ar-X bond is sufficiently greater than that of the Ar-H bond to result in a greater electron release by X. Similar considerations can be applied to the ground state, but presumably the effects would be smaller, due to the smaller electronegativity difference between the aromatic moiety and the various substituents. The authors are exploring the possibility that such factors play a role in the effect of substituents in ordinary chemical reactions and are attempting to incorporate these ideas in a semi-empirical quantitative relationship.[5] Obviously, the Hammett equation is of little use here, since the *sigma* constants not only have the wrong magnitude, but also are of the wrong sign.

The nature of the electronic transition being studied is also revealed in the solvent effects on the excitation energies. Note that the red shift accompanying increased solvent acidity is greater for the substituted nitrobenzenes than for nitrobenzene. Electron withdrawal by the *para* substituent in the ground state reduces hydrogen bond solvation of the nitro-group; in view of the Franck-Condon principle, this would act to reduce solvent stabilization of the excited relative to the ground state, thus contributing to a less pronounced red shift (*cf.* ref. 2). The solvent red shift is decreased even more for the nitrobenzenes substituted with the hydrogen bonding substituents such as formyl; thus in 20% perchloric acid the excitation energy of these compounds is now greater than that of nitrobenzene. This can be attributed to a decrease in hydrogen bond solvation of these groups in proceeding from the ground state (in which they have a partial negative charge) to the excited state (in which they have a partial positive charge).

(5) The polarizability of the Ar-X bond is dependent on the orbital character of the bonding. Within limits, this polarizability is assumed to be a constant in the hypothetical reaction: purely covalent Ar:X → actual Ar-X. Thus the polarizability of the bond in X attached to aromatic carbon (some π as well as σ bonding may be involved) may have a different value than that of the bond in X attached to aliphatic carbon.

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