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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF DUKE UNIVERSITY AND WAKE FOREST COLLEGE]

Influence of Ring Size and 2-Methyl Substituent on Two Modes of Alkaline Cleavage of 2-Acylcyclanones. Acylations of Cycloheptanone and Cyclooctanone[1]

PHILLIP J. HAMRICK, JR.,[2] CHARLES F. HAUSER, AND CHARLES R. HAUSER

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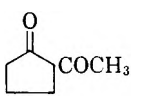
A semiquantitative study was made of the two possible modes of alkaline cleavage of the 2-acetyl derivatives of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone. 2-Acetylcyclopentanone underwent largely ring opening and 2-acetylcyclohexanone, mainly ring opening. However, only side chain cleavage was realized with 2-acetylcycloheptanone and 2-acetylcyclooctanone. Also, only side chain cleavage was observed with 2-benzoylcycloheptanone and 2-benzoylcyclooctanone. The 2-methyl derivatives of 2-acetylcyclopentanone and 2-acetylcyclohexanone underwent relatively less ring opening than the corresponding unsubstituted 2-acetylcyclanones. The boron fluoride–acid anhydride and the sodium amide–acid chloride methods of acylation of ketones were extended to cycloheptanone and cyclooctanone.

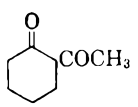
An earlier study[3] has indicated that 2-acetylcyclopentanone (I) undergoes ring opening with alkali to form keto acid II to a relatively greater extent than does 2-acetylcyclohexanone (III), to give keto acid IV.



I

$CH_3CO(CH_2)_4COOH$

II

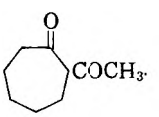


III

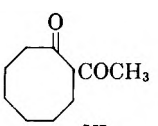
$CH_3CO(CH_2)_5COOH$

IV

This indicated influence of ring size on the two possible modes of alkaline cleavage has now been confirmed and extended employing not only the 2-acylcyclanones I and III but also 2-acetylcycloheptanone (V) and 2-acetylcyclooctanone (VI).



V



VI

In Table I are summarized the yields of the keto acids and of the ketones obtained on cleaving the β-diketones I, III, V, and VI with hot 10% sodium hydroxide. The ketones were isolated as their 2,4-dinitrophenylhydrazones from duplicate experiments carried out on the 0.1-mole scale. Blank experiments indicated that the yields were reproducible within ± 2%. The keto acids were isolated by distillation from experiments carried out on the 0.5-mole scale. The yields of keto acids II and IV given in Table I were obtained in three runs and two runs, respectively.

It can be seen from Table I that ring opening occurred in 85–90% yield with 2-acetylcyclopentanone and in 60–64% yield with 2-acetylcyclohexanone, but that only side chain cleavage was observed with 2-acetylcycloheptanone and 2-acetylcyclooctanone. Thus, the relative extent of the alkaline cleavage at *a* in VII decreased progressively and that at *b* increased as the size of the ring was increased from five to six carbon atoms and from six to seven or eight carbon atoms. Moreover there was a sharp

(1) Supported in part by the National Science Foundation.

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(3) C. R. Hauser, F. W. Swamer, and B. I. Ringler, *J. Am. Chem. Soc.*, **70**, 4023 (1948).

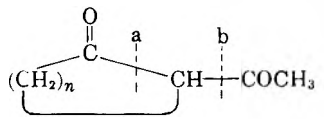
TABLE I

YIELDS OF KETO ACIDS AND KETONES FROM ALKALINE CLEAVAGES OF 2-ACETYLCYCLANONES

2-Acetyl-cyclanones	Keto Acid	Yield, %	Ketone	Yield, %	DNPH[a] M.P., °C.	Lit.[b] M.P.
I	II	85–90	Cyclopentanone	2–5	144–145	142
III	IV	60–64	Cyclohexanone	30–32	158–161	162
V			Cycloheptanone	95–98	148–150	148
VI			Cyclooctanone	96–99	174–176[c]	

[a] 2,4-Dinitrophenylhydrazone on which the yield of ketone is based. [b] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 316. [c] A sample melting at 176–177° was analyzed. *Anal.* Calcd. for $C_{14}H_{18}N_4O_4$; C, 54.89; H, 5.92; N, 18.29. Found: C, 54.79; H, 6.31, N, 18.42.

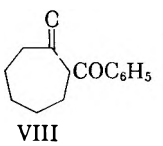
break in the mode of cleavage in passing from the six atom ring to the seven atom ring.



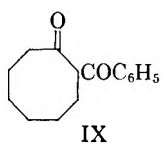
VII

These results are in line with what might be anticipated on the assumption that the mode of cleavage is dependent on the relative reactivity in each case of the ring carbonyl group *versus* that of the side chain carbonyl group towards the hydroxyl ion. The reactivity of the former group might be expected to be relatively decreased by a shielding effect due to puckering as the ring size is increased. An examination of molecular models appeared to be in agreement with this.

Similarly 2-benzoylcycloheptanone (VIII) and 2-benzoylcyclooctanone (IX) underwent cleavate at the side chain to form benzoic acid in yields of 94% and 96%, respectively. Presumably the corresponding ketones were also produced.

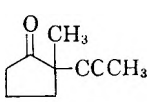


VIII

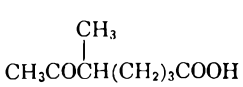


IX

It was further found that the 2-methyl derivatives of 2-acetylcyclopentanone and 2-acetylcyclohexanone undergo relatively less ring opening on alkaline cleavage than the corresponding unsubstituted 2-acylcyclanones. Thus, whereas 2-acetylcyclopentanone (I) gave keto acid II in 85–90% yield, the 2-methyl derivative X produced the keto acid XI in 65% yield under similar conditions.

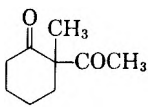


X

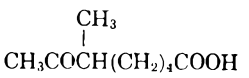


XI

Also, whereas 2-acetylcyclohexanone (III) formed keto acid IV in 60–64% yield, the 2-methyl derivative XII afforded keto acid XIII in only 25% yield under similar conditions, and a 54% yield of 2-methylcyclohexanone was obtained.



XII

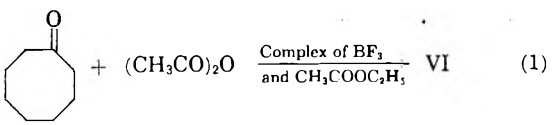


XIII

These results indicate that the 2-methyl group presents a greater shielding effect at the ring carbonyl group than at the side chain carbonyl group.

Acylations of cycloheptanone and cyclooctanone. In connection with the alkaline cleavages considered above, several new acylations of cyclanones were effected.

Cycloheptanone and cyclooctanone were acylated with aliphatic anhydrides by means of the boron fluoride–ethyl acetate complex that has previously been found particularly suitable for cyclopentanone and cyclohexanone.[4,5] The reaction may be illustrated by the acetylation of cyclooctanone (Equation 1).



(1)

In Table II are summarized the yields and other data for these acylations. Also in this table is given a new result with cyclopentanone. It can be seen that the yields are quite satisfactory (50–75%). One of the products, 2-acetylcycloheptanone (V), has recently been prepared[6] in 62% yield by the original boron fluoride method of Meerwein and Vossen.[7]

Cycloheptanone and cyclooctanone were benzoylated by the sodium amide–acid chloride method which has recently been developed[8] for the benzoylation of cyclopentanone and for certain other acylations that have been difficult to effect by the more common procedures. The reaction may be illustrated with cyclooctanone (Equation 2).

(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 106, 131 (1954).

(5) R. M. Manyik, F. C. Frostick, J. J. Sanderson, and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 5030 (1953).

(6) E. Buchta and J. Kronz, *Angew. Chem.*, **67**, 77 (1955).

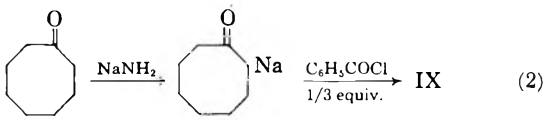
(7) H. Meerwein and D. Vossen *J. prakt. Chem.*, **141**, 149 (1934).

(8) B. O. Linn and C. R. Hauser, *J. Am. Chem. Soc.*, **78**, 6066 (1956).

TABLE II

PREPARATION OF 2-ACYLCYCLANONES FROM CYCLANONES AND ALIPHATIC ANHYDRIDES BY BORON FLUORIDE–ETHYL ACETATE COMPLEX

2-Acylcyclanones	Yield, %	B.P., °C.	Mm.	n_D^{25}	Calcd C	Calcd H	Found C	Found H
2-Acetylcycloheptanone (V)	74	90–92	5	1.5050	70.10	9.15	70.44	9.31
2-Propionylcycloheptanone	58	102–105	5	1.4962	71.39	9.59	71.42	9.66
2-(2-Ethylbutyryl)cycloheptanone	50	102–104	2	1.4908	74.24	10.54	74.45	10.39
2-Acetylcyclooctanone (VI)	75	102–105	5	1.5113	71.39	9.59	71.55	9.64
2-Propionylcyclooctanone	62	113–114	5	1.5063	72.49	9.95	72.49	9.95
2-(2-Ethylbutyryl)cyclopentanone	55	80–83	2	1.4798	72.49	9.95	72.72	10.06



(2)

Most of the excess ketone employed in this method was recovered. It is possible that the benzoylations of cycloheptanone and cyclooctanone could also be effected satisfactorily with phenyl benzoate or methyl benzoate by the more common sodium amide or sodium hydride procedures, since such methods are suitable with cyclohexanone.[9]

EXPERIMENTAL[10]

Preparation of 2-acylcyclanones by boron fluoride method. 2-Acetylcyclopentanone (I) and 2-acetylcyclohexanone (III) were prepared by acetylating cyclopentanone and cyclohexanone with acetic anhydride by means of the boron fluoride–ethyl acetate complex essentially as described previously.[4,5]

In a similar manner, 2-acetylcycloheptanone (V), 2-acetylcyclooctanone (VI) and certain other 2-acylcyclanones were synthesized employing the appropriate cyclanone and aliphatic anhydride. The results are summarized in Table II.

Alkaline cleavage of 2-acylcyclanones. Table I. A. Determination of ketones. A 0.1-mole sample of the ketone was weighed into a glass-stoppered flask and dissolved in 50 ml. of 10% sodium hydroxide solution. The flask was stoppered and warmed on the steam bath for 2 hr. The flask was then fitted to a continuous extraction apparatus and extracted with ether overnight. The ether extract was evaporated to leave the free ketone. After dissolving in 50 ml. of 95% ethanol the solution was treated with 125 ml. of 2,4-dinitrophenylhydrazine reagent containing 0.12 mole of the carbonyl reagent. After standing in the refrigerator overnight the solid was collected on a sintered glass funnel which had been previously weighed. After washing with ice cold water the solid was dried in a desiccator to constant weight. A series of blanks indicated that the ketones could be estimated to within ±2% by this method.

B. Determination of keto acids II *and* IV. The β-diketone (0.5 mole) was dissolved in excess 10% sodium hydroxide solution and the solution was refluxed for 2 hr. The mixture was acidified with 10% sulfuric acid and continuously extracted with ether overnight. The ether extracts were evaporated and the residue distilled to give δ-acetylvaleric acid in 85–90% yield in 3 runs. The acid boiled at 147–150° at 3 mm., reported[3] b.p. 147–149° at 3 mm. Similarly, 60–64% yields of ε-acetylcaproic acid were obtained from two runs, b.p. 159–162° at 5 mm., reported[3] 160–162° at 4 mm.

2-Benzoylcycloheptanone (VIII) *and 2-benzoylcyclooctanone* (IX). These β-diketones were prepared by treating three molecular equivalents each of sodio cycloheptanone and sodio cyclooctanone in ether with one equivalent of benzoyl chloride in this solvent essentially as described previously[8] for certain other acylations, except that no nitrogen was employed.

2-Benzoylcycloheptanone (VIII), obtained in 40% yield (crude), melted at 55–56° after several recrystallizations from petroleum ether.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.69; H, 7.54.

Most (81%) of the 2 extra equivalents of the cycloheptanone was recovered.

The product gave a positive enol test with methanolic ferric chloride and slowly formed a copper chelate with saturated aqueous cupric acetate solution.

2-Benzoylcyclooctanone (IX) was obtained in 45% yield melting at 54–57°. After recrystallization from methanol-water, the product melted at 59–61°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.87. Found: C, 78.15; H, 7.60.

Most (85%) of the 2 extra equivalents of the cyclooctanone was recovered.

The product gave a deep violet enol test with methanolic ferric chloride and formed a copper chelate with saturated aqueous cupric acetate solution.

Alkaline cleavage of β-diketones VIII *and* IX. Five-gram samples of the β-diketones VIII and IX were cleaved by 10% sodium hydroxide solution and the solution was acidified with dilute sulfuric acid to precipitate benzoic acid. From the cleavage of 2-benzoylcycloheptanone (VIII) there was obtained 2.63 g. of benzoic acid, m.p. 119–121° and mixed m.p. 119–121°, corresponding to 94% side chain cleavage. Similarly, 2-benzoylcyclooctanone (IX) gave 2.52 g. of benzoic acid, m.p. 120–121°, corresponding to a 96% side chain cleavage. A mixed m.p. showed no depression.

2-Acetyl-2-methylcyclopentanone (X) *and 2-acetyl-2-methylcyclohexanone* (XII). Potassium metal (21.45 g.; 0.5 g.-atom + 10%) was dissolved in hot *tert*-butyl alcohol (200 ml.). When solution was complete the mixture was cooled and 0.1 mole of 2-acetylcyclopentanone or 2-acetylcyclohexanone was dissolved in the solution. Methyl iodide (78.1 g.; 0.5 mole + 10%) was then added and the mixture stirred while cooling in an ice bath. Potassium iodide separated and the solution was allowed to come to room temperature. After 8 hr. the salt was filtered from the mixture and the alcohol evaporated under reduced pressure. The residue was distilled *in vacuo*.

There was obtained from 2-acetylcyclopentanone an 87% yield of the 2-methyl derivative (X), b.p. 82–86° at 10 mm.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.76; H, 8.84.

The product failed to give an enol test with ferric chloride solution indicating the absence of the unalkylated starting material.

There was obtained from 2-acetylcyclohexanone a 79% yield of the 2-methyl derivative (XII), b.p. 95–98° at 10 mm.

Anal. Calcd. for $C_9H_{14}O_2$: C, 78.22; H, 7.87. Found: C, 77.95; H, 7.67.

(9) See ref. 4, pp. 77–78 and 147.

(10) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The melting points and boiling points are uncorrected.

The product failed to give an enol test with ferric chloride solution indicating the absence of the unalkylated starting material.

This compound (b.p. 130–133° at 48 mm.) has previously been prepared in unreported yield by methylating 2-acetylcyclohexanone by means of sodium in benzene.[11]

Alkaline cleavages of β-diketones X *and* XII. Samples of these β-diketones were cleaved by alkali according to the procedure for the unalkylated β-diketones.

There was obtained from 2-acetyl-2-methylcyclopentanone a 65% yield of δ-acetylcaproic acid, b.p. 127–128° at 1.5 mm. Neut. equiv. Calcd. 158. Found: 159. The ethyl ester, prepared in 92% yield by the Fisher method, boiled at 77–79° at 0.6 mm.

Anal. Calcd. for $C_{10}H_{18}O_3$; C, 64.47; H, 9.74; Found: C, 64.23; H, 9.72.

There was obtained from 2-acetyl-2-methylcyclohexanone a 25% yield of ε-acetylheptylic acid, b.p. 128–129° at 0.7 mm. Neut. equiv. Calcd. 172. Found: 173. The ethyl ester, prepared in 93% yield by the Fisher method, boiled at 84–85° at 0.6 mm.

Anal. Calcd. for $C_{11}H_{20}O_3$; C, 65.96; H, 10.06. Found: C, 65.82; H, 10.06.

Also there was obtained from the cleavage of 2-acetyl-2-methylcyclohexanone a 54% yield of 2-methylcyclohexanone boiling at 165–167°; reported b.p. 166°.[12]

DURHAM AND WINSTON-SALEM, N. C.

(11) H. K. Sen and U. Bose, *J. Indian Chem. Soc.*, **4**, 62 (1927).

(12) A. Skita, *Ber.*, **56**, 1016 (1923).

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

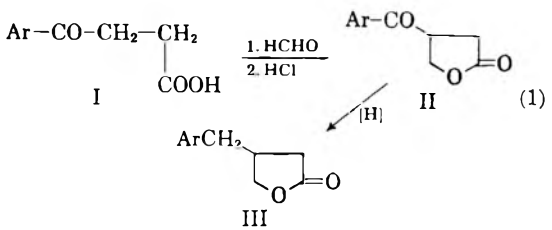
Substituted γ-Lactones. III. A General Route to β-Substituted γ-Butyrolactones[1]

JOHANNES ROTHE[2a] AND HANS ZIMMER[2b]

Received November 7, 1958

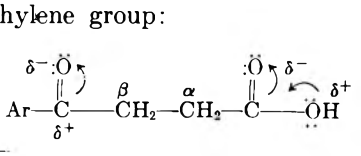
The reaction of β-aroylpropionic acids I with equimolecular amounts of formaldehyde in alkaline solution leads to β-aroylbutyrolactones II. This reaction appears to be a general one; with acetaldehyde, the corresponding β-aroyl-γ-valerolactones are obtained. A small yield of β-acetylbutyrolactone is formed from levulinic acid and formaldehyde. Catalytic hydrogenations and Meerwein-Ponndorf reductions of the II are described.

We were interested in preparing substituted β-benzylbutyrolactones as starting materials for further synthetic work. The hydroxymethylation of β-benzoylpropionic acid (Ia) or substituted β-benzoylpropionic acids, respectively, followed by lactonization and reduction of the carbonyl group, seemed to be a possible way:

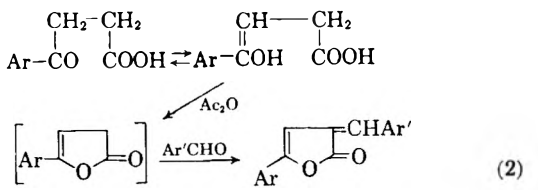


a: Ar = C_6H_5 *b*: Ar = 3,4-$(CH_3O)_2C_6H_3$

According to theoretical considerations, the β-methylene group in I should be more reactive than the α-methylene group:



It is a well known fact that the nucleophilic character of a keto-carbonyl-C-atom is stronger than that of a carboxyl-C-atom. Hence aldol-like condensations of aldehydes with I should preferably occur in the β-position. The reaction[3] of β-aroylpropionic acids with aldehydes under the influence of acetic anhydride to give α-arylidene-γ-arylcrotonolactones provides no argument against this assumption because, under the reaction conditions, enolization and lactonization seem to occur first, followed by condensation with the aldehyde:



In fact, reaction of ethyl β-benzoylpropionate and benzaldehyde with sodium ethylate in ethanolic solution yields up to 90% of β-benzylidene-β-benzoylpropionic acid.[3b]

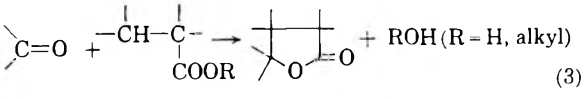
There are two classic examples for the preparation of lactones based on the principle of an aldol-like condensation of a carbonyl compound

(1) Paper II of this series, see H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 100 (1959).

(2) (a) Chattanooga Medicine Company Post-doctorate Research Fellow 1956–58. Recipient of a Fulbright Travel Grant. Present address: Department of Chemistry, Harvard University, Cambridge, Mass. (b) To whom inquiries concerning this paper should be directed.

(3) (a) *e.g.*, J. Thiele, *Ann.*, **306**, 145 (1899); W. Borsche, P. Hofmann, and H. Kuhn, *Ann.*, **554**, 23 (1943); F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **73**, 3528 (1951); C. Hanna and F. W. Schueler, *J. Am. Chem. Soc.*, **75**, 741 (1953). (b) W. Borsche, *Ber.*, **47**, 1108 (1914).

with an activated β-CH-group of a carboxylic acid derivative according to the scheme:



(3)

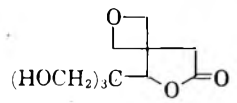
(1) The preparation of α-ketolactones (aldehyde or ketone with substituted pyruvic acids or esters,[4] (2) The Fittig paraconic acid synthesis (aldehydes with Na-succinate).[5,6]

Besides these well known reactions, we found surprisingly few examples[7–10] for the preparation of lactones according to Scheme 3. Haworth and Sheldrick[7] as well as Drake and Tuemmler[9] condensed substituted benzoylpropionic acids with formaldehyde but obtained partly the bis-hydroxymethylated products. Ladd and Paxton[8] prepared β-acylparaconic esters from α-acylsuccinic esters and aldehydes. Mikhlina and Rubtsov[10] obtained β-hydroxymethyl-β-4-pyridyl-γ-butyrolactone from ethyl β-(4-pyridyl)-propionate and an excess of formaldehyde.

In order to avoid any di-hydroxymethylation,[7,9,10] we regarded it as essential to apply only stoichiometric amounts of formaldehyde and to work under rather mild conditions. After several days standing at room temperature in alkaline solution [*p*H 8–10] we obtained from equimolecular amounts of Ia and 40% aqueous formalin a 45% yield of β-benzoyl-γ-butyrolactone (IIa). Similarly, from β-veratroylpropionic acid (Ib), up to 69% of β-veratroyl-γ-butyrolactone (IIb) was obtained. These neutral products are easily separated from unreacted starting material which can be recovered; the isolation and purification is simple. When the reaction with Ib was tried at a lower *p*H (7–8), the yield dropped to 2%, and 90% of the starting material was recovered. In one experiment, an excess of formalin was used; the m.p. of the product was lower in this case, and by fractional crystallization a low yield of the bis-hydroxymethylated product, β-hydroxymethyl-β-veratroyl-γ-butyrolactone, was isolated.

Using acetaldehyde instead of formaldehyde, we obtained the corresponding β-acyl-γ-valerolactones; this fact indicates that the reaction is not limited to formaldehyde, but that with other aldehydes a variety of β-acyl-γ-substituted butyrolactones may be synthesized.

In order to investigate further the limitations of the reaction, the simplest aliphatic α-keto acid, levulinic acid, was condensed with formaldehyde. This reaction has previously been investigated by Rave and Tollens[11] who worked with a large excess of the aldehyde and consequently obtained a poly-hydroxymethylated product which they formulated as IV. In our hands, with a 1:1 molar



IV

ratio, a small yield of β-acetyl-γ-butyrolactone was isolated. We believe, however, that the yield could be improved by a more suitable isolation technique. β-Acetyl-γ-butyrolactone is, to our knowledge, only described in form of its 2.4-dinitrophenylhydrazone.[12,*]

The second step of the intended synthesis (II→ III) involves the reduction -CO- → -CH_2-. It was decided not to apply the Clemmensen reaction in this case, because of a possible cleavage of the methoxy groups in IIb, and also because the lactonic ring might be affected.[13] Wolff-Kishner reduction seems to be applicable, but the method of choice is hydrogenation according to the method of Zelinsky.[14] The catalyst used by Zelinsky consisted of platinum-on-carbon, activated with palladium chloride solution. We applied palladium chloride without a carrier and obtained practically

(4) *e.g.*, W. Wislicenus and A. Jensen, *Ber.*, **25**, 3448 (1892); E. Erlenmeyer Jr., and co-workers, *Ann.*, **333**, 160 (1904); R. Kuhn and T. Wieland, *Ber.*, **75**, 121 (1942); H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947); B. Puetzer, C. H. Nield, and R. H. Barry, *J. Am. Chem. Soc.*, **67**, 832 (1945); H. Gault and co-workers, *Ann. chim.*, [12], **6**, 220 (1951); G. W. Stacy and G. D. Wagner, *J. Am. Chem. Soc.*, **74**, 909 (1952).

(5) R. Fittig and co-workers, *Ann.*, **216**, 26 (1882); **227**, 79 (1885); **255**, 1, 257 (1889).

(6) About the occurrence of paraconic esters in the Stobbe condensation (aldehyde or ketone with succinic esters), *cf.* W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(7) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 289 (1941).

(8) E. C. Ladd and H. W. Paxton, U. S. Pat. **2,598,803** (1952) [*Chem. Abstr.*, **46**, 10194d (1952)].

(9) N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.*, **77**, 1204 (1955).

(10) E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshcheĭ Khim.*, **27**, 691 (1957); [*Chem. Abstr.*, **51**, 16463f (1957)].

(11) P. Rave and B. Tollens, *Ann.*, **276**, 69 (1893).

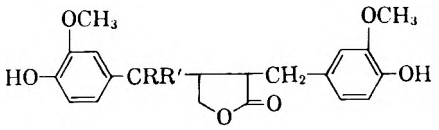
(12) (a) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952); (b) L. Birkofer and I. Storch, *Ber.*, **87**, 571 (1954).

(13) E. L. Martin, *Org. Reactions*, **1**, 155 (1942); *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(14) N. D. Zelinsky, K. Packendorff, and L. Leder-Packendorff, *Ber.*, **66**, 872 (1933); **67**, 300 (1934).

* NOTE ADDED IN PROOF: After submitting this manuscript our attention was directed to an article by S. Olsen [*Acta chem. scand.*, **9**, 101 (1955)] who experimentally disproved structure IV. He condensed levulinic acid with an excess of paraformaldehyde in acidic medium and obtained, among other products, a compound $C_6H_8O_3$ (b.p. 153°) which decolorized bromine in chloroform, gave a positive Baeyer reaction and which he assumed to be either β- or δ-methylenelevulinic acid or β-acetylbutyrolactone. Our analytical sample reacted neutral in aqueous solution and neither decolorized bromine in chloroform nor a dilute potassium permanganate solution in 5% sodium bicarbonate. Its IR-spectrum is in agreement with our assumed structure. It shows peaks at 5.62μ and 5.82μ resp., indicating the presence of a lactonic and a ketonic carboxyl groups. There is no peak between 5.82μ and 6.75μ indicating the absence of C=C unsaturation. In addition it shows no evidence for COOH absorption.

quantitative yields of IIIa and IIIb, respectively. After these experiments were completed, we learned that Freudenberg[15] had used the same catalyst for the reduction of (+)-oxo-matairesinol (*V*, R=O) to (−)-matairesinol (*V*, R′=R=H). Freu-



V

denberg[15] also reports that under milder conditions (palladium-on-kieselguhr) the hydrogenation stops at the carbinol stage (*V*, R=H, R′=OH). In our experiments, the desired β-benzyl-γ-butyrolactones were definitely obtained, as was shown by analytical results and IR spectra.

Meerwein-Ponndorf reduction of II led to the corresponding carbinols. With IIb, the yield was moderate, probably due to the fact that only one of the two possible racemic diastereoisomers was obtained as a crystalline solid; attempts to isolate the other isomer in crystalline form were so far unsuccessful. The reduction product of IIa was an oil, probably a mixture of the two isomers.

EXPERIMENTAL

The infrared spectra were obtained with a Baird double beam spectrophotometer and measured in nujol mull (solids) or neat (liquids). Melting points are not corrected. Analysis by A. Bernhardt, Max Planck Institute, Mulheim/Ruhr, Germany.

DL-*β-Benzoyl-γ-butyrolactone* (IIa). Twenty g. (0.145 mole) of potassium carbonate were dissolved in 100 cc. of water, and 35.6 g. (0.2 mole) of β-benzoylpropionic acid (Ia) were cautiously added, followed by 18 cc. (0.2 mole) of a solution of 36–38% formalin. The solution was kept at room temperature for 8 days. After the addition of 30 cc. of concentrated hydrochloric acid to effect lactonization, the mixture was warmed on a boiling water bath for 30 min., then cooled and repeatedly extracted with methylene chloride. The extracts were washed several times with 10% sodium carbonate solution, then with water, dried over sodium sulfate, and the solvent was evaporated. An oily residue was left which in the first experiment did not solidify until it had been redistilled several times. In all the following experiments, the oil was dissolved in hot methanol and precipitated upon cooling; no difficulty in crystallization was encountered. The analytical sample (b.p. 176–176.5°/4.5 mm.) melted at 60–61.5°. In later experiments, melting points of 65–66° were observed. The yield was 17.0 g. (45%).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.30; H, 5.43. Infrared spectrum: 5.66 μ (5-membered lactone-CO) and 5.97 μ (ketone-CO). 5.9 g. of Ia were recovered from the sodium carbonate washings; the yield based on consumed Ia is 53%.

2,4-Dinitrophenylhydrazone, m.p. 223.5–224°, orange-yellow microcrystalline powder from dioxane-methanol.

Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.13; H, 3.81; N, 15.13. Found: C, 55.37; H, 3.92; N, 15.02.

Phenylhydrazone, m.p. 168–169°, short needles from methanol.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 9.99. Found N, 10.10.

Semicarbazone, m.p. 144–145°, leaflets from methanol-water.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: N, 17.00. Found: N, 17.04.

Similarly, the following compounds were prepared: DL-*β-(3,4-Dimethoxybenzoyl)-γ-butyrolactone* (IIb), from Ib and 40% formalin (15 days; 69%). Plates from CH_3OH, m.p. 116–117°. Infrared spectrum: 5.65 μ and 6.00 μ.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found C, 62.34; H, 5.80.

2,4-Dinitrophenylhydrazone, m.p. 212–213°, orange microcrystalline powder from dioxane.

Anal. Calcd. for $C_{19}H_{18}N_4O_8$: C, 53.02; H, 4.22. Found: C, 53.27; H, 4.49.

DL-*β-Benzoyl-γ-valerolactone*, from Ia and acetaldehyde (12 days). Yellowish oil, b.p. 157–160°/5 mm., n_D^{26} 1.5455.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.27; H, 6.03.

2,4-Dinitrophenylhydrazone, m.p. 210–211°, small orange leaflets from ethanol.

Anal. Calcd. for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.21; H, 4.16; N, 14.74.

DL-*β-(3,4-Dimethoxybenzoyl)-γ-valerolactone*, m.p. 114–115° (from methanol-ether).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.48; H, 6.00.

2,4-Dinitrophenylhydrazone, m.p. 214.5–215.5°, orange flakes from dioxane-methanol.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.54. Found: C, 54.02; H, 4.53.

DL-*β-Hydroxymethyl-β-(3,4-dimethoxybenzoyl)-γ-butyrolactone*. Veratroylpropionic acid (95.3 g.), 48 g. of potassium carbonate, 32 cc. of 36–38% formalin, and 300 cc. of water were kept at room temperature for 15 days. After this time, 10 more g. of potassium carbonate and 30 cc. of 40% formalin were added and the mixture was stored for 13 more days. After the usual working up and one recrystallization from methanol, 59.9 g. of a product, m.p. 106–108°, were obtained. Another recrystallization from the same solvent gave 56.8 g. (56%) of IIb, m.p. 109–110.5°. The filtrates of these two recrystallizations were combined and evaporated to a small volume; 3.6 g. of crystals, m.p. 131–136°, were collected. After 6 further recrystallizations from methanol, the analytical sample of DL-β-hydroxymethyl-β-(3,4-dimethoxybenzoyl)-γ-butyrolactone melted at 145–146°.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found C, 60.18; H, 5.88.

2,4-Dinitrophenylhydrazone, m.p. 201–202° (from dioxane-methanol).

Anal. Calcd. for $C_{20}H_{20}N_4O_9$: C, 52.17; H, 4.38; N, 12.17. Found: C, 52.33; H, 4.47; N, 12.20.

DL-*β-Acetyl-γ-butyrolactone*. Fifty-five g. of levulinic acid (once distilled), 47.5 g. of potassium carbonate, 38 cc. of 40% formalin, and 100 cc. of water were kept at room temperature for 2 weeks. The mixture was then acidified, heated on a boiling water bath for 30 min., cooled, saturated with potassium sulfate, and extracted 3 times with 100-cc. portions of chloroform. The combined chloroform extracts were washed twice with 50-cc. portions of saturated sodium carbonate solution, and the alkaline layer once again extracted with 100 cc. of chloroform. The extracts were eventually washed with saturated potassium sulfate solution, dried (sodium sulfate), and the solvent evaporated. A yellowish liquid remained which upon distillation gave 5.2 g. (8.6%) of the lactone, b.p. 114–122°/5 mm. After 2 more distillations, a center cut (b.p. 118–120°/5 mm.; n_D^{19} 1.4630) was analyzed.

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.37; H, 6.30.

2,4-Dinitrophenylhydrazone, orange-yellow leaflets from dioxane, m.p. 193.5–194° (lit. m.p.: 191–192°[12a], 193°[12b]).

Anal. Calcd. for $C_{12}H_{12}N_4O_6$: C, 46.76 H, 3.92 N, 18.18. Found: C, 46.81 H, 4.04 N, 18.29.

DL-*β-Benzyl-γ-butyrolactone* (IIIa). Five and seven tenths g. of IIa in 250 cc. of methanol were hydrogenated with 0.3 g. of palladium chloride in a Parr apparatus at 50 p.s.i. initial pressure. After about 2 hr., the pressure had dropped

(15) K. Freudenberg and L. Knof, *Ber.*, 90, 2857 (1957).

to 44.5 p.s.i. and then remained constant. After removal of the catalyst and solvent, the product was distilled, yielding 5.2 g. (98%) of DL-β-benzyl-γ-butyrolactone, b.p. 161–163°/6 mm. The analytical sample, a center cut from a second distillation, had b.p. 162–163°/6 mm. Colorless liquid, n_D^{20} 1.5373.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97 H, 6.86. Found: C, 74.69; H, 6.68. Infrared spectrum: 5.64 μ (lactone-CO); a weak band appeared at 2.83 μ (indicating that the compound was contaminated by a trace of OH-containing material).

DL-β-(*3,4-Dimethoxybenzyl*)-γ-*butyrolactone* (IIIb) was similarly prepared from IIb, yield 95–97%. Slightly yellowish, rather viscous oil, b.p. 220°/6 mm., n_D^{20} 1.5519.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.08; H, 6.81. Infrared spectrum: 5.58 μ (lactone-CO); no absorption between 2 μ and 3.2 μ (no OH-containing impurity).

DL-β-(α-*Hydroxy-3,4-dimethoxybenzyl*)-γ-*butyrolactone.* A mixture of 10.1 g. of IIb, 8.2 g. of aluminum isopropoxide,[16] and 50 cc. of isopropanol (previously distilled over calcium oxide) was placed in a 500-cc. two-necked, round-bottom flask which was fitted with a Widmer column. The mixture was gently refluxed for 1 hr., then heated at such a rate that acetone distilled as it was formed. After 3 hr., 50 cc. of isopropanol were added. The reaction proceeded slowly, but after 8 hr. the distillate gave a negative test with 2,4-dinitrophenylhydrazine. The reaction mixture was then concentrated nearly to dryness, decomposed with 100 cc. of 10% hydrochloric acid, and kept overnight in the refrigerator. It was then extracted twice with chloroform, the chloroform layers dried over sodium sulfate, and the solvent evaporated. A yellowish oil remained which solidified partly after digestion with a large amount of ether and standing for several weeks. 4.8 g. (48%) of crude product, m.p. 77–81°, was obtained. One recrystallization from methanol-ether gave 2.2 g. of a product, m.p. 91–93°. Three more recrystallizations raised the m.p. to 96.5–97.5°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.95; H, 6.50. Infrared spectrum: 5.65 μ and 5.75 μ (double band) and 2.95 μ. Various attempts to isolate more crystalline material from the oily residues of the evaporated mother liquors were unsuccessful. Further investigation of this oil is in progress.

DL-β-(α-Hydroxybenzyl)-γ-butyrolactone was obtained similarly from 9.5 g. of IIa. The reaction product was a slightly yellowish oil which did not crystallize, and hence was distilled (b.p. 160–205°/5 mm., 7.3 g., 76%). After two more distillations, a fraction (4.1 g., 43%) with b.p. 195–197°/5 mm., n_D^{26} 1.5461, was analyzed.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.36; H, 6.31. Infrared spectrum: 5.65 γ and 2.90–2.95 μ (broad band).

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(16) The authors are indebted to Chattem Chemicals, Division of the Chattanooga Medicine Co., Chattanooga, Tenn., for a generous gift of this compound.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLI.[1,2] *Meso*-substituted Acridizinium Benzologs

C. K. BRADSHER AND T. W. G. SOLOMONS

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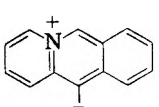
Benzacridizinium derivatives with a substituent in the central nucleus have been prepared by the acid-catalyzed cyclization of quaternary salts obtained by reaction of (1) 1-bromomethylnaphthalene with 2-pyridyl ketones or (2) benzyl (or naphthylmethyl) halides with 1-benzoylisoquinoline.

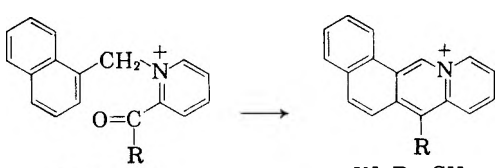
Only a single, highly activated, 1-benzoyl-2-benzylisoquinolinium salt (VIII) was found to cyclize in liquid hydrogen fluoride, but the remainder of the isoquinolinium salts could be cyclized in hot polyphosphoric acid.

In the preceding communication of this series it was shown that salts obtained by the quaternization of 2-pyridyl ketones could be cyclized to yield the first 11-substituted acridizinium salts I. It appeared interesting to examine the usefulness of



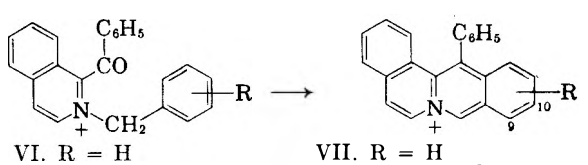
I

this approach in the synthesis of some acridizinium benzologs, since at least one of these would be isosteric with a known carcinogen and further information could be gained about the importance of steric and electronic effects on the ease of cyclization. For the synthesis of the monobenzologs two general approaches have been used, both involving the cyclization of quaternary salts. In the first, a



II. R = CH_3
IV. R = C_6H_5

III. R = CH_3
V. R = C_6H_5



VI. R = H
VIII. R = 3-OCH_3
X. R = 2-CH_3

VII. R = H
IX. R = 10-OCH_3
XI. R = 9-CH_3

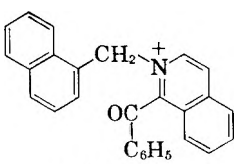
(1) For the preceding communication of this series, see *J. Am. Chem. Soc.*, in press.

(2) Taken in part from a thesis to be submitted in partial fulfillment of the requirements for the Ph.D. degree, Duke University. This research was supported by a research grant (NSF-G2364) of the National Science Foundation.

salt (II or IV) was formed by the reaction of 1-bromomethylnaphthalene with a 2-pyridyl ketone, while in the second 1-benzoylisoquinoline formed a quaternary salt (VI) by reaction with a benzyl halide. With the exception of the quaternary salt II from 2-acetylpyridine all were obtained in good yield (83–94%). Both of the pyridinium salts cyclized readily in liquid hydrogen fluoride. The product III from the 2-acetylpyridinium salt II was of particular interest because the new cation is isosteric with the highly carcinogenic 10-methyl-1,2-benzanthracene.[3]

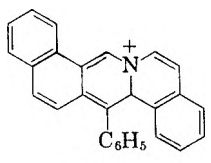
1-Benzoyl-2-benzylisoquinolinium ion (VI) is not cyclized by the action of liquid hydrogen fluoride and the 2-methylbenzyl analog X shows similar unreactivity. Since 1-benzyl-2-benzoylpyridinium bromide cyclizes in good yield under the same conditions,[1] it seems that the resistance of the benzylisoquinolinium salts (VI and X) to cyclization arises from the difficulty inherent in crowding the phenyl group into a confined position. The difficulty was overcome by carrying out the cyclization under more energetic conditions in polyphosphoric acid at 150–160° several hours. If the benzyl group is substituted by methoxyl (VIII) at a position para to the expected ring closure, cyclization is greatly facilitated, in fact a 91% yield of the 10-methoxy-13-phenylbenz[*a*]acridizinium perchlorate was obtained using hydrogen fluoride as the cyclizing agent.

Quaternization of 1-benzoylisoquinoline with 1-bromomethylnaphthalene yielded a salt XII which was cyclized to yield the first fully aromatic dibenz[*a,h*]acridizinium salt XIII.



(not isolated)

XII



XIII

EXPERIMENTAL[4]

Spectroscopy. All visible and ultraviolet spectra were determined in 95% ethanol solution, using the Warren Spectracord recording spectrophotometer and 1-cm. matched silica cells.

1-(1-Naphthylmethyl)-2-benzoylpyridinium perchlorate (IV). A mixture containing 1.83 g. of 2-benzoylpyridine, 2.21 g. of 1-bromomethylnaphthalene and 1 ml. of dimethylformamide were mixed together and allowed to stand at 10° for 50 days. The light yellow crystals which separated were washed with ether, 3.78 g. (94%), m.p. 132–136°. This material was used for the cyclization experiments, but a sample was converted to the *perchlorate* for analysis. The perchlorate gave small colorless irregular crystals from methanol, m.p. 164–165°.

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.17; H, 4.28; N, 3.31. Found: C, 65.49; H, 4.27; N, 3.29.

7-Phenylbenz[h]acridizinium perchlorate (V). Two grams of the crude bromide IV was placed in a polyethylene bottle and 25 ml. of liquid hydrogen fluoride added with magnetic stirring. After the hydrogen fluoride had evaporated the residue was taken up in ethanol, the solution treated with Norit, and filtered. The solution was concentrated, cooled, and perchloric acid added The small yellow crystals which separated were collected and washed with cold ethanol, 1.80 g. (90%), m.p. 315.5–316.5°. The analytical sample crystallized from dimethylsulfoxide-water as small rectangular yellow prisms, m.p. 316.5–317° (sealed capillary, in block preheated to 300°) λ_{max} (log ϵ), 231 (4.54), 275 (4.46), 305.5 (4.19), 320 (4.23), 379 (4.15), 399 mμ (4.29); λ_{min} 250 (4.07), 294 (4.07), 313.5 (4.14), 339 (3.54), 388 (3.98).

Anal. Calcd. for $C_{23}H_{16}ClNO_4$: C, 68.07; H, 3.97; N, 3.45. Found: C, 68.39; H, 3.78; N, 3.29.

1-(1-Naphthylmethyl)-2-acetylpyridinium bromide (II). The quaternization of 2.28 g. of 2-acetylpyridine with 4.15 g. of 1-bromomethylnaphthalene was carried out in 2.0 ml. of dimethylformamide at 10° for two weeks, followed by 38 days at room temperature. The yield of crude bromide suitable for cyclization was 3.65 g. (57%), m.p. 122–130° dec. (capillary). The analytical sample crystallized from ethanol-ethyl acetate as very small yellow rectangular prisms, m.p. 152–165° (with decomposition into gaseous products).

Anal. Calcd. for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09. Found: C, 63.43; H, 4.67; N, 4.16.

7-Methylbenz[h]acridizinium perchlorate (III). One-half gram of the pyridinium bromide salt II was added to 50 ml. of liquid hydrogen fluoride in small portions during the course of about 20 minutes. After the hydrogen fluoride had evaporated, the residue was precipitated as the perchlorate salt as in the case of the phenyl analog V. A quantitative yield of product melting above 360° was obtained. The analytical sample, prepared by recrystallization from dimethylsulfoxide-methanol consisted of yellow microscopic needles, λ_{max} (log ϵ), 231 (4.39), 276 (4.50), 307 (4.16), 320 (4.23), 361 (3.56), 379 [4.17), 400 mμ (4.37); λ_{min} 248 (3.97), 290 (3.97), 312.5 (4.10), 337 (3.55), 366 (3.86), 388 (3.91).

Anal. Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.08. Found: C, 62.67; H, 4.07; N, 4.08.

In another experiment 3.65 g. of the pyridinium bromide salt II was cyclized, and after the hydrogen fluoride had evaporated, the residue was taken up in 75 ml. of methanol, and passed through an ion-exchange column containing Amberlite IRA-410 resin loaded with chloride ion. The methanol was removed, and the residue crystallized from ethanol as small yellow needles of the *chloride*, m.p. 359–361° dec. (sealed tube). The melting point of the analytical sample was essentially unchanged.

Anal.[5] Calcd. for $C_{18}H_{14}ClN.2H_2O$: C, 68.46; H, 5.74. Found: C, 68.48; H, 5.70.

1-Benzoyl-2-benzylisoquinolinium bromide (VI). One gram of 1-benzoylisoquinoline[6] and 1.0 g. of benzyl bromide were allowed to react for 12 days at room temperature. Crystallization of the brown oil was induced by scratching, and after trituration with ethyl acetate, 1.30 g. (92%) of a yellow powder was obtained, m.p. 166–168°. The analytical sample was crystallized from methanol-ethyl acetate, m.p. 172.5–173.5°.

Anal. Calcd. for $C_{23}H_{18}BrNO$: C, 68.32; H, 4.49; N, 3.46. Found: C, 68.40; H, 4.39; N, 3.45.

(3) *Cf.*, M. J. Shear, *Am. J. Cancer*, **33**, 499 (1938). While the positive charge makes it appear unlikely that III will exhibit carcinogenic activity, it is planned to have it tested for this as well as for possible tumor-necrotizing activity.

(4) Unless indicated otherwise all melting points were taken on the Fisher-Johns block and are not corrected. Except as noted all analyses were by Galbraith Laboratories, Knoxville, Tenn.

(5) Analyses by Drs. Weiler and Strauss, Oxford, England.

(6) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

The *perchlorate* was prepared in water solution and recrystallized from methanol-ethyl acetate, m.p. 212–213°.

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.18; H, 4.28; N, 3.31. Found: C, 65.25; H, 4.44; N, 3.56.

13-Phenylbenz[a]acridizinium perchlorate (VII). To 32 g. of polyphosphoric acid in a beaker, 750 mg. of the benzylisoquinolinium salt was added with stirring. The top of the beaker was covered by means of a sheet of aluminum foil and the mixture heated at 150–160° for 12 hr. The mixture was diluted to a volume of about 75 ml. by the addition of ice and water, and 20 ml. of 14% perchloric acid was added slowly with stirring. Stirring was continued for 3 hr. after the addition was complete, then the mixture was cooled in ice, and the greenish yellow powder collected, yield 705 mg. (94%), m.p. 240–260°. Recrystallized from ethanol-ether (Norit) it yielded 500 mg. (67%) of yellow needles, m.p. 268–270°. The analytical sample melted at 266.5–267.5°, λ_{max} (log ϵ), 261.5 (4.56), 311.5 (4.34), 387 (4.15), 406 mμ (4.25), λ_{min} 242 (4.42), 289 (4.20), 344 (3.83), 396 mμ (4.08).

Anal. Calcd. for $C_{23}H_{16}ClNO_4$: C, 68.06; H, 3.97; N, 3.45. Found[5]: C, 67.96; H, 4.17; N, 3.92.

The *picrate* was prepared from the perchlorate in ethanol, m.p. 223–224°.

Anal. Calcd. for $C_{29}H_{18}N_4O_7$: C, 65.16; H, 3.39; N, 10.48. Found:[5] C, 64.97; H, 3.69; N, 10.05.

1-Benzoyl-2-(3-methoxybenzyl)isoquinolinium perchlorate (VIII). One gram of 1-benzoylisoquinoline was quaternized in dimethylformamide by the action of 1.2 g. of *m*-methoxybenzyl bromide and worked up in the usual way. The crude bromide suitable for cyclization consisted of yellow crystals, m.p. 148–150°, yield 1.55 g. (82%).

The *perchlorate* was prepared in water solution and crystallized from methanol-ethyl acetate, m.p. 146–147°.

Anal. Calcd. for $C_{24}H_{20}ClO_6$: C, 63.51; H, 4.44; N, 3.09. Found: C, 63.54; H, 4.41; N, 3.27.

10-Methoxy-13-phenylbenz[a]acridizinium perchlorate (IX). The cyclization of 600 mg. of the methoxybenzyl isoquinolinium salt VIII was carried out in hydrogen fluoride (75 ml.) in the usual way and the product precipitated as the perchlorate, m.p. 265.5–267.5°, yield 545 mg. (91%). Once recrystallized from methanol, it yielded 470 mg. (78%), m.p. 278.5–281°. The analytical sample was obtained from methanol as tiny yellow needles, m.p. 281.5–283°, λ_{max} (log ϵ), 223 (4.52), 269 (4.59), 311.5 (4.55), 400 (3.93), 421 mμ (4.03); λ_{min} 243 (4.07), 289 (4.37), 384 (3.72), 408 mμ (3.91).

Anal. Calcd. for $C_{24}H_{18}ClNO_5$: C, 66.13; H, 4.16; N, 3.21. Found: C, 66.00; H, 4.23; N, 3.21.

1-Benzoyl-2-(2-methylbenzyl)isoquinolinium perchlorate(X). One gram of 1-benzoylisoquinoline was quaternized in the usual way with 1.2 g. of *o*-methylbenzyl bromide. The crude bromide, 1.62 g. (86%), m.p. 134–139°, was suitable for further reactions.

The *perchlorate* was crystallized from methanol-ethyl acetate as colorless irregular plates, m.p. 175–177°.

Anal. Calcd. for $C_{24}H_{20}ClNO_5$: C, 65.79; H, 4.60; N, 3.20. Found: C, 65.56; H, 4.48; N, 3.47.

9-Methyl-13-phenylbenz[a]acridizinium perchlorate (XI). The cyclization of 500 mg. of the crude bromide salt X obtained in the preceding experiment was carried out as in the case of the lower homolog VI. The product was precipitated as the perchlorate from the diluted phosphoric acid mixture. Recrystallization of the greenish yellow powder from acetonitrile afforded 190 mg. (38%) of brown-yellow needles, m.p. 296–300°. The analytical sample melted at essentially the same temperature, λ_{max} (log ϵ), 224 (4.53), 266 (4.54), 314.5 (4.31), 396 (3.76), 416 mμ (3.84); λ_{min} 247 (4.09), 293 (4.86), 346.5 (3.75), 404 mμ (3.72).

Anal. Calcd. for $C_{24}H_{18}ClNO_4 \cdot {}^1/_2H_2O$: C, 67.21; H, 4.47; N, 3.27. Found:[5] C, 66.97; H, 4.35; N, 3.53.

15-Phenyldibenz[a,h]acridizinium bromide (XIII). A quaternary salt was formed by the reaction of 1.0 g. of 1-benzoylisoquinoline and 1.0 g. of 1-bromomethylnaphthalene at room temperature for 18 days. The crude bromide (presumably XII), m.p. 125–126°, yield 1.20 g. (61%), was not obtained in a pure condition, and was used directly in the cyclization reaction. The cyclization of 500 mg. of crude bromide was carried out in 28 g. of polyphosphoric acid at 140–150° for 8 hr. The mixture was cooled and diluted to 75 ml. and allowed to stand overnight. The greenish-yellow precipitate (presumably a phosphate) which formed was collected, yield 492 mg. Nearly all (400 mg.) of the precipitate was dissolved in 1 l. of methanol containing 30 ml. of 48% hydrobromic acid and the solution passed through an ion-exchange column containing Amberlite IRA-410 resin loaded with bromide ion. The resulting solution was concentrated *in vacuo* and the residue crystallized from methanol-ethyl acetate, yield 228 mg. (56%) of irregular yellow crystals, m.p. >360°.

The analytical sample melted at 372–374° (sealed tube), λ_{max} (log ϵ), 278.5 (4.42), 306.5 (4.56), 390 (4.31), 411 mμ (4.51); λ_{min} (log ϵ), 254 (4.29), 285.5 (4.41), 346.5 (3.78), 401 mμ (4.12).

Anal. Calcd. for $C_{27}H_{18}BrN \cdot {}^1/_2CH_4O$: C, 73.01; H, 4.46; N, 3.10. Found:[5] C, 72.93; H, 4.85; N, 3.22.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLII.[1,2] Synthesis of Benzo[*a*]- and Dibenzo[*a*,*c*]phenanthridizinium Salts. The Effect of Activating Groups

C. K. BRADSHER AND K. B. MOSER[3]

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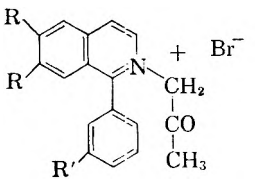
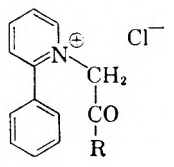
By introduction of alkoxyl groups at suitable positions, it has been possible to bring about the cyclization of the 1-phenyl-2-acetonylisoquinolinium (I) as well as the 5-acetonyl-6-phenylphenanthridinium system (IV). The cyclization products are the first benzo[*a*]- (IX) and dibenzo[*a*,*c*]phenanthridizinium (X) salts. Three new 9-arylphenanthridines have been prepared.

In an earlier paper[4] it was shown that 1-phenyl-2-acetonylisoquinolinium bromide (I) does not cyclize under conditions considerably more drastic than those employed in the acid-catalyzed cyclization of 2-phenyl-1-acetonylpyridinium chloride

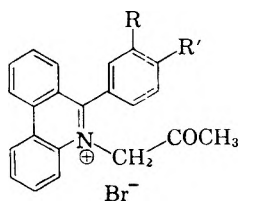


I. R = R′ = H
II. R—R = —O—CH₂O—, R′ = OCH₃

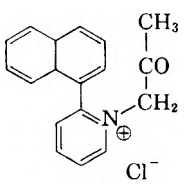


III

(III).[5] It seemed reasonable to assume that the failure of I to cyclize, arose from the overlapping of the hydrogen atom at position 8 of the isoquinoline ring with those of the *ortho* positions of the phenyl ring, since this would interfere with the achievement of the coplanarity necessary for ring closure. A similar explanation could be advanced for the failure of 5-acetonyl-6-phenylphenanthridinium bromide (IV) to undergo cyclization. Since 1-acetonyl-2-(1-naphthyl)pyridinium chloride (VIII) has a geometry closely related to that of I, yet undergoes cyclization[4] readily, it appeared likely that cyclization of systems such as I and IV could likewise be brought about if a highly active position were available for the attack of the carbonyl function. The present paper described the use of alkoxyl groups to promote such cyclizations.

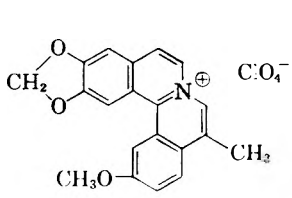


IV. R = R′ = H
V. R = OCH₃, R = H
VI. R = R′ = OCH₃
VII. R—R′ = —O—CH₂—O—

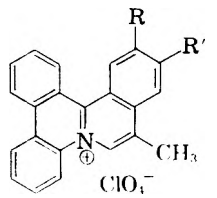


VIII

Activation in the 1-phenylisoquinoline was to be brought about by a methoxyl group in the *meta* position of the phenyl ring, but since 1-substituted isoquinolines are more readily prepared by the Bischler-Napieralski reaction[6] if cyclization can take place in an activated position, it seemed better to synthesize 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline. It was felt that the presence of the methylenedioxy group in the isoquinolinium salt II would not alter the outcome of the final cyclization experiment. The new 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline was synthesized and found to react readily with bromoacetone, affording a 95% yield of the quaternary salt II. Cyclization of II in boiling hydrochloric acid, followed by conversion to the perchlorate yielded a mixture of products[7] from which was isolated a pure compound, believed to be 2,3-methylenedioxy-12-methoxy-9-methylbenzo[*a*]phenanthridizinium perchlorate (IX)[8] rather than the 10-methoxy isomer. The ultraviolet absorption spec-



IX



X. R = OCH₃, R′ = H
XI. R = R′ = OCH₃
XII. R—R′ = —O—CH₂—O

(1) For the preceding communication of this series see *J. Org. Chem.*, **24**, 589 (1959).

(2) Taken in part from a thesis to be submitted in partial fulfillment of the Ph.D. degree, Duke University. This research was supported by a research grant (NSF-G2364) of the National Science Foundation.

(3) Monsanto Chemical Company Fellow (1957–58).

(4) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(5) While it was shown [C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 453 (1955)] that 2-phenyl-1-acetenylpyridinium chloride (III) can be cyclized in 51 hours (75% yield) the comparable isoquinolinium bromide (I) was recovered unchanged (84%) after 10 days refluxing with hydrobromic acid.

(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 90 (1951).

(7) The absence of infrared absorption in the 5.75 μ region testifies to the absence of the starting material in the product mixture.

trum compared with that of the starting material II shows the expected shift toward longer wave lengths.

The demonstration that activation could overcome the inhibition due to steric interference led us to investigate activated 5-acetonyl-6-phenylphenanthridinium salts (V–VII). The requisite 6-arylphenanthridines are readily prepared from 2-aminobiphenyl by the cyclization[9] of suitable 2-phenylanilides. The formation of the quaternary salts (V–VII) proved slow even at the boiling point of acetone, and a considerable portion of the phenanthridine was converted to the hydrobromide. Separation of the desired quaternary salt from the hydrobromide proved difficult.

Once pure samples of the 5-acetonylphanthridinium salts were prepared, cyclization in hydrochloric acid afforded 55–70% of the expected 11-methyldibenzo[a,c]phenanthridizinium salts (X–XII). In every case the cyclized products gave evidence of increased conjugation by an ultraviolet absorption shift toward the visible region.

Three new phenanthridines were prepared. All three, the 6-(2-naphthyl)-, the 6-(2,3-dimethoxyphenyl)-, and the 6-(3,4,5-trimethoxyphenyl) gave unsatisfactory results in the quaternization attempts.

EXPERIMENTAL[10]

N-(3-Methoxybenzoyl)homopiperonylamine.[11] To 13.85 g. of hompiperonylamine hydrochloride[12] in 250 ml. of ice-cold 3% sodium hydroxide solution, 12.8 g. of 3-methoxybenzoyl chloride was added dropwise with stirring. After addition was complete (1 hr.), stirring was continued for three more hours at ice-bath temperature. The solids were collected and added to a mixture of 2% sodium hydroxide and ether. The layers were separated and the basic layer extracted with ether. The combined ether layers were extracted once with *N* hydrochloric acid and then concentrated and cooled, yielding 17.4 g. (85%) of colorless needles, m.p. 73–76°. The analytical sample was obtained by crystallization from ethanol, m.p. 74.5–76°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.40; H, 5.79; N, 4.94.

1-(3-Methoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline.[11] A mixture containing 11.8 g. of *N*-(3-methoxybenzoyl)homopiperonylamine, 80 ml. of anhydrous toluene and 30 ml. of phosphorus oxychloride was refluxed for 2.5 hr. When the reaction mixture was cooled in ice, two layers formed, and addition of petroleum ether initiated crystallization of the entire lower layer. The mixture was cooled in ice for 4 hr., the mother liquor was decanted, and the residue was dissolved in warm ethanol. The ethanol solution was made alkaline by addition of ethanolic potassium hydroxide, and the mixture was poured on 300 g. of crushed ice. The solid was collected and dried, yielding 10.6 g. (95%) of crude product, m.p. 157–161.5°. Recrystallization from benzene-petroleum ether yielded 9.85 g. (89%) of colorless crystals, m.p. 158.5–161.5°. The analytical sample melted at 160.5–161.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.92; H, 5.55; N, 5.18.

1-(3-Methoxyphenyl)-6,7-methylenedioxyisoquinoline. Three g. of 1-(3-methoxyphenyl)-3,4-dihydroisoquinoline was mixed with 0.3 g. of 10% palladium charcoal in a large test tube. A stream of dry nitrogen gas was directed on the surface of the mixture while the test tube was slowly lowered into a metal bath at 175–185°. When evolution of gas had almost ceased (30 min.) the dark residue was alternately extracted with 10% hydrochloric acid and with benzene until all the organic matter had dissolved. The combined benzene layers were extracted with 10% hydrochloric acid and filtered acid extracts made basic. The mixture was cooled for 3 hr. and the aqueous solution decanted. The light tan residue was crystallized from benzene-hexane as colorless prisms, yield 1.4 g. (47%), m.p. 98–101°. The analytical sample melted at 100–101°.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.44; H, 4.86; N, 5.29.

1-(3-Methoxyphenyl)-2-acetonyl-6,7-methylenedioxyisoquinolinium bromide (II). A solution containing 0.95 g. of 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline, 2.0 g. of bromoacetone, and 10 ml. of anhydrous reagent grade acetone was refluxed until formation of quaternary salt caused severe bumping. The mixture was allowed to stand for 2 days and the precipitated salt was collected and washed with dry acetone. A second crop was obtained by addition of ethyl acetate to the combined and concentrated filtrate and washings. The total yield of light yellow powder, m.p. 223–226° was 1.35 g. (95%). The analytical sample was crystallized from methanol-ethyl acetate, m.p. 224–226.5°.

Anal. Calcd. for $C_{20}H_{18}BrNO_4$: C, 57.70; H, 4.36; N, 3.36. Found: C, 57.62; H, 4.47; N, 3.52.

The *picrate* crystallized from ethanol as yellow crystals, m.p. 197–198.5°.

Anal. Calcd. for $C_{26}H_{20}N_4O_{11}$: C, 55.32; H, 3.57; N, 9.93. Found: C, 55.43; H, 3.80; N, 10.05.

2,3-Methylenedioxy-12-methoxy-9-methylbenzo[a]phenanthridizinium perchlorate (IX). A solution of 1.31 g. of the acetonyl derivative II in 15 ml. of concentrated hydrochloric acid was refluxed for 5.5 hr. The acid was removed *in vacuo* and the residue dissolved in hot water. Addition of 72% perchloric acid brought about the precipitation of an orange solid which, when crystallized from methanol, afforded 0.90 g. (69%) of crude product, m.p. 243–267°. This product showed no infrared absorption in the 5.75 μ region. Recrystallized three times from methanol and twice from acetone, the product was obtained as soft yellow-orange needles, m.p. 269–272°, λ_{max} (log ϵ), 226 (4.47), 245 (4.57), 284 (4.41), 403 (4.22) and 424 mμ (4.44); λ_{min}, 232 (4.39), 260 (4.35), 343 (3.43), and 409 mμ (4.20).

Anal. Calcd. for $C_{20}H_{16}ClNO_7$: C, 57.49; H, 3.86; N, 3.35. Found[13]: C, 57.51; H, 4.27; N, 3.47.

5-Acetonyl-6-(3-methoxyphenyl)phenanthridinium bromide (V). A solution containing 5.0 g. of 6-(3-methoxyphenyl)-phenanthridine,[14] 10 g. of bromoacetone, and 25 ml. of dry reagent grade acetone was refluxed on the steam bath for 60 hr., and the precipitated salt collected and washed with dry acetone. The combined filtrate and washings were concen-

(8) The possibility that our pure product is the 10-methoxy, formed by cyclization *ortho* to the methoxyl group has been excluded solely on the basis of analogy, *cf.*, C. K. Bradsher, F. C. Brown and P. H. Leake, *J. Am. Chem. Soc.*, **79**, 1471 (1957).

(9) *Cf.* R. S. Rheobald and K. Schofield, *Chem. Revs.*, **46**, 171 (1950).

(10) Except as noted all analyses are by Micro-Tech Laboratories, Skokie, Ill. The abbreviation s.t. is used to indicate melting points taken in a sealed capillary, and unless otherwise indicated all melting points are uncorrected.

(11) *Cf.*, W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5555 (1951).

(12) M. Erne and E. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(13) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(14) P. Mamalis and V. Petrow, *J. Chem. Soc.*, 703 (1950).

trated and refluxed for 6.5 days, with occasional interruptions for isolation of the insoluble quaternary salt. The total yield was 4.0 g. (54%), m.p. 195–205°. After recrystallization from ethanol, and from methanol–ethyl acetate, an analytical sample was obtained as a light yellow hygroscopic powder, m.p. 208–209°. The sample was dried to constant weight at 100° before analysis.

Anal. Calcd. for $C_{23}H_{20}BrNO_2$: C, 65.41; H, 4.77; N, 3.32. Found: C, 65.22; H, 4.83; N, 3.45.

The *picrate* crystallized from ethanol as yellow crystals, m.p. 215–217°.

Anal. Calcd. for $C_{29}H_{22}N_4O_9$: C, 61.05; H, 3.89; N, 9.82. Found: C, 61.17; H, 3.91; N, 10.00.

14-Methoxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (X). A solution containing 1.5 g. of 5-acetonyl-6-(3-methoxyphenyl)phenanthridinium bromide (V), m.p. 202–205°, in 15 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The acid was evaporated *in vacuo* and the residue dissolved in hot distilled water. Addition of perchloric acid to the hot aqueous solution afforded a yellow-orange precipitate that was crystallized first from acetone-ethanol and then from methanol as yellow needles, m.p. 263–266°, yield 0.82 g. (55%).

The analytical sample, recrystallized from methanol, exhibited a very bright green fluorescence, m.p. 264.5–266°, λ_{max} (log ϵ), 228 (4.36), 257 (4.57), 292 (4.52) and 430 mμ (4.07); λ_{min}, 225 (4.35), 231 (4.35), 282 (4.46) and 355 mμ (3.58).

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.17; H, 4.28; N, 3.31. Found[13]: C, 64.65; H, 4.22; N, 3.31.

5-Acetonyl-6-(3,4-dimethoxyphenyl)phenanthridinium bromide (VI). The quaternization of 2.5 g. of 6-(3,4-dimethoxyphenyl)phenanthridine[14] was carried out as in the case of the 3-methoxy analog. The total yield was 1.30 g. (35%) of soft yellow crystals, m.p. 229.5–231.5°. After several recrystallizations from ethanol the analytical sample, m.p. 232–235° was apparently obtained as a hydrate.

Anal. Calcd. for $C_{24}H_{22}BrNO_3 \cdot H_2O$: C, 61.28; H, 5.14; N, 2.98. Found[13]: C, 61.69; H, 5.37; N, 2.93.

13,14-Dimethoxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (XI). The cyclization of 1.25 g. of the acetonylphenanthridinium derivative VI was carried out as in the case of the analog V. The product, isolated as the perchlorate, crystallized from acetonitrile–ethyl acetate as yellow needles, m.p. 314–316°, dec. (s.t., corr.). The analytical sample was recrystallized from methanol, m.p. 319–321°, dec. (s.t., corr.), λ_{max} (log ϵ), 229 (4.45), 256 (4.57), 292 (4.59) and 414 mμ (4.19); λ_{min}, 223 (4.39), 239 (4.41), 266 (4.46) and 323 mμ (3.72).

Anal. Calcd. for $C_{24}H_{20}ClNO_6$: C, 63.51; H, 4.44; N, 3.09. Found[13]: C, 63.11; H, 4.42; N, 3.21.

5-Acetonyl-6-(3,4-methylenedioxyphenyl)phenanthridinium salts (VII). The quaternization of 2.0 g. of 6-(3,4-methylenedioxyphenyl)phenanthridine[14] with bromoacetone was carried out in the usual way. A total of 1.55 g. (50%) of crude bromide decomposing at about 240° (s.t.) was obtained. For analysis the bromide was converted to the *perchlorate* which formed yellow needles from methanol, m.p. 293–295.5° with previous shrinking and decomposition at 288° (s.t., corr.).

Anal. Calcd. for $C_{23}H_{18}ClNO_7$: C, 60.60; H, 3.98; N, 3.07. Found: C, 60.41; H, 4.13; N, 3.15.

13,14-Methylenedioxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (XII). The cyclization of 1.45 g. of the crude bromide VII was carried out in the usual way and the perchlorate crystallized from methanol as a brilliant orange solid, m.p. 297°, dec. (s.t., corr.) yield 0.7 g. (56%).

The analytical sample was crystallized from dimethylformamide-ether as a yellow-brown powder, m.p. 304°, dec. (s.t., corr.). Best results were obtained when the sample was not heated in the presence of dimethylformamide, λ_{max} 228, 258, 284, and 415 mμ; λ_{min} 239, 266, and 321 mμ.

Anal. Calcd. for $C_{23}H_{16}ClNO_6$: C, 63.09; H, 3.68; N, 3.20. Found[13]: C, 63.02; H, 3.64; N, 3.42.

2'-Phenyl-2-naphthanilide.[15] A stirred suspension of 19.8 g. of 2-naphthoic acid in 100 ml. of anhydrous benzene was refluxed while 25 ml. of thionyl chloride was added dropwise over a period of 15 min. The reaction mixture was refluxed for 6 hr., and the benzene and excess thionyl chloride were removed *in vacuo*. The crude 2-naphthoyl chloride was added cautiously to a cooled solution of 19.5 g. of 2-aminobiphenyl in 40 ml. of anhydrous pyridine. The mixture was heated on the steam bath for 1 hr. and while still hot poured into a mixture containing ice and 6*N* hydrochloric acid. The oil which formed crystallized readily and was collected and recrystallized from ethanol (Norit) to give 32.4 g. (87%) of product, m.p. 126.5–130°. The analytical sample crystallized from ethanol as colorless needles, m.p. 129.5–130.5°.

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found[13]: C, 85.16; H, 5.39; N, 4.49.

6-(2-Naphthyl)phenanthridine.[15] A solution of 20 g. of 2'-phenyl-2-naphthanilide in 40 ml. of phosphorus oxychloride was refluxed for 70 min. and the excess phosphorus oxychloride was removed *in vacuo*. The residue was heated on the steam bath with 50 ml. of water until a yellow solid was produced. The water was removed and the solid dissolved in 150 ml. of methanol, and methanolic potassium hydroxide solution added until the solution was alkaline. This solution was poured into 500 ml. of water and allowed to stand overnight. The precipitate was collected and washed, and then recrystallized from methanol, m.p. 156.5–159.5°, yield 11.0 g. (58%). The analytical sample consisted of colorless needles, m.p. 158–159.5°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95. Found[13]: C, 90.35; H, 4.63.

2,3-Dimethoxy-2'-phenylbenzanilide was prepared from 18.2 g. of 2,3-dimethoxybenzoic acid[16] as in the preparation of the 2'-phenyl-2-naphthanilide. The product was crystallized from ethanol, m.p. 131.5–134°, yield 29.6 g. (89%). The analytical sample formed colorless needles from ethanol, m.p. 133–134°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found[13]: C, 75.87; H, 5.74; N, 4.40.

6-(2,3-Dimethoxyphenyl)phenanthridine. A solution of 20 g. of 2,3-dimethoxy-2-phenylbenzanilide and 25 ml. of phosphorus oxychloride in 50 ml. of nitrobenzene was refluxed for 2.5 hr. Then the mixture was poured into a flask containing ice and an excess of 20% sodium hydroxide solution. The resulting mixture was steam distilled to remove the nitrobenzene. Recrystallization of the residue from ethanol gave 17.4 g. (92%) of almost colorless crystals, m.p. 130–133°. The analytical sample was prepared by recrystallization from ethanol, m.p. 132.5–134°.

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found[13]: C, 79.84; H, 5.31; N, 4.40.

3,4,5-Trimethoxy-2'-phenylbenzanilide was prepared from 21.2 g. of 3,4,5-trimethoxybenzoic acid essentially as the other phenylbenzanilides were prepared. The product was crystallized from ethanol, m.p. 119–120°, yield 27.3 g. (75%). The analytical sample melted at 120–120.5°.

Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82. Found[13]: C, 72.83; H, 5.42.

6-(3,4,5-Trimethoxyphenyl)phenanthridine was prepared from 22.2 g. of 3,4,5-trimethoxy-2'-phenylbenzanilide essentially as in the case of 6-(2,3-dimethoxyphenyl)phenanthridine. The product was crystallized from ethanol-water as colorless needles, m.p. 124–125°, yield 16.6 g. (79%). The analytical sample was recrystallized from ethanol, m.p. 124.5–125°.

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55. Found[13]: C, 76.74; H, 5.61.

DURHAM, N. C.

(15) *Cf.*, E. Ritchie, *J. Proc. Roy. Soc., N. S. Wales*, **78**, 147 (1944).

(16) *Cf.*, R. L. Shriner and E. C. Kleiderer, *Org. Syntheses*, Coll. Vol. II, 538 (1943).

[CONTRIBUTION OF THE RESEARCH LABORATORY OF THE DIAMOND ALKALI CO.]

Low Temperature Amination of Aromatic Polyhalides[1]

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The reaction of metal amides with aromatic polyhalides in liquid ammonia was used for the preparation of halogenated aromatic amines. The position of the introduction of the amino group is in accord with the formation of the benzyne intermediate, and with the orienting influence of a substituent on the benzyne intermediate. The conditions for the amination of 1,2,4-trichlorobenzene were studied and it was found that lithium amide produces 3,4-dichloroaniline in 62% yield. The low-temperature amination reactions were demonstrated to serve as a method of separation and purification of mixtures of aromatic halides. When 1,2,4-tribromobenzene was treated with sodium amide in liquid ammonia, 1,3,5-tribromobenzene was one of the products.

The amination of aryl halides with metal amides in liquid ammonia was first reported by Bergstrom *et al.*[2] From halobenzenes they isolated aniline, as well as diphenyl- and triphenylamine. They also studied the order of ease of replacement of the halogen atom in phenyl dihalides of the type p-C_6H_4XY without actually isolating any of the organic product(s). Such amination reactions were recently extended by Roberts *et al.*[3] who also prepared substituted anilines from substituted monohalobenzenes. With the exception of the preparation of fluoroaniline from p-bromofluorobenzene[3] (F is not replaced by NH_3 at $-33°$), the literature is void of reports of the preparation of haloaromatic amines by the low temperature amination of polyhalides. This paper deals with such reactions. The orienting influence of substituents in such aminations was studied as well as some reaction conditions for the preparation of certain amines in high yields.

The reactants, reaction conditions, and products are listed in Table I.

EXPERIMENTAL

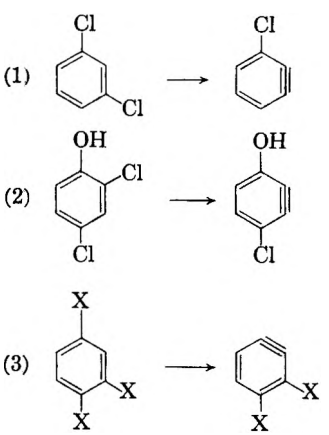
The halide in liquid ammonia was treated with the metal amide and the suspension stirred for a period of time as indicated in Table I. After evaporation of ammonia, the residue was treated with water and a representative sample analyzed for halide-ion concentration. The organic portion was taken into ether, and hydrogen chloride was passed through the dry ether solution. The precipitated amine hydrochloride was filtered and the amine liberated with base. The neutral and the amine portions were separated and distilled. The distillates were crystallized from appropriate solvents. No attempt was made to isolate the di- or triarylamines or the diamines formed in the reactions. The identity of the products was established by boiling points, melting points, conversion to solid N-acetyl and/or benzoyl derivatives, and by comparison of values listed in the literature. In cases of obvious discrepancies, at least two derivatives were made and the values compared with authentic samples.

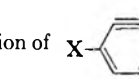
DISCUSSION

Orientation in aminations of polyhalobenzenes. Roberts *et al.*[4] established that the amination of halobenzenes in liquid ammonia involves an elimination-addition mechanism *via* a "benzyne" intermediate I. The acidities of the benzenoid hydrogens seem to be determined by the inductive effect of substituents.[5] The formation of the benzyne intermediate by the elimination of hydrogen halide is thus a function of such acidities.[3]


I

In the present study the isolated haloanilines have the structure in accord with the addition of NH_2^- to the preferentially formed benzyne intermediate. Thus, in cases where more than one benzyne is possible, the predictions by Roberts[3] were realized, the benzynes formed being those indicated in Equations (1)–(3). In the last case there should



be an equal possibility for the formation of  but no amine derived from such a benzyne was found. Because of ortho substituents, the other halides listed in Table I were capable of the formation of only one benzyne intermediate.

The direction of the addition of the NH_2^- to an asymmetrically substituted benzyne intermediate was predicted[3] to take place so as to provide the most favorable location of the negative charge with respect to the inductive effect of the substituent on the benzyne. Because of the inductive

(1) Presented at the 134th National Meeting of the American Chemical Society, Chicago, September 1958.

(2) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

(3) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenov, *J. Am. Chem. Soc.*, **78**, 611 (1956).

(4) J. D. Roberts, D. A. Semenov, H. E. Simmons, and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(5) G. E. Hall, R. Piccolini and J. D. Roberts, **77**, 4540 (1950).

TABLE I

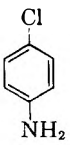
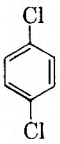
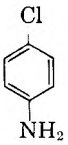
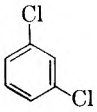
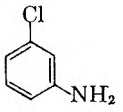
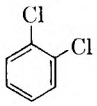
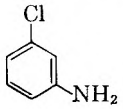
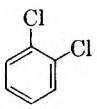
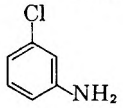
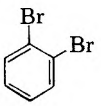
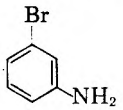
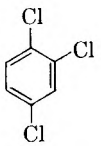
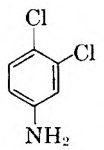
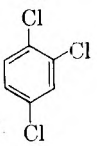
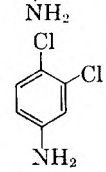
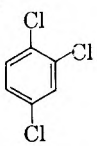
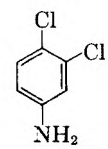
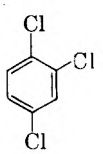
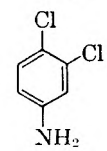
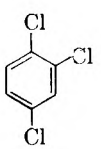
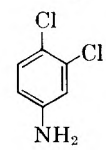
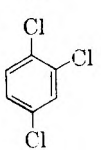
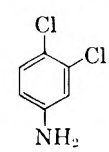
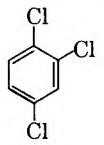
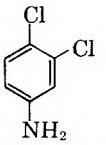
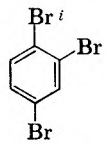
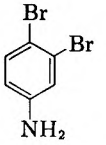
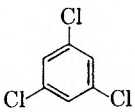
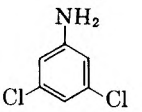
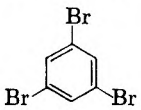
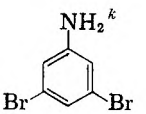
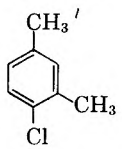
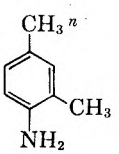
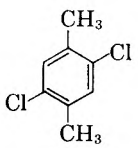
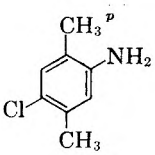
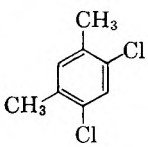
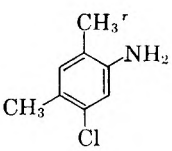
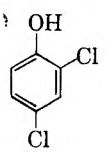
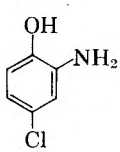
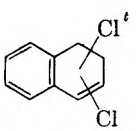
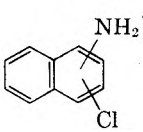
Experiment	Reactant	Mol.	MNH_2	Mol.	Reaction Time, Hr.	% X^{-w} Found	Halide, % Recovered	Product	Yield %	Yield Total[x] Acctd. for
1		0.5	Na	0.6	18	73	8		14	22
2		0.5	Li	0.5	20	41	39		17	56
3		0.5	Na	0.75	19	65	48		28	76
4		0.5	Na	0.75	16	54	42		26[a]	68
5		0.5	Li	0.75	5	36	51		18[a]	69
6		0.03	Na	0.06	3	129	20[b]		35[c]	55
7		0.5	Na	1.1	22	127	10		27	37
8		0.5	Na[d]	0.5	5	50	52		20	72
9		0.5	Na[d]	1.5	5	146	5		25	30
10		0.5	Na[e]	1.0	8	98	24		37[f]	61
11		0.5	Li	1.0[g]	20	94	6		62[h]	68
12		0.5	K	0.6	16	110	45		20	65

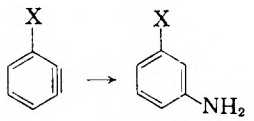
TABLE I (*Continued*)

Experiment	Reactant	Mol.	MNH_2	Mol.	Reaction Time, Hr.	% X^{-w} Found	Halide, % Recovered	Product	Yield %	Yield Total[z] Acctd. for
13		0.3	Ba	0.3	18	58	43		22	65
14		0.3	Na	0.6	18	86	33[j]		24	57
15		0.5	Li	1.0	18	83	13		43	56
16		0.05	Na	0.1	3	100	20		45	65
17		0.4	Na	0.9	2	74	2[m]		14	16
18		0.1	K[o]	0.2	16	100	34		55	89
19		0.8	Na	1.6	18	71	16		54	70
20		0.3	Li[s]	0.6	2	...	79		6	85
21		0.5	Na	0.7	18	52	61[u]		21	82

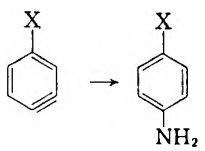
[a] *o*-Chloroaniline was also present as evidenced by vapor chromatography. [b] Vapor chromatography showed it to be identical with starting halide. [c] No *m*-bromoaniline was found. [d] Room temperature and pressure. [e] Cooled to −50°. [f] When the reaction was cooled to −70° the yield was only 13%. [g] When 0.6 mole of $LiNH_2$ was used, the yield was 60%. [h] When the reaction was cooled to −50° the yield was 66%. [i] The halide was purchased from the Eastman Kodak Co. and melted at 40–43°. (Eastman Organic Chemicals, List No. 40, p. 193, P. 6466, lists m.p. of 33–38°.) The literature lists its m.p. 43–45°. A fractional crystallization from petroleum ether (b.p. 30–60°) gave six fractions melting in the range of 40–45°. Vapor chromatography showed only one band, and its infrared spectrum showed only traces of 1,3,5-tribromobenzene. [j] The neutral "recovered" fraction was 1,3,5-tribromobenzene, m.p. 121–122°. The structure was confirmed by elementary and spectroscopic analyses. Vapor chromatography showed the absence of the starting halide (1,2,4-tribromobenzene). [k] M.p. 59–60°). Anal. Calcd. for $C_6H_3Br_2N$: C, 28.7; H, 2.0. Found: C, 29.5; H, 2.3. *N*-acetyl derivative m.p. 230–231° (lit. 231°). [l] The sample contained 0.1 mole of 2-chloro-*m*-xylene. [m] All of the 2,6-dimethylchlorobenzene was recovered. Spectroscopic analysis showed it to be 97% pure. [n] Since the mother liquor was not vapor chromatographed, the presence of 3,5-dimethylaniline is not excluded. [o] Using $NaNH_2$ the yield of amine was 47% (80% of Cl^- was found) and with $LiNH_2$ no amine was produced (2% of Cl^- was found). [p] The m.p. was 91–92°. The literature lists only the b.p. of the amine and the m.p. of 176°

for the *N*-acetyl derivative. Since the m.p. found was 182°, the structure of the amine was established by diazotization and conversion to 2,5-dichloro-*p*-xylene, m.p. 67–68°, reported m.p. 68–70°. [r] The structure was also confirmed by diazotization and conversion to 2,4-dichloro-*m*-xylene, m.p. 67–68°. [s] Using $NaNH_2$, only black tar was isolated. [t] Commercial (Eastman Kodak Co.) dichloronaphthalene was used which was a mixture of 1,4:1,5:1,8 and 1,2 isomers of unknown ratio. The m.p. of this mixture was 43–45°. [u] The m.p. was 66–67°. The reported m.p. for 1,4-dichloronaphthalene is 67–68°. From vapor phase chromatographic analysis this was the major component of the starting mixture. [v] The chloronaphthylamines boiled at 123–126° at 2 mm. About 30% of this liquid crystallized, m.p. 88–91°, (*N*-acetyl derivative, m.p. 192–193°) and was identified as 1-amino-4-chloronaphthalene. The liquid portion formed a *N*-acetyl derivative, m.p. 142–145°. No definite product was isolated in attempts to replace the amino group with chlorine *via* the diazonium salt. [w] Based on the amount of starting polyhalide. [x] Higher amination products and/or tars by difference.

effect, Cl and Br are electron attracting groups and thus meta directing in a 3-substituted benzyne and para directing in a 4-substituted benzyne. On the other hand, the methyl

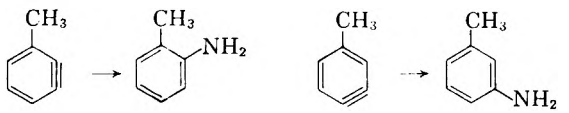


3-substituted benzyne

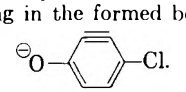


4-substituted benzyne

group is an electron donating group and ortho directing in a 3-substituted benzyne and meta directing in a 4-substituted benzyne.



In all of the cases studied, the amino group appeared in the predicted position. However, 4-chloro-*m*-xylene (Exp. 17) yielded 4-amino-*m*-xylene and there was no evidence that the equally predictable 5-amino-*m*-xylene was also formed. Similarly, 1,3,5-trichlorobenzene (Exp. 15) yielded 3,5-dichloroaniline and no 2,4-dichloroaniline was found. In the amination of 2,4-dichlorophenol (Exp. 20), the formation of 2-amino-4-chlorophenol indicates that the phenoxide ion is ortho directing in the formed benzyne intermediate,



In three cases the postulation of a benzyne intermediate best explains the experimental findings. The major product of amination of *o*-dichlorobenzene (Exp. 4) and *o*-dibromobenzene (Exp. 6) was *m*-chloroaniline and *m*-bromoaniline, respectively. The amination of a mixture of 4-chloro-*m*-xylene and 2-chloro-*m*-xylene (Exp. 17) yielded only the product from the isomer capable of formation of a benzyne intermediate. Since in most cases the amino group appeared in the position previously occupied by the halogen atom, we do not discount the possibility that direct substitution may have also taken place.[6,7] Consequently the failure of 2-chloro-*m*-xylene to react might be explained by the shielding of the chlorine by the two methyl groups.

The rearrangement of 1,2,4-tribromobenzene to 1,3,5-tribromobenzene (Exp. 14) was unexpected. To test the possibility that other *o*-dibromo-substituted aromatic compounds are subject to such a rearrangement, *o*-dibromobenzene was treated with sodium amide in liquid ammonia (Exp. 6). However, there was no evidence for the presence of *m*-dibromobenzene in the recovered halide. At this time we are not able to propose a reasonable and consistent mechanism of reaction for this novel rearrangement.

(6) J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.* **78**, 6265 (1956).

(7) F. Scardiglia and J. D. Roberts, *J. Org. Chem.*, **23**, 629 (1958).

The yields of amines. The conventional preparation of amines is a copper catalyzed high temperature amination or the reduction of nitro compounds. It was hoped that substituted aromatic amines could be prepared in satisfactory yields by low temperature amination. Of special interest were amines which cannot be conveniently secured by the conventional routes.

In the amination of polyhalides (Table I) the yields of primary amines depended on the extent of reaction. When amination did not proceed, the starting halide was recovered and there was no, or a low, concentration of halide ions. Furthermore, secondary reaction products could have been also responsible for low yields of primary amines. In such cases higher reaction products, di- or triarylamines, diamines, and tars were formed, and analyses showed a high concentration of halide ions.

The amination of 1,2,4-trichlorobenzene was studied in greater detail because of the ready availability of the halide from benzene hexachloride manufacture. The most active of the metal amides, potassium amide (Exp. 12), produced 3,4-dichloroaniline in only 20% yield. The chloride ion concentration was 110% (based on the molar quantity of the organic halide) indicative of more extensive amination. The least active lithium amide (Exp. 11) gave the highest yield (62%) of amine even in the presence of twice the molar ratio of amide to the halide. With sodium amide (Exp. 7 to 10) the yields were generally below that of $LiNH_2$. Some improvements were realized (Exp. 10) by conducting the experiments with sodium amide at −50° and a shorter reaction time. More of the starting halide was thus recovered and fewer chloride ions were found even at an amide-halide molar ratio of two. A high amide concentration (Exp. 9) produced a high chloride ion concentration, and little of the starting halide was recovered. On the other hand, an equimolar ratio of amide to halide (Exp. 8) decreased the chloride ion concentration and the yield of amine, but increased the amount of recovered halide, even with reaction at room temperature. Use of the sparingly soluble barium amide (Exp. 13) offered no advantage over the use of sodium amide.

The amination reactions of 2,5-dichloro-*p*-xylene (Exp. 18) clearly demonstrated that the yield depends on the activity of metal amide. No amination was observed when the relatively inactive lithium amide was used. Sodium amide produced the amine in 47% yield, and the yield was 55% when potassium amide was used. The produced chloride ion concentration also increased with the increase in the activity of the metal amide.

The low temperature amination provides a simple method for the purification of certain aromatic halides. The chlorination of naphthalene produces a mixture of dichloronaphthalenes which is difficult to separate. The amination is sufficiently selective to enable the recovery of pure 1,4-dichloronaphthalene (Exp. 21). Similarly, the monochlorination of *m*-xylene yields a mixture of 2- and 4-chloro-*m*-xylenes, b.p. 185–187 and 186–187°, respectively, which cannot be conveniently separated by distillation. From the amination reaction (Exp. 17), essentially pure 2-chloro-*m*-xylene was recovered.

PAINESVILLE, OHIO

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

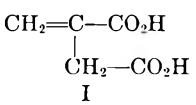
Polymerization Reactions of Itaconic Acid and Some of Its Derivatives

C. S. MARVEL AND THOMAS H. SHEPHERD[1]

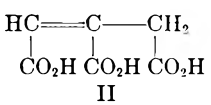
Received September 24, 1958

The homopolymerization of itaconic acid and dimethyl, diethyl, and di-*n*-butyl itaconate has been carried out. Copolymers of itaconic acid with acrylic acid, aconitic acid, and butadiene have been prepared, as well as copolymers of dimethyl itaconate with butadiene. Polydimethyl itaconate has been reduced to poly-2-hydroxyethylallyl alcohol. The conversion of a butadiene–dimethyl itaconate copolymer to a butadiene-2-hydroxyethylallyl alcohol copolymer has also been effected. Bis(*N*,*N*-dimethyl)itaconamide and 2-hydroxyethylallyl alcohol have been prepared; the conversion of the former to bis(*N*,*N*-dimethyl)-mesaconamide has been effected.

It has been reported in the literature[2] that itaconic acid (I) does not homopolymerize, although it has been found to enter into copolymerization reactions in numerous instances.[3–8] Since itaconic esters do homopolymerize to materials of fairly high molecular weight,[9–11] the failure to bring about polymerization of the acid appeared to be anomalous. When an aqueous solution of itaconic acid was treated with catalytic amounts of potassium



I



II

persulfate, no polymerization was effected. Polymerization also failed to proceed in alkaline solution. Itaconic acid did, however, undergo homopolymerization in solution in 0.5*N* hydrochloric acid using persulfate initiation. The polymer was produced in 35 per cent conversion in 68 hours at 50°.

The polyitaconic acid is extremely water soluble, and is soluble in methanol. It was found to be insoluble in other common organic solvents, including ethanol. The polymer, as obtained by freeze drying the aqueous solution, contained water of hydration which amounted to about one mole of water for each itaconic acid unit. When an attempt was made to dry the acid at 100° and 0.1 mm. pressure, this water of hydration was lost and anhydride formation occurred to some extent as indicated by a high carbon analysis. Viscosity determinations on the polyacid were not too useful in estimating its molecular size; hence the acid was esterified with ethanol to give an organic solvent–soluble material which gave viscosity data indicating a molecular weight of the order of about 5×10^4 if we estimate the molecular weight using constants determined on the related polymethyl methacrylate.[12]

The copolymerization of itaconic acid and acrylic acid was carried out in aqueous solution at 26°. Potassium persulfate initiation was used, and the polymerization required about seven days to reach 90 per cent conversion. A greater amount of itaconic acid than was initially soluble in the solution system was used, and this excess slowly dissolved as polymerization proceeded. Thus, an essentially constant concentration of itaconic acid was present in the reacting phase during the polymerization. The itaconic acid–acrylic acid copolymer is very hard and brittle, but forms a tough, flexible transparent film when a water solution of the polymer is evaporated. The copolymer is soluble in water as well as in methanol and ethanol. Analytical difficulties were encountered with this polymer because it, too, held water of hydration and further drying caused anhydride formation. It is much higher in molecular weight than the homopolymer of acrylic acid on the basis of the viscosity determined on the partial ester. The physical properties (tensile, etc.) of the polymer indicated the same thing. An estimate of the composition of the copolymer was made by determining the amount of unreacted itaconic acid in a standard polymerization. The evidence indicates that there are about two moles of itaconic acid for every three moles of acrylic acid in the

(1) This is a partial report of work done under contract with three Utilization Research and Development Divisions, Agricultural Research Service, U. S. Department of Agriculture, and authorized by the Research and Marketing Act. The contract was supervised by Dr. J. C. Cowan of the Northern Division. This paper is based on portions of a thesis submitted by Thomas H. Shepherd to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of doctor of philosophy.

(2) C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley and Sons, Inc., New York (1952), p. 308.

(3) R. G. Fordyce and G. E. Ham, *J. Am. Chem. Soc.*, **69**, 695 (1947).

(4) J. Exner and Miloslav Bohdanecky, *Chem. listy*, **48**, 483 (1954).

(5) J. B. Dickey and H. W. Coover, Jr., U.S. Patent **2,533,207** (Dec. 12, 1950).

(6) G. F. D'Alelio, U.S. Patent **2,531,408** (Nov. 28, 1950).

(7) G. Pitzl, U.S. Patent **2,570,478** (Oct. 9, 1951).

(8) S. B. Lippincott and L. A. Mikeska, U.S. Patent **2,542,542** (Feb. 20, 1951).

(9) H. Stobbe and A. Lippold, *J. prakt. Chem.*, **90**, 336 (1914).

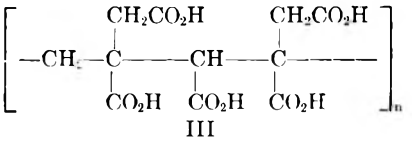
(10) E. Hope, Brit. Patent **264,550** (Oct. 26, 1925).

(11) L. W. Mixon and R. Watson, U.S. Patent **2,672,446** (March 16, 1954).

(12) P. J. Flory, *Principles of Polymer Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 312.

copolymer. For each molecule of acid there is one molecule of water of hydration.

Itaconic acid copolymerized with aconitic acid (II) in aqueous solution, yielding a polymer which is believed to have a regular structure (III), resulting from alternation of monomer units in the polymer chain. Analysis of the copolymer and



III

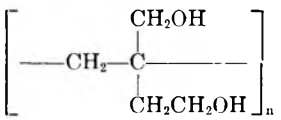
analysis of the acid mixture recovered from polymerization confirm the opinion that this alternating structure (III) is the correct one. This itaconic acid–aconitic acid copolymer is hard and brittle, and forms a rather weak transparent film. The copolymer is soluble in water and methanol, but not in ethanol. Inherent viscosity measurements on dilute solutions of the partially esterified polymer indicated a molecular weight of the order of 3×10^4 if calculated using the constants previously employed.[12]

Emulsion polymerization of a vinyl monomer is favored by water insolubility and oil solubility of the monomer.[13] Since itaconic acid is very water soluble and exhibits only insignificant oil solubility, its copolymerization with butadiene in an emulsion system is quite surprising. The recipe used was similar to that employed for the copolymerization of butadiene and acrylic acid.[14] When a 3:1 ratio of butadiene over itaconic acid was used, a polymer with 20 per cent incorporation of the acid was produced. This copolymer had an inherent viscosity of 1.4 in tetrahydrofuran solution. The polymer was completely soluble in tetrahydrofuran, but only partially soluble in benzene. The polymer dispersed in methanol and alkaline water. It was not soluble in water, but became tacky when moist.

Since it was desired to investigate the feasibility of preparing polyalcohols by reduction of polyesters, the homopolymerization of itaconic esters was investigated. Homopolymers of dimethyl, diethyl, and di-*n*-butyl itaconate were prepared. The use of emulsion systems in the polymerizations gave polymers of higher inherent viscosity than those reported in the literature, which were prepared in bulk systems.[11,15] The homopolymers are thermoplastic materials, forming clear melts at temperatures ranging from about 125° for polydimethyl itaconate and 85° for polydiethyl itaconate to about 50° for polydi-*n*-butyl itaconate. The latter polymer exhibits cold flow at room temperature, but shatters under a sudden impact. It is thought that the lower melting point, and observable cold flow of the polydi-*n*-butyl itaconate, is caused by internal plasticization by the butyl groups.

The failure of itaconic acid, and its esters, to homopolymerize to materials having molecular weights of the order of those found in the polyacrylates is attributed to the presence of allylic hydrogen atoms in the molecules. Such hydrogen atoms act as chain transfer agents according to Bartlett,[16,17] thus a situation where "self-modification" can occur exists in the polymerization of itaconic acid and its esters.

Polydimethyl itaconate was reduced to the poly-2-hydroxyethylallyl alcohol (IV) by treating it with



IV

lithium aluminum hydride in tetrahydrofuran solution. Microanalysis of the product indicated that reduction was about 97 per cent complete; however, a weak carbonyl band remained in the infrared spectrum. The poly-2-hydroxyethylallyl alcohol is soluble in a dioxane-water mixture, but was insoluble in all other solvents. When the polyalcohol was allowed to stand in water which was only slightly acidic (*p*H of 5), cross linking occurred. It is thought that these are ester cross links, resulting from transesterification reactions involving unchanged ester groups in the polymer. The polyalcohol is hard and brittle, but can be ground into a white powder.

Although a copolymerization of dimethyl itaconate with butadiene in an emulsion system has been reported in the literature,[18,19] a study of the copolymerization was made to determine conditions for the preparation of a copolymer containing desired amounts of the ester.

The copolymerization was carried out at 50° using persulfate initiation in an ORR soap emulsion. The composition of copolymers produced with high monomer conversion (100 per cent) approached that of the monomer charge. When the polymerization was stopped at about 60 per cent conversion, the resultant copolymer contained a larger proportion of dimethyl itaconate than was present in the monomer charge. This indicated that the butadiene radical adds to dimethyl itaconate at a faster rate than it adds to butadiene, since the addition of the dimethyl itaconate radical to dimethyl itaconate is relatively slow at 50°. The butadiene–dimethyl itaconate copolymers exhibit inherent

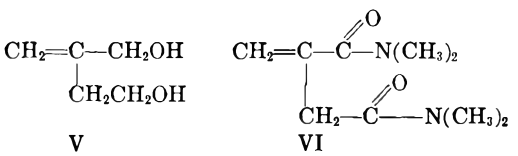
(13) W. D. Harkins, *J. Am. Chem. Soc.*, 69, 1428 (1947).
(14) C. S. Marvel, R. M. Potts, J. Economy, G. P. Scott, W. K. Taft, and B. G. Labbe, *Ind. Eng. Chem.*, 47, 2221 (1955).
(15) C. J. Knuth and P. F. Bruins, *Ind. Eng. Chem.*, 47, 572 (1955).
(16) P. D. Bartlett and K. Nozaki, *J. Polymer Sci.*, 3, 216 (1948).
(17) P. D. Bartlett and R. Altschul, *J. Am. Chem. Soc.*, 67, 816 (1945).
(18) G. F. D'Alelio, U.S. Patent 2,366,495 (Jan. 2, 1945).
(19) J. W. Meier, U.S. Patent 2,748,027 (May 29, 1956).

viscosities of about 2.3, and have typical elastomeric properties.

Butadiene–dimethyl itaconate copolymers were reduced to the alcohol copolymers in tetrahydrofuran solution with lithium aluminum hydride using a modification of a procedure previously described.[14] When a copolymer containing about 20 per cent of the ester was reduced, no carbonyl band appeared in the infrared spectrum of the product in 10 per cent chloroform solution. However, another spectrum obtained on the alcohol copolymer in 40 per cent chloroform solution revealed a weak carbonyl band. A comparison of absorption intensities in the infrared spectra of the reduced copolymer and the ester copolymer indicated that reduction was about 90 per cent complete. Thus the copolymer contains about one per cent unchanged dimethyl itaconate recurring units.

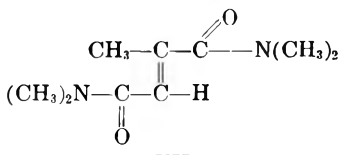
This copolymer, however, when dried free from solvent, failed to dissolve. This insolubility is not due to oxidative cross linking since the copolymer, after being saturated with antioxidant, only swelled in solvents after drying, but remained completely soluble if not completely dried. It is thought that the cross linking was due to transesterification reactions involving unchanged ester groups in the polymer.

In the course of the investigation, 2-hydroxyethylallyl alcohol (V) was prepared by the reduction of dimethyl itaconate with lithium aluminum hydride, and bis(*N*,*N*-dimethyl)itaconamide (VI) was prepared by treating itaconyl chloride with dimethylamine. Since neither of these compounds has been reported, their preparation is given in the experimental section.



V VI

In an attempt to cause homopolymerization of VI by treating it with sodium in liquid ammonia, a rearrangement occurred. The product was subsequently identified as bis(*N*,*N*-dimethyl)mesaconamide (VII)



VII

The elemental composition and molecular weight of VII were the same as that of VI. The rearrangement product exhibited a λ_{max} of 235 mμ with an extinction coefficient of 8700, while neither itaconamide, acrylamide nor bis(*N*,*N*-dimethyl)itaconamide showed an absorption maximum in the ultraviolet region. The nuclear magnetic resonance spectrum of VII had peaks corresponding to an olefinic hydrogen, an olefinic methyl group, and four *N*-methyl groups. The characteristic band for methylene hydrogens was absent.

Hydrolysis of VII with dilute sodium hydroxide yielded mesaconic acid after acidification of the hydrolyzate. This was identified by a mixed melting point with an authentic sample of mesaconic acid. Treatment of maleic acid and fumaric acid with base under the same conditions caused no isomerization of these acids, thus it is likely that no isomerization occurred in the hydrolysis of VII.

In the treatment of bis(*N*,*N*-dimethyl)itaconamide with sodium in liquid ammonia, 0.04 g. (0.0017 g.-atom) of sodium yielded 1.8 g. (0.01 mole) of the rearrangement product, indicating that a chain reaction occurred.

EXPERIMENTAL[20]

All polymerizations were carried out in 4-oz. screw-capped bottles sealed with Buna-N gaskets. Prior to sealing the bottles, air was removed by flushing with nitrogen, except when butadiene was employed as a comonomer. Butadiene was added in excess and allowed to boil away until the proper weight was reached, thus flushing air from the system.

Water employed in the polymerizations was distilled in an all-glass apparatus, and freed from air by heating it to boiling and bubbling nitrogen through the liquid until it cooled to room temperature. Reagents were added to the polymerization vessels in the order listed in the recipes. All liquid monomers were redistilled, and solid monomers were recrystallized to a constant melting point before use.

Inherent viscosities were determined on dilute solutions of the polymers in a modified Ostwald viscometer at 25 ± 0.2°.

Homopolymerization of itaconic acid. A solution of 20 g. of itaconic acid, 50 ml. of 0.5*N* hydrochloric acid, and 0.10 g. of potassium persulfate was allowed to stand at 50° for 68 hr. Some itaconic acid remained undissolved. The solution was then dripped slowly into acetone and polymer precipitated. The polymer was removed by filtration, redissolved in water, reprecipitated from acetone, and dried under diminished pressure. An analytical sample was freeze-dried from aqueous solution. Seven g. (35%) of a white powder was obtained.

Anal. Calcd. for $[(C_5H_6O_4)_5(H_2O)_4]_n$: C, 41.56; H, 5.30; for $(C_5H_6O_4)_n$: C, 46.16; H, 4.65. Found: C, 41.89; H, 5.32. When this polymer was further dried over phosphorus pentoxide at 100° and 0.1 mm. pressure, anhydride formation occurred as indicated by the analysis, C, 48.16; H, 4.73. This corresponds to about 30% anhydride–70% acid.

Results of the viscosity determination on dilute aqueous solution of the hydrated polymer are given in Figure 1.

Copolymerization of itaconic acid and acrylic acid. Six polymerization bottles were charged with 10 g. of itaconic acid, 50 ml. of water, 10 g. of redistilled acrylic acid, and 0.10 g. of potassium persulfate. The polymerization was allowed to proceed 8 days at 26°. Not all the itaconic acid was initially soluble in the system, but gradually dissolved as the polymerization proceeded. The viscous solutions were then triturated with acetone to precipitate the polymer. The poly-

(20) We are indebted to Mr. Jozsef Nemeth, Miss Claire Higham, Mrs. Maria Stingl, and Mrs. Ruby Ju of the Microanalytical Laboratory of the University of Illinois for the microanalyses, to Mr. James Brader and Mr. Paul McMahom, University of Illinois, for the infrared data, and to Mr. Jen Chiu of the University of Illinois for the ultraviolet analyses.

TABLE I

RESULTS OF COPOLYMERIZATION OF ITACONIC ACID AND ACONITIC ACID

No.	Itaconic Acid, G.	Aconitic Acid, G.	Initiator,[a] G.	Activator,[b] G.	Water, Ml.	Time, Days	Temp., °C.	Polymer, G.	Inherent[c] Viscosity
1	5.0	5.00	0.05		50.0	6	25	1.5	1.60
2	3.75	5.00	0.05		50.0	6	26	0.9	1.30
3	3.75	5.00	0.05		50.0	7	26	1.3	
4	3.75	5.00	0.05		50.0	8	26	1.5	
5	3.75	5.00	0.05		50.0	9	26	1.5	
6	3.75	5.00	0.05		50.0	10	26	1.4	
7	3.75	5.00	0.05		50.0	11	26	1.7	1.25
8	8.2	5.00	0.05		50.0	2	26	1.0	0.30
9	8.2	10.0	0.05		50.0	2	−5	1.5	0.28
10	7.5	10.0	0.05	0.0276	50.0	3	26		
11	7.5	10.0	0.05	0.0276	50.0	3	50	3.1	0.62
12	7.5	10.0	0.15	0.0276	25.0	4	26	7.0	0.24
13	7.5	10.0	0.05	0.0276	50.0	3	26	3.1	0.62
14	7.5	10.0	0.10	0.0276	50.0	3	26	3.6	0.55
15	7.5	10.0	0.15	0.0276	50.0	3	26	3.7	0.54
16	7.5	10.0	0.20	0.0276	50.0	3	26	3.7	0.56
17	7.5	10.0	0.10	0.0276	50.0	7	26	6.0	0.50
18	7.5	10.0	0.10	0.0552	50.0	7	26	6.1	0.40

[a] Ammonium persulfate. [b] Sodium sulfite.[21] [c] Determined on 0.25 g./100 ml. aqueous solutions.

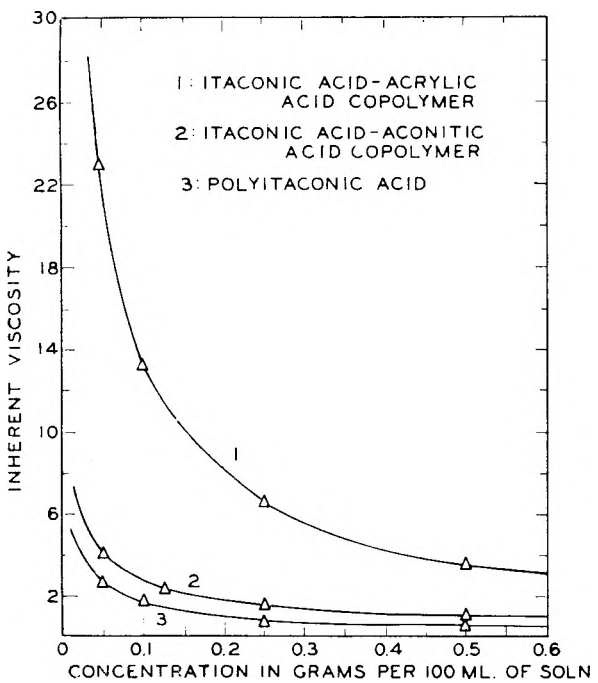


Fig. 1. Viscosity-concentration relationships for dilute aqueous solutions of polyacids

mer was redissolved in water and was reprecipitated by slowly adding the aqueous solution to 8 times its volume of acetone. The polymer was then dried to a constant weight under diminished pressure. An 88% conversion (105 g.) was realized. An analytical sample was freeze-dried from aqueous solution, and then dried at 78° under a pressure of 0.05 mm. Hg.

Anal. Found: C, 46.55; H, 5.53.

Results of inherent viscosity determinations on dilute aqueous solutions of this polymer are given in Figure 1. An attempt to carry out the above polymerization at 0° failed to yield any polymer.

A polymerization mixture containing 10 g. of itaconic acid, 45 ml. of water, 5 g. of acrylic acid, and 0.05 g. of potassium persulfate was allowed to stand 72 hr. at 25°. At this time some itaconic acid was still present as a solid phase. The contents of the bottle were slowly added to 1 l. of acetone, and the precipitated polymer was removed. One g. of hydroquinone was added to the acetone solution, and the solution was evaporated to dryness under vacuum to remove water and acrylic acid. The crystalline residue was then washed with a few milliliters of benzene to remove hydroquinone and acrylic acid. Itaconic acid (7.8 g., m.p. 146–161°) was recovered. The polymer was dried under diminished pressure and 3.9 g. of polymer was obtained. The inherent viscosity of a solution of 0.25 g. of polymer in 100 ml. of water was 3.1. A portion of the copolymer was reprecipitated, freeze-dried from aqueous solution, and dried under a pressure of 0.05 mm. Hg. On the basis of the polymer yield and the recovered itaconic acid this copolymer would be expected to contain 2 moles of itaconic acid for every 3 moles of acrylic acid. From previous experience with these polyacids, about one molecule of water for each molecule of acid would also be anticipated.

Anal. Calcd. for $[(C_5H_6O_4)_2(C_3H_4O_2)_3 5H_2O]_n$: C, 44.01; H, 6.50. Found: C, 44.39; H, 5.59.

Copolymerization of itaconic acid and aconitic acid. The bottles were charged with the recipes listed in Table I and the solutions were allowed to stand for the desired time at the desired temperature. The polymers were isolated by pouring the solutions into acetone to precipitate the polymers which were then dried under diminished pressure.

The product from polymerization No. 1 in Table I was purified by dissolving it in water and reprecipitating it from acetone. The polymer was then freeze-dried from aqueous solution.

Anal. Calcd. for itaconic acid ($C_5H_6O_4$): C, 46.16; H, 4.65; for aconitic acid ($C_6H_6O_6$): C, 41.39; H, 3.47; for $[(C_5H_6O_4)(C_6H_6O_6)]_n$: C, 43.72; H, 4.02. Found: C, 43.83; H, 4.43.

The results of inherent viscosity determinations on solutions of this polymer are plotted in Figure 1.

From the acetone used to precipitate polymer No. 7 (Table I), 6.12 g. of unchanged monomer was isolated. Two-tenths g. of this monomer mixture required 32.70 ml. of 0.1000*N* sodium hydroxide for neutralization to a phenolphthalein end point, for a neutralization equivalent of 61.2. This figure corresponds to a 50/50 molar composition of ita-

(21) R. G. R. Bacon, *Trans. Faraday Soc.*, **42**, 140(1946).

conic and aconitic acids. Carbon analysis also corroborated this composition of the recovered acids.

Anal. Calcd. for a 50/50 molar mixture of itaconic and aconitic acids: C, 43.43; H, 3.98. Found for mixture: C, 43.41; H, 4.11.

Neut. Equiv. Calcd. for 50/50 molar mixture: 61.5. Found: 61.2.

Esterification of polyitaconic acid and the itaconic acid–aconitic acid copolymer. The following procedure was used for the preparation of the ethyl ester of both polyitaconic acid and the itaconic acid–aconitic acid copolymer. The transesterification was necessary, since these polymers are insoluble in ethanol.

A 100-ml., three-necked flask was fitted with a dropping funnel and a 12 × 1/2 inch column packed with glass helices and fitted with a distillation head. In the flask were placed 1.5 g. of the polymer and 50 ml. of methanol. The solution was heated until distillation began. *p*-Toluenesulfonic acid (0.5 g.) was introduced, and ethanol was added until the distillation temperature reached 78°. The solution was then heated under reflux overnight. The reaction mixture was cooled and poured into 300 ml. of water. The polymer precipitated, was removed, and dried *in vacuo*.

Anal. Calcd. for polydiethyl itaconate ($C_9H_{14}O_4$): C, 58.05; H, 7.58. Found: C, 50.39; H, 6.11. Thus, esterification of polyitaconic acid proceeded to the extent of about 40%.

Anal. Calcd. for ethyl ester of the itaconic–aconitic acid copolymer: C, 53.70; H, 7.30. Found: C, 48.24; H, 6.05. Thus the itaconic acid–aconitic acid copolymer was about 45% esterified.

Esterification of the itaconic acid–acrylic acid copolymer. Into a 500-ml., one-necked flask fitted with a fractionating column equipped with a Dean-Stark reflux trap and condenser were placed 1.5 g. of the copolymer, 200 ml. of benzene, and 100 ml. of ethanol. About 0.2 g. of *p*-toluenesulfonic acid was added, and the solution was heated under reflux until the ternary azeotrope ceased to separate (about 3 days). The benzene-ethanol solution was then decanted from the polymer which was insoluble in the reaction mixture. The polymer was dissolved in ethanol, reprecipitated from water, and dried under diminished pressure.

Anal. Calcd. for ethyl ester of the itaconic acid–acrylic acid copolymer: C, 58.62; H, 7.85. Found: C, 55.66; H, 7.59. Thus about 75% esterification was achieved.

TABLE II

INHERENT VISCOSITIES OF DILUTE SOLUTIONS OF THE PARTIALLY ESTERIFIED POLYACIDS IN ETHANOL

Partially Esterified Polymer	Concentration of Solution G./100 Ml.	Inherent Viscosity
Polyitaconic acid	0.25	0.23
	0.125	0.22
Itaconic acid–aconitic acid copolymer	0.20	0.18
	0.10	0.15
Itaconic acid–acrylic acid copolymer	0.25	1.72
	0.125	1.73

Copolymerization of itaconic acid and butadiene. Two polymerization bottles were charged with 5 g. of itaconic acid, 1 g. of Triton X-301,[22] 0.02 g. of *n*-decyl mercaptan, 35.0 ml. of water, 0.05 g. of potassium persulfate, and 15 g. of butadiene. The bottles were tumbled for 23 hr. at 50° and then cooled and opened. After unchanged butadiene had evaporated, the contents were slowly added to 150 ml. of alum coagulant. White polymer coagulated. The material was washed with water to which a few milliliters of hydrochloric acid had been added, and then was dissolved in tetrahydrofuran and reprecipitated from acidified water. The polymer was washed with methanol, redissolved in tetrahydrofuran in which 1 g. of *N*-phenyl-β-naphthylamine had been dissolved, and reprecipitated from water. The polymer was dried *in vacuo*. Eight g. of polymer (20% conversion) was obtained. The polymer was 100% soluble, and had an inherent viscosity of 1.41 in tetrahydrofuran solution. Analysis shows the copolymer contains 20 wt. % of the itaconic acid.

Anal. Calcd. for butadiene (C_4H_6): C, 88.81; H, 11.18; for itaconic acid ($C_5H_6O_4$): C, 46.10; H, 4.61. Found: C, 79.65; H, 10.02.

Homopolymerization of diethyl itaconate. A mixture of 7.2 g. of diethyl itaconate, 20 g. of ORR soap solution,[23] 0.05 g. of lauryl mercaptan (Hooker Electrochemical Co.), and 0.05 g. of potassium persulfate was placed in 2 bottles which were tumbled at 50° for 65 hr. The contents of 2 such polymerization charges were poured into 100 ml. of sodium chloride–sulfuric acid coagulant to coagulate the polymer. The polymer was shredded and thoroughly washed with water. The polymer was then dissolved in acetone and the solution was filtered to remove soap. The polymer was then reprecipitated with water. The polymer was dried, dissolved in benzene, reprecipitated from petroleum ether, and dried under diminished pressure. Twelve g. of polymer, having an inherent viscosity of 0.11 in ethanol solution, was obtained.

A small portion of the polymer was redissolved in benzene, freeze-dried, and submitted for analysis.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.62; H, 7.82.

When the polymerization was attempted at 0° and at 26° using this recipe, no polymer was obtained.

In a similar manner polymerization bottles were charged with 40 g. of ORR soap solution, 14 g. of dimethyl itaconate, a drop of lauryl mercaptan (Hooker Electrochemical Co.), and 0.045 g. of potassium persulfate and tumbled at 50°. The contents of each bottle were then poured into 50 ml. of sodium chloride coagulant solution to coagulate the polymers. The polymer was shredded, washed with water, and dried. The polymer was then dissolved in benzene and reprecipitated with pentane, and then dried under reduced pressure. Analytical samples were freeze-dried from benzene solution. The results of these experiments are given in Table III.

Somewhat better conversions were obtained when the following recipe was used: 10 g. of dimethyl itaconate, 1 g. of Triton X-301, 35 g. of water, a drop of lauryl mercaptan (Hooker Electrochemical Co.) and 0.045 g. of potassium persulfate. The contents of each bottle were then added to 40 ml. of alum coagulant. The polymer coagulated as a fine

TABLE III

EMULSION HOMOPOLYMERIZATION OF DIMETHYL ITACONATE

Time, Hr.	Modifier, G.	Conversion, %	Inherent Viscosity[a]
ORR Soap Recipe			
50	0.025	43	0.15
70	0.01	50	0.35
72	0.00	50	0.28
Triton X-301 Recipe			
46	0.01	100	0.22
48	0.00	94	0.25

[a] 0.25 g./100 ml. of benzene.

(22) A 20% solution of sodium alkyl aryl polyether sulfate supplied by Rohm & Haas Co.

(23) A special soap made to Office of Synthetic Rubber specifications from tallow fatty acids by Procter and Gamble Co. Used as a 2.8% aqueous solution.

powder and was removed by filtration. The polymers were dissolved in chloroform and reprecipitated from a solution of 500 ml. of methanol and 100 ml. of water. The products were redissolved in chloroform, reprecipitated from petroleum ether, and dried under diminished pressure. These experiments are also summarized in Table III.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.40; H, 6.29.

Similarly charges of 10 g. of di-*n*-butyl itaconate, 35 g. of ORR soap solution, 0.01 g. of lauryl mercaptan (Hooker Electrochemical Co.) and 0.06 g. of potassium persulfate were used in the soap recipe, and of 10 g. of ester, 1 g. of Triton X-301, 35 ml. of water, 0.01 g. of lauryl mercaptan (Hooker Electrochemical Co.) and 0.06 g. of potassium persulfate were used in the Triton X-301 recipe.

The bottles were allowed to tumble at 50° for 44 hr. The polymers were isolated and purified by the same procedure used before. The results on the butyl esters are recorded in Table IV.

TABLE IV

EMULSION HOMOPOLYMERIZATION OF DI-*n*-BUTYL ITACONATE

Recipe	Polymer, G.	Conversion, %	Inherent Viscosity
Triton X-301	7.2	72	0.23
ORR soap	10.0	100	0.26

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.25; H, 9.08.

Reduction of polydimethyl itaconate. In a 2-l. flask fitted with a Vibrostirrer, gas inlet tube, and Soxhlet extractor was placed a solution of 10.0 g. (0.0635 mole) of polydimethyl itaconate in 1200 ml. of tetrahydrofuran.[24] In the thimble of the extractor was placed 9.8 g. (0.26 mole) of lithium aluminum hydride. Stirring was commenced, and the reaction mixture was heated under reflux while a slow stream of nitrogen was passed through the apparatus. The first extraction resulted in a vigorous reaction. The reaction was continued 11 hr. and a finely divided gel precipitated in the reaction flask. Heating was then discontinued, and the reaction mixture was allowed to stir overnight. About 50 ml. of ethyl acetate was then added to decompose excess hydride. About 300 ml. of 2*N* sulfuric acid was then slowly added, causing the reaction mixture to separate into 2 phases. The polymer adhered to the walls of the flask. The solutions were removed by decantation and the polymer was dissolved in a water-dioxane mixture. The polymer was insoluble in tetrahydrofuran, chloroform, acetone, dioxane, and water, but dissolved in the mixture of water and dioxane. The polymer was purified by precipitating from solution in acetone, washing with water to remove aluminum salts, redissolving in a dioxane-water mixture, and reprecipitating from acetone. The polymer was dried *in vacuo*. Four and two-tenths g. (70%) of polymer was obtained.

Anal. Calcd. for dimethyl itaconate ($C_7H_{10}O_4$): C, 53.16; H, 6.37; for alcohol ($C_5H_{10}O_2$): C, 58.80; H, 9.87. Found: C, 58.46; H, 8.84.

A slight residue was obtained on ignition which could arise from incomplete hydrolysis of alkoxy-aluminum bonds, which could account for the low hydrogen analysis. A weak carbonyl band was present in the infrared spectrum.

Copolymerization of dimethyl itaconate with butadiene. A modified mutual recipe[25] consisting of 40 g. of ORR soap solution, 0.025 g. of lauryl mercaptan (Hooker Electrochemical Co.), 0.06 g. of potassium persulfate, and 20 g. of monomers was used. The polymerizations were carried out at 50° in a tumbling bath. Ten ml. of methanolic *N*-phenyl-β-naphthylamine was added to each before coagulation of the latex was effected with sodium chloride–sulfuric acid coagulant. The polymers were then shredded, washed thoroughly with water, and dried to a constant weight under diminished pressure. Polymers to be used in subsequent reduction reactions were dissolved in benzene and reprecipitated from methanol. Analytical samples were purified 3 times by this process and dried *in vacuo*. The results are recorded in Table V.

The infrared spectra of these polymers, determined in chloroform, exhibited the following bands: 2980, 2900, 1725, 1635, 1440, 1200, 1020, 975, and 915 cm.$^{-1}$.

Preparation of a butadiene-2-hydroxyethylallyl alcohol copolymer. The procedure used for this reaction is similar to the one used for the reduction of a butadiene–methyl acrylate copolymer.[26]

TABLE V

EMULSION COPOLYMERIZATION OF DIMETHYL ITACONATE WITH BUTADIENE

Sample No.	Monomer[a] Ratio	Time, Hr.	Conversion, %	% Incorp. of Ester	Solubility, %	Inherent Viscosity[b]
1	10/10	20	100	48.7	14.6	6.1
2	15/5	20	93	29.2	10.0	8.3
3	17.5/2.5	7	95	17.6	100.0	1.4
4	17.5/2.5	5	60	19.7	100.0	2.2
5	18.4/1.6	5.5	75	10.9	100.0	2.4

[a] Butadiene/dimethyl itaconate. [b] Determined on soluble portions only.

TABLE VI

RESULTS OF ELEMENTAL ANALYSES OF BUTADIENE–DIMETHYL ITACONATE COPOLYMERS

Anal. Calcd. for butadiene (C_4H_6): C, 88.82; H, 11.18; for dimethyl itaconate ($C_7H_{10}O_4$): C, 53.16; H, 6.37.

Found:

Sample No.	% Carbon	% Hydrogen	% Incorporation of Ester
1	71.28	8.99	48.7
2	78.49	9.69	29.2
3	83.85	11.01	17.6
4	81.75	10.29	19.6
5	84.94	10.63	10.9

In a 5-l. flask fitted with a Vibrostirrer, gas inlet tube, and Soxhlet extractor was placed 12.0 g. of the dimethyl itaconate–butadiene copolymer (Sample No. 4, 80% butadiene–

(24) Purified by passing through a column of Linde Molecular Sieves, No. 13X.

(25) R. L. Frank, J. R. Blegen, G. E. Inskeep, and P. V. Smith, *Ind. Eng. Chem.*, **39**, 893 (1947).

(26) C. S. Marvel, R. M. Potts, and C. King, *J. Am. Chem. Soc.*, **77**, 177 (1955).

20% dimethyl itaconate). To this was added 1500 ml. of pure tetrahydrofuran, and the mixture was stirred until the the solution of the polymer was complete. In the thimble of the extractor was placed 6.0 g. of lithium aluminum hydride. Nitrogen was bubbled through the system, and the solution was heated under reflux with stirring to extract the lithium aluminum hydride into the reaction mixture. The first extraction resulted in a vigorous reaction as did the second; however, the reaction subsided thereafter. The mixture was heated under reflux 6 hr. About 40 ml. of ethyl acetate was then added to the gelled mixture to decompose excess lithium aluminum hydride. Then 1*N* sulfuric acid was added to the reaction mixture until the *p*H reached 4 (about 200 ml.). The mixture was then stirred 16 hr. Additional acid was added during this time to keep the *p*H at the mentioned level. The polymeric material had not dissolved, so the solution was decanted, and the polymer was stirred with a chloroform-dioxane mixture. A portion of the material dissolved. The gel solution was spun in a centrifuge and then filtered through a 100-mesh screen. A portion of the filtrate was slowly added to methanol, and polymer precipitated. The polymer was pressed as free as possible from solvent and was redissolved in chloroform (10% solution) and submitted for infrared spectral analysis. No carbonyl band appeared in the spectrum. A second spectrum was obtained on this material in 40% chloroform solution, and a weak carbonyl band appeared.

Another portion of the dioxane-chloroform solution of the polymer was precipitated from a saturated methanolic solution of *N*-phenyl-β-naphthylamine. The polymer was allowed to stand in this solution until the amine began to crystallize. The polymer was then removed and dried *in vacuo*. This material only swelled when allowed to stand in a 50% chloroform-dioxane solution. The addition of a small portion of ethanol to this solution did not aid dispersion. The remainder of the polymer which was precipitated and dried without the antioxidant also remained insoluble.

Preparation of 2-hydroxyethylallyl alcohol. A slurry of 13.3 g. (0.35 mole) of lithium aluminum hydride in 500 ml. of ether was placed in a 1-l., three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. Stirring was started, and a solution of 50.0 g. (0.27 mole) of diethyl itaconate in 100 ml. of ether was slowly added at such a rate that a gentle reflux was maintained (3 hr. were required for the addition). The reaction mixture was allowed to stir for an additional 30 min., and 50 ml. of ethanol was carefully added to decompose excess hydride. About 100 ml. of 1*N* sulfuric acid was then added, and aluminum hydroxide precipitated. This was removed by filtration and the filtrate was dried over a mixture of anhydrous sodium carbonate and sodium sulfate. The precipitate was placed in water and acid was added until it dissolved. The solution was extracted twice with 100-ml. portions of ether, and the extract was added to the filtrate. The filtrate was concentrated *in vacuo*, and the residue was distilled under reduced pressure. Five and two-tenths g. (20%) of material, b.p. 125–126°/16 mm. Hg, was obtained; however, 22 g. of polymeric material was present in the distillation pot. The distillate was redistilled through a 6-in. Holtzmann column, with a copper coil placed in the pot to inhibit polymerization. Four and six-tenths g. of product, b.p. 62–63°/0.01 mm. Hg, n_D^{20} 1.4689, was obtained.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.74; H, 10.02.

An infrared spectrum of this product exhibited the following bands: 3600, 3350, 2900, 1645, 1450, 1430, 1210, 1025, 910, and 855 cm.$^{-1}$.

Preparation of bis(N,N-dimethyl)itaconamide. Itaconyl chloride was prepared by the method of Feuer and Pier.[27] When molar quantities of reactants were used, the yield was 98 g. (60%) of clear liquid, b.p. 98–100°/16 mm. Hg.

A solution of 44.4 g. (0.26 mole) of itaconyl chloride in 200 ml. of chloroform was placed in a 300-ml. flask fitted with a stirrer and gas inlet tube, and cooled in an ice bath. Anhydrous dimethylamine was bubbled into the agitated solution for 7 hr. At the end of this time the reaction mixture was filtered to remove precipitated salt. The solution was then diluted with twice its volume of diethyl ether to precipitate dimethylamine hydrochloride. The mixture was again filtered and concentrated. The residue was distilled through a 6-in. Vigreux column. The yield was 33 g. or 68% of the theoretical amount, b.p. 105–115°/0.05 mm. Hg. The distillate was fractionally distilled through a 12-in. Vigreux column. The main fraction (30 g.) boiled at 105°/0.01 mm. Hg, $n_D^{20°}$ 1.5018.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.54; H, 8.88; N, 15.27.

The infrared spectrum of this product, determined in chloroform solution, exhibited the following bands: 3000, 1690, 1650–1620, 1500, 1450, 1400, 1260–1200, 1150, 1100, and 925 cm.$^{-1}$

Anionic rearrangement of bis(N,N-dimethyl)itaconamide. In an attempt to cause homopolymerization of the amide, a rearrangement was effected by the following procedure.

In 100 ml. of liquid ammonia in a 200-ml. flask cooled to −78° in a Dry Ice–acetone bath was dissolved 0.04 g. of clean sodium. A deep blue color prevailed in the solution. To the solution was quickly added 9.1 g. of bis(*N,N*-dimethyl)itaconamide. The blue color was discharged immediately. The solution was allowed to warm to room temperature to remove the ammonia by evaporation. A brownish red residue remained. This was washed with ether to remove monomer, and dried *in vacuo*. A light tan solid (1.8 g.) was obtained. The solid crystallized to white needles from heptane. After 3 recrystallizations from heptane, the material (VII) melted at 83–84°.

Anal. Calcd. for ($C_9H_{16}N_2O_2$): C, 58.67; H, 8.75; N, 15.21. Found: C, 58.86; H, 8.63; N, 15.12; C, 58.84; H, 9.00; N, 15.21.

Mol. wt. calcd.: 186. Found: 198 (Rast).

The rearrangement product (VII) only slowly decolorized bromine solution, and slowly gave a Von Baeyer test. Bis(*N,N*-dimethyl)itaconamide reacts instantaneously with bromine and potassium permanganate. An ultraviolet absorption spectrum determined on VII in ethanol solution showed a λ_{max} at 235 mμ with a molar extinction coefficient of 8700. Ultraviolet spectra of bis(*N,N*-dimethyl)itaconamide, itaconamide, or acrylamide in ethanol solution at similar concentrations exhibited no absorption maxima in the 200–350 mμ region. A nuclear magnetic resonance spectrum determination of VII in chloroform solution at 41.08 m.c. gave the following Δ c.p.s. values relative to chloroform: 64.4 (olefinic hydrogen, triplet); 182.1 (amide methyl groups, 3 peaks—2 shifted); 218.0 (methyl group attached to olefin, doublet). The infrared spectrum of VII (chloroform) exhibited the following bands: 2965, 2910, 1655, 1625, 1500, 1450, 1420, 1405, 1335, 1265, 1150, 1110, 1060, 1040, 940, 850, and 660 cm.$^{-1}$.

Alkaline hydrolysis of VII. In a 25-ml. flask was placed 0.5 g. of VII, 15 ml. of water, and 0.5 g. of sodium hydroxide. The solution was heated on a steam bath for 11 hr. The odor of dimethylamine was present in the hydrolyzate. The solution was cooled and acidified to a *p*H of 2 with dilute hydrochloric acid. The solution was evaporated slowly to dryness. The white residue was extracted with chloroform to remove any dimethylamine hydrochloride. The residue was recrystallized twice from water, m.p. 200–202° (corr.). A mixture of the crystals with an authentic sample of mesaconic acid melted at 201–203° (corr.).

After treatment of both maleic acid and fumaric acid with base under the conditions employed in the hydrolysis, no isomerization was noted. Thus it is likely that no isomerization occurred in the hydrolysis.

(27) H. Feuer and S. M. Pier, *Org. Syntheses*, **33**, 41 (1953).

URBANA, ILL.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF CHICAGO]

New Metal Salt-Induced Homolytic Reactions. II. Modification of Free Radical Reactions by Copper Salts[1]

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The following reactions are profoundly influenced by small quantities of cuprous salts: (1) the pyrolysis of dicumene; (2) the decomposition of benzoyl peroxide in octene-1 and octene-2; (3) the decomposition of benzoyl peroxide in cumene; (4) the decomposition of benzoyl peroxide in a mixture of valeraldehyde and carbon tetrachloride; (5) the decomposition *tert*-butyl peroxide in benzaldehyde; (6) the decomposition of *tert*-butyl peroxide in cumene. The influence of copper salts is discussed.

It is well established that the course of ionic reactions can be altered by catalysts. The aim of this work was to show that there are compounds, which if present in catalytic amounts, can drastically change the course of free radical reactions. This publication deals with the effect of copper salts on some well known homolytic reactions. Future publications will deal with some new homolytic reactions, which can be carried out while using copper and other metal salts as catalysts. There were several considerations which directed us to copper salts as the most promising catalysts to alter homolytic reactions.

Many metal salts are capable of initiating homolytic reactions by acting as one-electron oxidizing and reducing agents, for example, the reactions of hydroperoxides initiated by iron, copper, cobalt, and manganese salts.[4]

Metal salts can also initiate homolytic reactions if advantage is taken of the property that in their most stable form, the valence of some metals is different in organometallic compounds than in some salts. For example, if potassium cyanide is added to cupric salts, the initially formed cupric cyanide is unstable and breaks down into cuprous cyanide and cyanogen.[5] In a similar fashion, certain

$$CuSO_4 + 2KCN \longrightarrow Cu(CN)_2 + K_2SO_4 \qquad (1)$$

$$2Cu(CN)_2 \longrightarrow 2CuCN + (CN)_2$$

salts such as cuprous, cobaltous, and manganous salts initiate the formation of free radicals and Grignard reagents.[6] Depending on the nature of

$$RMgBr + CoCl_2 \longrightarrow RCoCl + MgBrCl \qquad (2)$$

$$RCoCl \longrightarrow R\cdot + CoCl$$

the salt, the reaction takes a different course. The reaction between *tert*-butylmagnesium bromide and ethyl bromide, with cobaltous chloride as catalyst yields as disproportionation products isobutane and isobutylene exclusively. The same reaction with manganous chloride as catalyst yields 43% of the dimerization product, hexamethylethane. On the basis of these findings, it was expected that the presence of metal salts would alter other homolytic reactions, reactions which are usually carried out in the absence of any metal salt.

The copper-catalyzed Ullmann reaction, condensation of an aromatic amine with an aromatic halide, is widely used in the vat-dyestuff industry. Its homolytic nature has long been suspected, notwithstanding the fact that some of its characteristics, like the advantage of using nitrobenzene as a solvent, would appear to bear evidence to the contrary. Similarly, it has been suggested several times that the Meerwein and Sandmeyer reactions are free radical in nature. As a starting place, it was decided to study the effect of copper salts on homolytic reactions.

Pyrolysis of dicumene. If a solution of dicumene in bromobenzene is heated in a sealed tube to 255° for 10 hours, all of the dicumene will have disappeared. After distilling off the lower boiling material, only a tarry material weighing 12% of the dicumene charged remains. At an elevated temperature, dicumene is expected to disassociate, to some extent into α-cumyl radicals (Equation 3), which will induce a decomposition into cumene and α-methylstyrene (Equation 4). In the presence

$$[C_6H_5(CH_3)_2C]_2 \longrightarrow 2C_6H_5(CH_3)_2C\cdot \qquad (3)$$

$$C_6H_5(CH_3)_2C\cdot + [C_6H_5(CH_3)_2C]_2 \longrightarrow C_6H_5(CH_3)C{=}CH_2 + C_6H_5(CH_3)_2CH + C_6H_5(CH_3)_2C\cdot \qquad (4)$$

of two mole percent of cuprous bromide, 70% of the charged weight of the high-boiling material remained, even after heating at 255° for 24 hours. After recrystallization, 37% of pure dicumene could be isolated. The melting point was 119°, undepressed by the starting material.

(1) *Cf.* M. S. Kharasch and A. Fono, *J. Org. Chem.*, **23**, 324 (1958).

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(4) M. S. Kharasch and A. Fono, *J. Org. Chem.* **24**, 72 (1959).

(5) G. Jacquemin, *Bull. Soc. Chim.*, (2) **43**, 556 (1885).

(6) M. S. Kharasch, T. W. Hancock, W. Nudenberg, and P. O. Tawney, *J. Org. Chem.*, **21**, 322 (1956). M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *J. Am. Chem. Soc.*, **65**, 493 (1943).

Reaction of benzoyl peroxide with octene-1 in the presence and the absence of cuprous salts. It is claimed that substances having the physical consistency of vaseline are formed when benzoyl peroxide is heated with octene-1, dissolved in organic solvents.[7] Unfortunately, the chemical nature of the products formed were not investigated, as the authors were primarily interested in producing "lubricants of high viscosity and low pour point".

In our study, the matter of primary concern was the modification induced by cuprous salts on the decomposition of benzoyl peroxide in the presence of simple olefins. The strong effect of trace amounts of such salts (one mole percent on the basis of the peroxide used) on the distribution of the products formed, when benzoyl peroxide is decomposed in octene-1 is shown in Table I.

TABLE I

PRODUCTS FORMED BY THE DECOMPOSITION OF BENZOYL PEROXIDE (1 MOLE) IN OCTENE-1 (8 MOLES) AT 100° IN THE PRESENCE AND ABSENCE OF CUPROUS CHLORIDE (1 MOLE %)

Without Additive	Cu_2Cl_2
1. Benzoic acid (6 mole %)	1. Benzoic acid (72 mole %)
2. 1:1 adduct (20 mole %)[a] Unsaturation in adduct (30%)	2. 1-Phenyloctene-2 (8 mole %)
3. 1:2 adduct (25 mole %) Unsaturation in adduct (30%)	3. 1:1 adduct (34 mole %) Unsaturation in adduct (77%)[b]
4. High mol. wt. adduct (average mol. wt., 600; containing four octenes to one benzoyloxy group (57 mole %). Total wt. on peroxide used—340 g. Unsaturation—(60%)	4. 1:2 adduct (34 mole %) Unsaturation in adduct (100%)
5. CO_2 (80 mole %)	5. High mol. wt. adduct—negligible (only about 7 g.). Since only 0.2 mole of peroxide was used, the amount of the material formed was too small for further work (1.4 g.)
	6. CO_2 (42 mole %)

[a] On the basis of the infrared spectrum and analyses of this material (after hydrolysis) it is estimated that it contains about 40% of a phenyloctane. [b] Probably the low unsaturation in this adduct (77%) is caused by the very low solubility of the cuprous chloride; note also that this salt was not finely powdered.

The important difference in the decomposition of benzoyl peroxide in octene-1 in the presence, and in the absence of cuprous salts is not in the products formed, but in the relative amounts of the products. First: only seven grams of high molecular weight products are formed in the presence, 340 grams in the absence, of cuprous salts. Second: a higher amount of unsaturation is found in the 1:1 and 1:2 adducts (1 benzoyloxy group to 2 octenes) formed in the presence of cuprous salts. Third: A large amount of benzoic acid (72 mole %) is formed in the reaction with cuprous salts; a small amount (6 mole %) is formed in their absence. Fourth: 42 mole % of carbon dioxide is evolved in their presence; approximately 80 mole % is evolved in the absence of cuprous salts.

All of these products, according to their infrared spectra contain a *trans* double bond, and with the exception of the benzoyloxyoctene (1:1 adduct) formed in the presence of copper salts, there is no indication of a terminal double bond in any of these adducts. The benzoyloxyoctene contains about 30% terminal double bond.

The decomposition of the peroxide in the absence of cuprous salt can be described by the following reaction scheme, in agreement with other well known radical reactions.

$$(C_6H_5COO)_2 \xrightarrow{\Delta} 2C_6H_5COO\cdot \quad (5)$$

$$C_6H_5COO\cdot + C_5H_{11}CH_2CH{=}CH_2 \longrightarrow C_6H_{11}CH_2\dot{C}HCH_2OCOC_6H_5 \quad (6)$$

(A)

$$2A \xrightarrow{\text{Disp.}} C_5H_{11}CH_2CH_2CH_2OCOC_6H_5 + C_5H_{11}CH{=}CHCH_2OCOC_6H_5 \text{ (1:1 adducts)} \quad (7)$$

$$A + C_6H_{13}CH{=}CH_2 \longrightarrow C_6H_{13}CHCH_2OCOC_6H_5 \quad (8)$$

(B)

$$2B \xrightarrow{\text{Disp.}} B_{+H} + B_{-H} \text{ (1:2 adducts)} \quad (9)$$

$$B + 2(C_6H_{13}CH{=}CH_2) \longrightarrow C_6H_{13}CH{-}CH_2OCOC_6H_5$$

$$\text{with } CH_2CHC_6H_{13} \text{ and } CH_2CHC_6H_{13} \quad (10)$$

(C)

$$2C \longrightarrow C_{+H} + C_{-H} \quad (11)$$

(High molecular weight material)

The radical C may disproportionate with itself as in Equation 11 to give 50% unsaturation in the "high molecular weight material"; or it may disproportionate with the free radicals A and B. Since the 1:1 and 1:2 adducts are less than 50% unsaturated, while the "high molecular weight material" is 60% unsaturated, it is reasonable to assume that the radicals A and B, when they disproportionate with C, capture a hydrogen atom.

In the presence of cuprous salts, very little "high molecular weight material" is formed. The unsaturation in the 1:1 and 1:2 adducts is very much higher than the unsaturation in the adducts formed in the absence of cuprous salts. This suggests that cuprous salts must facilitate the termination reaction. This conclusion is substantiated by the large amount of benzoic acid (78 mole %) formed in the reaction in the presence of cuprous salts and the very small amount of benzoic acid (6 mole %) formed in the absence of these salts.

The reaction of benzoyl peroxide with octene-1 took a similar course, when instead of a large excess of octene, ethyl acetate was used as a solvent. Using an aromatic solvent, (benzene, chlorobenzene,

(7) F. M. Seger, Pittman, W. Garwood, Haddonfield, and A. N. Sachanen, U. S. Patent 2,551,641.

xylene) the reaction takes a somewhat different course. No 1-phenyloctene-2 is formed. The main reaction product is 1-phenyloctene-1, in 45% yield, n_D^{20} 1.5225,[8] absorption peak in the ultraviolet at 247 millimicrons (characteristic of styrenes). The benzoyloxyoctenes (1:1 adduct) formed in 23% yield. Judging their composition from the infrared absorption spectra, they contained mainly 1-benzoyloxyoctene-2, but also some 1-benzoyloxyoctene-1, indicated by a peak at 1778 $cm.^{-1}$ (characteristic for vinyl esters) and approximately 20% 3-benzoyloxyoctene-1. 15% of a 1:2 adduct was also isolated (1-benzoyloxy group for 2 octene groups).

Reaction of benzoyl peroxide with octene-2 in the presence and absence of cuprous salts. Examination of Table II will indicate that the decomposition of benzoyl peroxide in the presence and absence of cuprous salts is somewhat similar to the thermal decomposition of the peroxide in octene-1. The differences observed in the yields of the various products (namely large amounts of 1:1 adduct, and very small amounts of higher adducts) as compared with the products formed when octene-1 is used were attributed to the lower reactivity of the double bond in octene-2.

TABLE II

PRODUCTS FORMED BY THE DECOMPOSITION OF BENZOYL PEROXIDE (1 MOLE) IN OCTENE-2 (8 MOLES) AT 95° IN THE PRESENCE AND ABSENCE OF CUPROUS CHLORIDE (1 MOLE %)

Without Additives	Cu_2Cl_2
1. Benzoic acid (29 mole %)	1. Benzoic acid (69 mole %)
2. 1:1 adduct (85 mole %) Unsaturation in adduct (60%)	2. 1:1 adduct (73 mole %)[a] Unsaturation in adduct (93%)
3. 1:1 adduct (13 mole %)	3. High boiling residue (7.5g.) Mol. wt., 350
4. High boiling residue (20g.) Mol. wt., 380	

[a] This product contains approximately 5 per cent of a phenyloctene.

Reaction of benzoyl peroxide with cumene in the presence and absence of cuprous chloride. The decomposition of benzoyl peroxide in cumene has been studied by a number of investigators. The products which have been isolated are listed in Table III. For comparison purposes, the products formed when benzoyl peroxide is decomposed in cumene, in the presence of cuprous chloride are included in the same table.

The data recorded in Table III suggest two mechanisms for the decomposition of benzoyl peroxide in cumene. By one of these, a hydrogen atom is removed from cumene to give a free cumyl radical. The second is the phenylation of cumene, which leads to various isopropyl biphenyls.[9]

The effect of minute amounts of cuprous salts on the decomposition of benzoyl peroxide in cumene is quite remarkable. In the presence of the cuprous salt, (see Table III), the yield of dicumene is practically negligible, less than 2%. However, α-cumyl benzoate is formed in an amount nearly equivalent to the dicumene formed in the absence of the cuprous salt. A second striking effect is that cuprous salts have practically no effect on the yield of the isopropylbiphenyls. Hence, in the decomposition of the peroxides in solvents, cuprous salts have apparently a pronounced effect only on the reactions which involve very unreactive radicals; and only a minor effect on reactions involving reactive radicals.

There is evidence however, that cuprous salts play a role in the formation of isopropylbiphenyls. The decomposition of the benzoyl peroxide in toluene, in the presence of cuprous salts gives products similar to those formed in the absence of the same salts. Yet, the rate of the decomposition of the peroxide is considerably greater and an appreciably less high molecular weight oil is formed.

The decomposition of benzoyl peroxide in a mixture of valeraldehyde and carbon tetrachloride in the presence of cuprous chloride. It has been established that isovaleroyl chloride and chloroform are formed[10] when a mixture of isovaleraldehyde and carbon tetrachloride, in the presence of benzoyl peroxide (10 mole %) is refluxed for 24 hours. Similarly, when a mixture of valeraldehyde (one mole), benzoyl peroxide (0.5 mole), carbon tetrachloride (5–6 moles) is heated to 76° for six hours, the reaction products are chloroform, hydrogen chloride, and valeroyl benzoyl anhydride, and a mixture of the two unsymmetrical anhydrides. The mixed anhydride is undoubtedly formed in this instance from the valeroyl chloride and the benzoic acid.

$$CH_3(CH_2)_3C(=O)Cl + C_6H_5COOH \longrightarrow CH_3(CH_2)_3COOCOC_6H_5{}^{11} + HCl \quad (12)$$

(8) S. Reich, R. Van Wijck, and C. Waelle, *Helv. Chim. Acta*, **4**, 242 (1921) prepared what they thought to be pure 1-phenyloctene-1 from phenylheptylcarbinol and reported refractive index n_D^{17} 1.50728. Because of the method used, it may have contained 1-phenyloctene-2. The refractive index reported by us is similar to those of other long chain vinylbenzenes. 1-Phenylpentene n_D^{18} 1.5302, T. Levy, Dvoleitska, and Gombinska, *Bull. Soc. Chim.*, (4) **49**, 1765 (1931). 1-Phenylhexene n_D^{25} 1.5377, C. S. Marvel, F. D. Hager, and D. D. Coffman, *J. Am. Chem. Soc.*, **44**, 2323 (1927).

(9) As to the respective yields of isopropylbiphenyl, the results obtained by Dannley and Zaremsky (see Table III), although somewhat low are comparable to those obtained by the other investigators. The exceptionally low yield of dicumene obtained by Dannley and Zaremsky cannot readily be dismissed. Prof. Dannley mentioned in private discussions that it is possible that his reaction mixture contained a trace amount of copper salts.

(10) S. Winstein and F. H. Seubold, *J. Am. Chem. Soc.*, **69**, 2916 (1957).

(11) Since mixed anhydrides are thermally unstable, and break down into two symmetrical anhydrides, it is not surprising that some of these symmetrical anhydrides were also obtained during the distillation of the unsymmetrical anhydride.

TABLE III

DECOMPOSITION OF BENZOYL PEROXIDE IN CUMENE AT 80°

Investigator	[a]	[b]	[c]	Kharasch, Fono[d]
Reagents in moles				
Benzoyl peroxide	1.0	1.0	1.0	1.0
Cumene	16.0	—	80.0	10.0
Cuprous chloride (1 mole %)	Absent	Absent	Absent	Present
Products				
CO_2	1.1	—	—	1.0
Benzoic acid	0.78	0.41	0.60	0.45
Isopropylbiphenyls	0.18	0.27	0.24	*ca.* 0.20
Dicumene	0.08	0.31	0.35	Less than 0.02
α-Cumyl benzoate	None	None	None	0.33
Residue in gr.	76.0	Not given	66.0	70.0
Moles of benzoic acid formed upon hydrolysis of the crude reaction mixture	Not given	Not given	0.09	0.50

[a] R. L. Dannley and B. Zaremsky, *J. Am. Chem. Soc.*, **77**, 1588 (1955). [b] C. S. Rondestvedt, Jr., and H. S. Blanchard, *J. Am. Chem. Soc.*, **77**, 1769 (1955). [c] D. H. Hey, B. W. Pengilly, and G. H. Williams, *J. Chem. Soc.*, 1463 (1956). [d] M. S. Kharasch and A. Fono. In addition to the products cited, there is formed (in the presence of cuprous salts) about 13 mole % of a mixture of α-cumyl alcohol and acetophenone. The mechanism of formation of these products will be discussed in detail in a forthcoming publication.

When one mole percent of cuprous chloride was added to a mixture of benzoyl peroxide (0.5 mole), valeraldehyde (1 mole) and carbon tetrachloride, and the mixture heated to 76°, the peroxide completely decomposed in approximately 30 minutes. Under these conditions, no hydrogen chloride or chloroform was formed. The major reaction products were benzoic acid (0.64 mole), the mixed anhydride, benzoyl valeroyl anhydride and the two symmetrical anhydrides. In this reaction, the mixed anhydride must be formed by a mechanism different from the one indicated in Scheme 12.

Reaction of tert-butyl peroxide with benzaldehyde in the presence and absence of copper salts. It is well established that the chief reaction products formed by decomposing *tert*-butyl peroxide in benzaldehyde are equal quantities of the *meso* and racemic forms of benzpinacol dibenzoate.[12] The same products were obtained by Kharasch and McBay by decomposing acetyl peroxide in benzaldehyde.[13] In their investigation, Rust, Suebold, and Vaughan isolated the *meso* compound in crystalline form. They assumed that the oil which they obtained was the racemic form.

The racemate could be crystallized by us from a mixture of ether and ligroin (b.p. 30–35°). It melts at 115° in an evacuated tube. The rate of the reaction of the benzaldehyde and the *tert*-butyl peroxide is first order, with respect to the peroxide used, and is quite slow.[12] After 30 hours at 130°, only about 70% of the peroxide decomposes. The following mechanism was proposed to account for the products formed in this reaction.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{\Delta} 2(CH_3)_3CO\cdot \qquad (13)$$

$$C_6H_5CHO + (CH_3)_3CO\cdot \longrightarrow (CH_3)_3COH + C_6H_5CO\cdot \qquad (14)$$

$$C_6H_5CHO + C_6H_5CO\cdot \longrightarrow C_6H_5\overset{H}{\underset{\cdot}{C}}—OCOC_6H_5 \qquad (15)$$
(D)

$$2D \longrightarrow \begin{matrix} H \\ C_6H_5C—OCOC_6H_5 \\ | \\ C_6H_5C—OCOC_6H_5 \end{matrix} \qquad (16)$$
(E) meso and racemic forms

An entirely different reaction takes place when *tert*-butyl peroxide is decomposed in benzaldehyde in the presence of small amounts of cuprous salt (chloride or benzoate). Instead of a practically quantitative yield of E, benzopinocol dibenzoate, on the basis of the peroxide used, only a negligible yield (5%) was obtained. However, there is a very high yield (83%) of *tert*-butyl benzoate. It is pertinent that as far as the mechanism is concerned, the decomposition of *tert*-butyl peroxide in benzaldehyde is very much faster in the presence than in the absence of copper salts. Where only 70% of the peroxide was decomposed when heated to 140° for 18 hours, in benzaldehyde, complete decomposition occurred after 6 hours at 140°, in the presence of cuprous salts. Further, the decomposition of the *tert*-butyl peroxide, in benzaldehyde, in the presence of cuprous chloride appeared to be a zero order reaction, rather than the first order reaction which occurred in the absence of a cuprous salt.

At this point, we should indicate that when cuprous bromide is used, some of the benzoyl-radicals are oxidized and the yield of the *tert*-butyl benzoate decreases.

Reaction of tert-butyl peroxide in cumene, in the presence and absence of cuprous chloride. A *tert*-butyl peroxide (1 mole) and 10 fold cumene, heated to 145° gives dicumene, methane, acetone (0.4 mole), and *tert*-butyl alcohol (1.1 mole).

(12) F. F. Rust, F. H. Seubold, and W. E. Vaughan, *J. Am. Chem. Soc.*, 70, 3258 (1948).

(13) Unpublished work.

The rate of decomposition is first order.[14] The rate of the reaction, in the presence of the cuprous chloride is much faster, almost O order. In the latter reaction, less acetone (0.4 mole) and more *tert*-butyl alcohol (1.6 moles) is formed.

DISCUSSION

A mechanism is sought which explains how copper salts modify homolytic reactions. Many mechanisms can be proposed for each individual reaction. Instead of carefully studying an individual reaction, the authors chose to study the effect of copper salts on a large variety of different reactions, trying to find a mechanism which is consistent with all the observations: a mechanism which explains why copper salts act in some reactions as free radical inhibitors, in others only as deactivators and yet in others, promote induced decomposition of peroxides. The mechanism has to be able to account for the increased solvent effect in homolytic reactions catalyzed by copper salts. In addition to the arguments given in the previous publication of this series, more evidence is presented here to substantiate the hypothesis that free radicals are not completely free in many homolytic reactions, in either the presence or the absence of copper salts.

Copper salts are capable of inhibiting some free radical chain reactions. It was found that chloroform can be brominated with *N*-bromosuccinimide to bromotrichloromethane, using light or benzoylperoxide as an initiator. This reaction can be completely inhibited when one mole percent cuprous chloride is added to the reaction mixture.[15] Copper

$$(C_6H_5CO_2)_2 \longrightarrow C_6H_5CO_2\cdot \qquad (17)$$

$$C_6H_5CO_2\cdot + CHCl_3 \longrightarrow C_6H_5COOH + \cdot CCl_3$$

$$\cdot CCl_3 + Su > NBr \longrightarrow BrCCl_3 + Su > N\cdot$$

$$Su > N\cdot + CHCl_3 \longrightarrow Su > NH + \cdot CCl_3$$

salts do not affect all reactions of *N*-bromosuccinimide in the same fashion. The bromination of octene-1 with *N*-bromosuccinimide is slowed down, but not inhibited by the presence of copper salts.[16]

These observations indicate that copper salts are capable of deactivating some radicals. For example, copper salts deactivate trichloromethyl radicals to the extent that they are unable to abstract a bromine from *N*-bromosuccinimide. We propose

$$\cdot CCl_3 + Cu^+ \rightleftharpoons Cu^+CCl_3 \qquad (18)$$

$$2Cu^+CCl_3 \longrightarrow 2Cu^+ + Cl_3C{-}CCl_3$$

that the trichloromethyl radical reacts with a cuprous cation to give an unstable organocupric compound, as a reaction intermediate. Two of these trapped radicals, similar to the metal salt catalyzed Grignard reagent, will react with each other to give hexachloroethane in a chain ending step. We propose the name "free radical trapper" for substances which are capable of modifying homolytic reactions, through their ability to form loosely bound compounds with free radicals.

A similar mechanism accounts for the observation that if the pyrolysis of dicumene is carried out in the presence of copper salts, the initially formed cumyl radicals do not disproportionate. They are trapped on the copper salt and subsequently dimerize.

A trapped "free radical" does not necessarily retard or inhibit a reaction. Free radicals trapped on cuprous salt readily cause an induced decomposition of peroxides. The peroxides decompose in less time, at lower temperatures, in the presence of copper salts than they do in the absence of them. Careful rate studies were not made, but experimental observation indicates lower than first order rate, a characteristic of induced decompositions. The nature of the reaction products is further evidence in favor of induced decomposition.

When benzoyl peroxide is decomposed in octene-2, both in the presence and the absence of copper salts, the initial reaction is the addition of a benzoyloxy radical to the double bond.

$$(C_6H_5CO_2)_2 \longrightarrow 2C_6H_5CO_2\cdot \qquad (19)$$

$$C_6H_5CO_2\cdot + C_8H_{16} \longrightarrow \underset{(F)}{C_6H_5CO_2C_8H_{16}\cdot}$$

In the absence of a metal salt, radical F, for the most part disproportionates into a saturated and an unsaturated compound. In the presence of copper salts, radical F is reversibly trapped on a cuprous salt, and can readily attack a peroxide molecule.

$$C_6H_5CO_2C_8H_{16}\cdot Cu^+ + (C_6H_5CO_2)_2 \longrightarrow C_6H_5CO_2C_8H_{15} + C_6H_5CO_2H + C_6H_5CO_2\cdot + Cu^+ \qquad (20)$$

No disproportionation occurs, indicated by the observation that no saturated compound is formed. In agreement with the proposed mechanism, benzoyloxyoctene and benzoic acid are formed in about equimolar quantities.

As an alternate mechanism, the benzoyloxy radical formed in Equation 19 oxidizes cuprous to cupric, in turn, the cupric oxidizes radical F to benzoyloxyoctene. The relative importance of these two mechanisms can be discerned by studying the decomposition of benzoylperoxide in cumene, in the presence of copper salts. The cumyl radicals in this reaction may either be trapped on the cuprous salts and attack the benzoylperoxide causing an induced decomposition, or they may be further oxidized by a cupric ion. The reactions lead to two different reaction products as indicated in the following equations:

$$C_6H_5(CH_3)_2C\cdot + Cu^+ \rightleftharpoons C_6H_5(CH_3)_2C\cdot Cu^+ \qquad (21)$$

(14) J. H. Raley, F. F. Rust, W. E. Vaughan, *J. Am. Chem. Soc.*, **70**, 1336 (1948).

(15) M. S. Kharasch and S. Lemberg, unpublished work.

(16) R. Malec, Ph.D. thesis, University of Chicago, 1957.

$$C_6H_5(CH_3)_2C\cdot Cu^+ + (C_6H_5CO_2)_2 \longrightarrow C_6H_5(CH_3)_2CO_2CC_6H_5 + C_6H_5CO_2\cdot + Cu^+ \quad (22)$$

$$C_6H_5(CH_3)_2C\cdot + Cu^{++} \longrightarrow \text{Cumyl alcohol and acetophenone} \quad (23)$$

The reaction products indicate that Equation 22 is about three times more important than Equation 23.

It is of no importance if the catalytic amounts of copper salts added are cuprous or cupric, as both oxidizing and reducing agents are always present. If the equilibrium in Equation 21 is shifted to the right or to the left depends on the nature of the solvent. It is expected that homolytic reactions, carried out in the presence of copper salts will show an unusually strong solvent effect. An interesting example of this may be made by comparing the nature of the phenyloctenes formed, when benzoylperoxide is reacted with octene-1, in the presence of copper salts in either aromatic or aliphatic solvents. In an aliphatic solvent, only 1-phenyloctene-2 is formed. In an aromatic solvent, 1-phenyloctene-1 is predominately formed.

$$C_6H_5C_8H_{16}Cu^+ \xrightarrow{(C_6H_5CO_2)_2} C_6H_5CH_2-CH=CH-C_5H_{11}$$

$$C_6H_5CH_2-\underset{\displaystyle Cu^+}{CH}-CH_2C_5H_{11} \qquad (24)$$

$$\xrightarrow{Cu^{++}} C_6H_5CH=CH-CH_2C_5H_{11}$$

Equation 22 postulates that the reaction between an organo copper compound and a peroxide is homolytic. Indirect evidence in favor of this hypothesis is in the nature of the products formed when the peroxide used is *tert*-butyl perbenzoate. The copper salt catalyzed decomposition through an organo copper intermediate introduces the benzoyloxy group. The ionic reaction of *tert*-butyl perbenzoate, with a Grignard reagent introduces the *tert*-butoxy group.[17]

A good example of the induced decomposition of the peroxides in the presence of copper salts is the decomposition of *tert*-butyl peroxide, in benzaldehyde, in the presence of cuprous chloride. This was the first time that the induced decomposition of *tert*-butyl peroxide was observed. The initially formed benzoylradical is trapped on the cuprous salt. It is unable to add to another benzaldehyde. However, it can readily attack the *tert*-butyl peroxide.

$$C_6H_5CO\cdot + CuCl \longrightarrow C_6H_5COCuCl$$

$$C_6H_5COCuCl + (CH_3)_3COOC(CH_3)_3 \longrightarrow C_6H_5CO_2C(CH_3)_3 + (CH_3)_3CO\cdot + CuCl \quad (25)$$

In the presence of cuprous chloride, there is practically no oxidation of the intermediate radical by a cupric salt. In future publications, we shall show that oxidation would lead through intermediately formed benzoic acid to benzoic anhydride.

(17) S. O. Lawson, unpublished work.

However, the decomposition of benzoyl peroxide in benzaldehyde is an induced decomposition, even in the absence of copper salts. The only difference to observe in these reactions is that in the absence of copper salts both benzopinacol dibenzoate and benzoic anhydride will form: in the presence of copper salts, only benzoic anhydride will form. The mechanism is similar to the one outlined.

The mechanism of the decomposition of benzoyl peroxide in a solution of valeraldehyde in carbon tetrachloride, in the presence of cuprous chloride is again similar. The copper salts play a dual role. In part they prevent any chain reaction in which trichloromethyl radicals would participate. Trapped trichloromethyl radicals are very inactive, as seen in the bromination of chloroform. Copper salts promote the reaction between the trapped valeryl radical and the peroxide.

Previously, we have shown that carbon free radicals can readily form radical complexes with hydroperoxides and with organic acids.[4,18]

$$R\cdot + R'OOH \longrightarrow \underset{\text{(free radical complex)}}{\overset{H}{R\cdot OOR'}} \quad (26)$$

The radical complexes are the postulated intermediates in the formation of peroxides and esters. The peroxide, and especially the ester formation is greatly enhanced in the presence of copper salts. This suggests that cuprous salts can trap not only free radicals, but even more readily, free radical complexes, thus promoting reactions which proceed through free-radical complex intermediates.

In the reactions just discussed, it was not important that it was the copper salt that trapped the free radical or free radical complex. The complexing agent could have been another substrate molecule or the solvent.

The experimental observation that cuprous chloride causes an induced decomposition of *tert*-butyl peroxide without effecting the formation of dicumene forces us to the hypothesis that the reaction proceeds through a free radical complex. The mechanism envisaged for this reaction is:

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot + C_6H_5(CH_3)_2CH \longrightarrow C_6H_5(CH_3)_2C\cdot + (CH_3)_3COH$$

$$C_6H_5(CH_3)_2C\cdot + C_6H_5(CH_3)_2CH + CuCl \longrightarrow \underset{\text{(G)}}{\overset{H}{C_6H_5(CH_3)_2C\cdot C(CH_3)_2C_6H_5CuCl}}$$

$$(G) + (CH_3)_3COOC(CH_3)_3 \longrightarrow C_6H_5(CH_3)_2CC(CH_3)_2C_6H_5 + (CH_3)_3COH + (CH_3)_3CO\cdot + CuCl \quad (27)$$

(18) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **23**, 324 (1958).

(19) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 105 (1951).

The *tert*-butoxy radical formed in this reaction has a different origin than the one formed from the first order decomposition of *tert*-butyl peroxide. Therefore it was expected that the ratio of the *tert*-butyl alcohol to acetone would be different.[19] The existence of complex G would predict that in the presence of copper salts, a cumyl radical could abstract a hydrogen from another cumyl radical.

Cadogan, Gold, and Satchell[20] have shown that free radicals formed from xylene can abstract a hydrogen from another xylene molecule, *i.e.* that reactions of the type in Equation 28 do occur.

$$RH + R\cdot \longrightarrow R\cdot + RH \qquad (28)$$

Eliel, Wilken, Fang, and Wilen[21] repeated this work, but their experimental results contradicted those of the former authors.

Considering the influence of copper salts on homolytic reactions, we are forced to the hypothesis that at least in the presence of copper salts, a carbon radical can form a free radical complex, not only with an oxygen, hydrogen, or nitrogen bond, but even with a carbon hydrogen bond.

$$\begin{matrix} H \\ R\cdot R'Cu^{+} \end{matrix} \qquad (29)$$

The chemical bond in this free radical complex is probably a resonance hybrid of a hydrogen bond, and of a charge transfer complex.[22] A more direct proof for the existence of such a free radical complex would be, if it could be shown, that the difference between the experiments of Eliel and his co-workers, and Cadogan and his co-workers was due to the presence of trace amounts of metal salt impurities.

EXPERIMENTAL

Reagents and procedure. The reagents were distilled prior to use. Commercial (Eastman) benzoyl peroxide was used in all experiments. The air in the apparatus was always displaced by nitrogen gas. Moisture (and air) were rigidly excluded. The gases generated during the reaction were collected over a saturated solution of sodium chloride in water, saturated with carbon dioxide. No reaction was considered complete unless the reaction mixture gave a negative test for the peroxides. The infrared spectra measurements were made on a Perkins-Elmer Model 21, double beam spectrophotometer. The molecular weights of the compounds were determined cryoscopically (benzene). The extent of the unsaturation in the compounds was determined either by ozonolysis, or by a bromate-bromide titration, or by both methods.

Pyrolysis of dicumene in bromobenzene. A mixture containing dicumene (3 g.) and bromobenzene (24 g.) was heated in a bomb tube at 255° for 10 hr. After distilling out the low boiling materials, there remained only 0.35 g. of a residue which could not be crystallized from methylalcohol.

We repeated the same experiment, adding 0.05 g. of cuprous bromide. The mixture was heated for 24 hr. After distillation, we obtained 2.1 g. of a higher boiling residue. This recrystallized from methyl alcohol yielding 1.1 g. of dicumene, m.p. 119°, giving no depression with the starting material.

Reaction of benzoyl peroxide in octene-1 in the presence and absence of cuprous chloride. (a) A mixture of octene-1 (0.7 mole) and benzoyl peroxide (0.083 mole) was heated to 100°. A strong exothermic reaction followed and all of the peroxide was consumed in approximately 1 hr. Carbon dioxide (0.066 mole) was evolved during the reaction.

The reaction mixture was washed with a dilute solution of sodium carbonate to remove benzoic acid (0.0055 mole). The organic layer was washed with water, and dried with sodium sulfate. The drying agent was collected on a filter and the filtrate distilled at reduced pressure to remove the unreacted octene-1. The boiling point, index of refraction and the infrared spectrum indicated that the distillate was pure octene-1. No isomerization of the octene-1 to octene-2 took place during the course of the reaction.

After removing the octene-1, the Residue I was distilled at reduced pressure, and the fraction boiling at 85–90°/0.1 mm. was collected (Fraction I). The remaining material was transferred to a molecular still and the material distilling at 100–105°/10^{-4} mm. was collected (Fraction II). The Residue (II) remaining after this distillation was a semi-solid material of the consistency of vaseline (26 g.).

Fraction I (0.017 mole; n_D^{20} 1.4916; mol. wt. 222) was shown by analyses and infrared spectrum to be a mixture of 60% of the 1:1 adducts, [($C_5H_{11}CH_2CH_2CH_2OCOC_6H_5$) and ($C_5H_{11}CH{=}CHCH_2OCOC_6H_5$)], and 40% of phenyloctene. The unsaturation (30%) in this same material was determined by ozonolysis and bromate-bromide titration.

Fraction II (0.021 mole; n_D^{20} 1.4900; mol. wt. 335) was presumed an impure 1:2 adduct. The unsaturation (30%) in this material was determined by ozonolysis.

Residue II could not be distilled. Lower boiling materials were removed from it in a molecular still. The material appeared to be an adduct containing one benzoyloxy unit to four octane units, or a mixture of adducts having a similar ratio of benzoyloxy and octene units.

Residue II. *Anal.* $C_{39}H_{68}O_2$ (60%) + $C_{39}H_{70}O_2$ (40%). Calcd. for: C, 82.15; H, 12.23; mol. wt. 570. Found: C, 82.5; H, 11.7; mol. wt. 605.

The unsaturation of Residue II (60%) was determined by ozonolysis. Residue II was quite soluble in petroleum ether, ether, chloroform and ethyl acetate. It was readily soluble in benzene. A solution of Residue II in alcoholic potassium hydroxide, when heated, gave sodium benzoate and an oil. Examination of the infrared spectrum of the oil established that it did not contain benzoyloxy or aromatic groups.

The yields of the various fractions are given in Table I.

Reaction of benzoyl peroxide with octene-1 in the presence of cuprous salts. Cuprous bromide (1 mole % on the basis of the peroxide used) was added to a solution of benzoyl peroxide (0.25 mole) in octene-1 (2 moles) and heated to 100°. A rapid exothermic reaction followed and no peroxide could be detected in the reaction mixture after 15 min. Carbon dioxide (0.11 mole) was evolved during the reaction.

The reaction mixture was shaken with a water solution of sodium carbonate and the extracted benzoic acid (0.18 mole) was recovered from the alkaline solution. The organic layer was dried over sodium sulfate. After removal of the inorganic salt, the organic layer was distilled at reduced pressure. The unchanged octene was collected first. The residue was then distilled at low pressure and the following fractions collected: Fraction I: b.p. 83–84.5°/1 mm., d_4^{23} 0.871; n_D^{23} 1.4932. Fraction II: b.p. 90–100°/0.1 mm., n_D^{23} 1.4985. Residue I.

Fraction I (0.02 mole) was a somewhat impure mixture of phenyl octane and a phenyl octene, containing a small quantity of benzoyloxy octene.

Calcd. for phenyl octene: $C_{14}H_{20}$: C, 89.3; H, 10.7, mol. wt. 188. Found: C, 88.2; H, 11.0, mol. wt. 192.

The infrared spectrum of this material indicated the presence of a *trans* double bond.

(20) J. J. Cadogan, W. Gold, and D. P. N. Satchell, *J. Chem. Soc.*, 561 (1955).

(21) E. L. Eliel, P. H. Wilken, F. T. Fang, and S. H. Wilen, *J. Am. Chem. Soc.*, **80**, 3303 (1958).

(22) R. S. Mulliken, *J. Chim. Phys.*, **51**, 341 (1954).

Fraction II (0.09 mole) was shown to be a mixture of the benzoyloxyoctane and benzoyloxyoctene.

Calcd. for benzoyloxyoctene: $C_{15}H_{20}O_2$: C, 77.5; H, 8.7; mol. wt. 232. Found: C, 77.0; H, 8.8; mol. wt. 226.

Ozonolysis of this material indicated that it contained 75% double bonds. This value was in excellent agreement with a bromate-bromide titration (78%). The infrared spectrum of this same material showed about 70% trans double bond and 30% terminal double bonds.

Residue I was transferred to a molecular still and the material which distilled at 100–110°/10^{-4} mm. was collected (Fraction III).

Fraction III (0.9 mole, n_D^{23} 1.4950) was evidently an adduct containing one double bond for one benzoyloxy unit and two octene units. The infrared spectrum indicated only non-terminal double bonds.

Calcd. for: $C_{23}H_{36}O_2$: C, 80.2; H, 10.5; mol. wt. 334. Found: C, 80.6; H, 10.5; mol. wt. 325.

Ozonolysis of Fraction III indicated that there was one double bond per molecule.

After removing Fraction III from the molecular still, there remained 3.8 grams of a material, probably a high-addition-polymerization adduct of the type previously discussed. It was not investigated.

Reaction of benzoyl peroxide in octene-1, in the presence of benzene as solvent. A mixture of benzoyl peroxide (0.1 mole), octene (0.5 mole), cuprous chloride (1 mole % on the basis of the peroxide used) was warmed in benzene (2 moles) at 65° for 12 hr. To complete the reaction, it was heated to 80° for an additional 5 hr. The reaction mixture was worked up as in the previous case. We isolated benzoic acid (0.092 mole): Fraction I; b.p. 70–71°/0.15 mm., n_D^{20} 1.5225: Fraction II; b.p. 95–100°/0.1 mm., n_D^{20} 1.5070: and, a residue; (5 g.) n_D^{20} 1.5050.

Fraction I was almost pure 1-phenyloctene-1 (45%).

Calcd. for $C_{14}H_2O$: C, 89.3; H, 10.7. Found: C, 89.6; H, 10.4.

A comparison of its infrared spectrum with that of 1-phenyloctene-2 showed that absorption peaks at 740 cm.$^{-1}$ and 3000 cm.$^{-1}$ are much stronger. Instead of a single peak at 1500 cm.$^{-1}$, Fraction I had a double peak, 1500 cm.$^{-1}$ and 1478 cm.$^{-1}$ The ultraviolet adsorption showed a maximum at 247 millimicrons.

Fraction II, benzoyloxyoctene (23%). Infrared spectrum showed about half as much terminal double bond, as the 1:1 adduct obtained in excess octene. Fraction II had an additional medium peak at 1778 cm.$^{-1}$ After alkaline hydrolysis, the infrared spectrum indicated the presence of an aldehyde (peaks at 2700 cm.$^{-1}$ and 1725 cm.$^{-1}$). Fraction II gave a dinitrophenylhydrazone, m.p. 106°,[23] (caprilic aldehyde).

Reaction of benzoyl peroxide with octene-2. A mixture of benzoyl peroxide (0.04 mole) and octene-2 (0.32 mole) was slowly heated to 95° and maintained at that temperature for 2 hr. A strong exothermic reaction ensued and most of the carbon dioxide (0.019 mole) was liberated in the first 10 min. The reaction mixture was shaken with a water solution of sodium carbonate to remove the benzoic acid (0.012 mole) formed during the reaction. The organic layer was dried and the unchanged octene-2 was removed by distillation. The residue was distilled at reduced pressure and the following fractions were collected: Fraction I: b.p. 87–93°/0.2 mm. Fraction II: b.p. 120–125°/0.2 mm. Residue: 1 gram.

Fraction I (0.035 mole; n_D^{20} 1.4825) was a mixture of the saturated (40%) and unsaturated (60%) adducts of one benzoyloxy unit to one octene unit. The molecular weight of this material was 225 as compared with a calculated value of 232.

Fraction II (0.0054 mole; n_D^{20} 1.4930) was presumed to be a mixture of adducts (saturated and unsaturated) consisting of one benzoyloxy unit to two units of octene. The molecular weight of this material was 330 as compared with a calculated value of 324.

Reaction of benzoyl peroxide with octene-2 in the presence of cuprous salts. Cuprous chloride (2 mole % on the basis of the peroxide used) was added to a solution of benzoyl peroxide (0.041 mole) in octene-2 (0.28 mole). The mixture was heated to 95°. A fast exothermic reaction followed, and the carbon dioxide (0.02 mole) was liberated in 10 min. The heating was continued for 1 hr. longer. The reaction mixture was then washed with a water solution of sodium carbonate. The layers were separated, and the benzoic acid (0.028 mole) was isolated from the alkaline solution.

The organic layer was dried with anhydrous sodium sulfate and the drying agent collected on a filter. The octene-2 was then distilled off from the filtrate. The residue was distilled at reduced pressure and collected.

Fraction I (b.p. 93°/0.2 mm.; 0.03 mole; n_D^{20} 1.4957) was a mixture of saturated (7%) of unsaturated (93%) adducts of one benzoyloxy unit and one octene unit. The molecular weight of the material (cryoscopic in benzene) was 226 as compared with a calculated value of 230.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.5; H, 8.7. Found: C, 77.9; H, 9.0.

Fraction I was hydrolyzed with alcoholic potassium hydroxide and the benzoic acid formed during the reaction was removed by the usual procedure. The infrared spectrum of the non-acidic material (mostly octenol) showed a weak band at 700 cm.$^{-1}$, indicating the presence of no more than 5% of the phenylated octene.

The residue (1.5 g.) most probably consisted of higher addition-polymerization product. It was not investigated.

Decomposition of benzoyl peroxide in cumene, in the presence of copper salts. Benzoyl peroxide (0.1 mole) was dissolved in cumene (1.5 moles), in the presence of cuprous chloride (0.0006) and was heated to 85°, under vigorous stirring. The peroxide decomposed in an exothermic reaction in approximately 10 min., accompanied by the evolution of 0.1 mole of CO_2. The crude reaction mixture was washed with dilute sodium carbonate solution. After acidification, benzoic acid (0.05 mole) was recovered from the aqueous layer. The organic layer was dried over anhydrous sodium sulfate, filtered, and distilled in vacuo. After collecting the unreacted cumene, three fractions were separated, leaving 7 grams of residue.

The first fraction, b.p. 50–60°/0.2 mm. was acetophenone, containing a α-cumyl alcohol (0.013 mole). The second fraction, b.p. 90–95°/0.10 mm. consisted of a mixture of isopropylbiphenyls (0.02 mole). The third fraction, b.p. 110–112°/0.10 mm. was shown to be α-cumyl benzoate, 0.03 mole, n_D^{20} 1.5560.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.7; mol. wt. 240. Found: C, 80.15; H, 6.9; mol. wt. 231.

The infrared spectrum indicated a monosubstituted benzene ring in the 700–900 cm.$^{-1}$ region, and a benzoyloxy group on the side chain, adsorption peak at 1715 cm.$^{-1}$ Alkaline hydrolysis gave benzoic acid and α-cumyl alcohol, identified as its thioglycolic acid derivative. Pyrolysis yielded benzoic acid and α-methylstyrene dimers.

All fractions were tested for dicumene, by attempted crystallization in both alcohol and nitromethane, at −80°. Dicumene, even 2% by weight would have been detected, were it present. The infrared spectra of the isopropyl biphenyls indicated the same composition as that which occurred in the absence of copper salts. The α-cumyl benzoate was identical with an authentic sample. The residue had a molecular weight of 290 and its infrared spectra suggested it to be mostly phenyl α-cumyl benzoate.

Reaction of tert-butyl perbenzoate in cumene, in the presence of copper salts. Tert-butyl perbenzoate (0.068 mole) was added, dropwise, to a well stirred suspension of cuprous chloride (0.0006 mole) in cumene (0.7 mole) over a period of 6 hr. The reaction was worked up in the usual manner. We isolated benzoic acid (0.034 mole), 50%; a mixture of

(23) H. Stephen, *J. Chem. Soc.*, 127, 1874 (1925).

acetophenone and carbinol (approx. 0.02 mole), 30%; and α-cumyl benzoate (0.07 mole), 40%.

Reaction of valeraldehyde, benzoyl peroxide, and carbon tetrachloride in the presence and absence of cuprous salts. (a) A mixture of valeraldehyde (0.0475), benzoyl peroxide (0.0246 mole) and carbon tetrachloride (0.25 mole) was heated at 76° for 6 hr. At the end of that time, all gas evolution (0.02 mole) had ceased. The benzoic acid (0.003 mole) formed in the reaction was separated by the usual procedure. The chloroform formed in the reaction was separated by distillation and identified. The formation of hydrogen chloride during the course of the reaction was also demonstrated.

The major reaction product was a mixture (0.29 mole) of the unsymmetrical benzoyl valeroyl anhydride and the two symmetrical anhydrides.

(b) A mixture of valeraldehyde (0.1 mole), benzoyl peroxide (0.05 mole), carbon tetrachloride (0.3 mole) and cuprous chloride (0.2 gram) was heated to 76° for less than 1 hr. The gas evolution (carbon dioxide 0.017 mole) ceased at the end of 30 min. The benzoic acid (0.032 mole) formed during the reaction was separated by the usual procedure. Under the conditions described in (a), no chloroform and hydrogen chloride (volatile acid) were formed in the reaction. The reaction product (0.05 mole) appeared to be valeroyl benzoyl anhydride (b.p. 100°/15 mm., n_D^{20} 1.4835) and a mixture of the two symmetrical anhydrides.

Reaction of tert-butyl peroxide in benzaldehyde in the presence and the absence of cuprous salts. (a) A mixture of benzaldehyde (0.47 mole) and *tert*-butyl peroxide (0.068 mole) was heated at 140° for 24 hr. The evolved methane gas (0.0043) was collected. The low boiling materials (benzaldehyde and unreacted peroxide) were removed by distillation at reduced pressure. The residue (0.054 mole, calculated on the basis that it was a mixture of the *meso* and racemic forms of benzopinacol dibenzoate) was crystallized from methanol. The *meso* form of benzopinacol dibenzoate (0.015 mole) obtained melted at 244°. The methanol filtrate was evaporated, leaving an oily residue. Repeated crystallization of this residue material from a mixture of ether and petroleum ether gave a solid material (0.018 mole), which melted quite sharply in an evacuated melting point tube at 115°. This solid was presumed to be the racemic form of benzopinacol dibenzoate.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.6; H, 5.3; mol. wt. 422. Found: C, 79.8; H, 5.5; mol. wt. 440 (camphor).

(b) A mixture of benzaldehyde (0.45 mole), *tert*-butyl peroxide (0.072 mole) and cuprous chloride (0.7 g.; 0.001 mole) was heated at 140° for 6 hr. The reaction mixture was worked up in the usual way. The major reaction product (83%) was *tert*-butyl benzoate (b.p. 92°/10 mm.; n_D^{20} 1.4915). *Tert*-butyl benzoate is known to boil at 94°/10 mm.[24]

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.3; H, 7.9.

The minor reaction products were the *meso* and racemic forms of benzopinacol dibenzoate (5%).

The infrared spectrum of the *tert*-butyl benzoate obtained with peaks at 1710 cm.$^{-1}$ (benzoate), and 1375 cm.$^{-1}$ and 1395 cm.$^{-1}$ (*tert*-butyl group) was in agreement with the structure assigned to this compound. *Tert*-butyl benzoate was stable when warmed in an alcoholic solution of potassium hydroxide. However, an acetic acid solution of the ester was rapidly hydrolyzed by strong acids.

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CHICAGO, ILL.

(24) V. R. Stimson, *J. Chem. Soc.*, 2673 (1955) states that *tert*-butyl benzoate boils at 50°/0.5 mm. (n_D^{20} 1.4900).

[CONTRIBUTION FROM SOUTHERN REGIONAL RESEARCH LABORATORY[1] UNITED STATES DEPARTMENT OF AGRICULTURE]

Reaction of Epichlorohydrin with Cyclohexylamine

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The addition of epichlorohydrin to cyclohexylamine through the epoxide group has been reinvestigated. Two chlorohydrins, *N*-(3-chloro-2-hydroxypropyl)cyclohexylamine and *N*,*N*-bis(3-chloro-2-hydroxypropyl)cyclohexylamine, have been isolated. These compounds have been converted to their respective epoxides and hydrochlorides.

Modern research[3,4,5] has shown various amines react with epichlorohydrin to form *N*-(3-chloro-2 hydroxypropyl)amines. In view of these findings it seemed advisable to reconsider the earlier investigation of Wedekind and Bruch.[6] These latter investigations showed that when cyclohexylamine was treated with epichlorohydrin (3.5 to 1 mole ratio of amine to epoxide) on a water bath, small yields of 1,3-bis(cyclohexylamino)-2-propanol were obtained, in addition to considerable quantities of cyclohexylamine hydrochloride and unidentified tars. We have confirmed this observation, since the reaction easily gets out of hand even when the correct ratio of amine to epoxide is used. However, this investigation has demonstrated that a slow, smooth reaction, which gave the desired products, occurred when mutual solvents were used at room temperature.

In order to prepare the mono- and diepichlorohydrin derivatives of cyclohexylamine, increasing mole ratios of epichlorohydrin to amine were in-

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(3) N. S. Drozdov and O. M. Cherntzov, *J. Gen. Chem. (U.S.S.R.)*, **4**, 969 (1934); through *Chem. Abstr.*, **29**, 2148 (1935).

(4) R. Rothstein and K. Binovic, *Compt. rend.*, **236**, 1050 (1953).

(5) G. Chanpetier, G. Montegudet, and J. Petit, *Compt. rend.*, **240**, 1896 (1955).

(6) E. Wedekind and E. Bruch, *Ann.*, **471**, 95 (1929).

vestigated. At a 1:1 (epichlorohydrin to amine) molar ratio a 60–63% yield of *N*-(3-chloro-2-hydroxypropyl)cyclohexylamine (I) was obtained; but the investigation was laregly made at a 2:1 (epichlorohydrin to amine) molar ratio. When the latter molar ratio was used with petroleum ether as a solvent, and the reaction mixture kept at 25° or below, a large quantity of crystalline precipitate formed after 4–5 hours. If the reaction was allowed to continue for 16–20 hours, or if the temperature was lowered to 8–10°, a highly viscous liquid was also precipitated. The isolated crystals were largely I. In addition to this compound, there were small quantities of crystals (II) insoluble in hot petroleum ether, which were identified as the hydrochloride of I. The viscous liquid formed was composed mainly of *N,N*-bis(3-chloro-2-hydroxypropyl)cyclohexylamine (III). When the reaction was carried out in petroleum ether, there was no evidence to show the formation of cyclohexylamine hydrochloride[7] (V) (lit. m.p. 204°). In experiments conducted in dioxane, however, trace quantities of V were isolated. Whether it forms as in reaction 5 or by amine attack on carbon with the displacement of the chloride group is not known. No 1,3-dicyclohexylamino-2-propanol, the only compound identified by Wedekind and Bruch,[6] was observed under the mild conditions of this investigation.

In view of the products obtained, the following reaction scheme appears probable at temperatures less than 25°:

$$C_6H_{11}NH_2 + CH_2ClCH\!-\!CH_2 \longrightarrow C_6H_{11}NH\!-\!CH_2\!-\!CHOH\!-\!CH_2Cl \quad (I) \quad (1)$$
(30–70% yield)

$$C_6H_{11}NH\!-\!CH_2\!-\!CHOH\!-\!CH_2Cl + CH_2Cl\!-\!CH\!-\!CH_2 \longrightarrow C_6H_{11}N(CH_2CHOHCH_2Cl)_2 \quad (III) \quad (2)$$
(28 and upwards % yield)

$$C_6H_{11}NHCH_2\!-\!CHOHCH_2Cl \xrightarrow{\Delta} C_6H_{11}NHCH_2\!-\!CH\!-\!CH_2 \ (IV) + HCl \quad (3)$$

$$C_6H_{11}NHCH_2CHOHCH_2Cl + HCl \longrightarrow C_6H_{11}NHCH_2CHOHCH_2Cl\cdot HCl \quad (II) \quad (4)$$
(less than 1%)

$$C_6H_{11}NH_2 + HCl \xrightarrow{\text{dioxane}} C_6H_{11}NH_2\cdot HCl \ (V) \quad (5)$$

The relative yields of I, II, and III were apparently dependent on speed and temperature of the reaction; a high yield of the monosubstituted product I occurring when the reaction was run at 20–25°, and the lower yield when the reaction mixture was maintained at 8–10°. At the higher temperature, the insoluble monochlorohydrin formed faster but precipitated quickly from the reaction medium. When the medium was initially colder, the monochlorohydrin formed slowly enough that it was converted to the dichlorohydrin before its solubility was exceeded. Compound III formed in either case. If the reaction temperature was increased, and this was especially true when no solvent was used, polymer formation with further evolution of heat occurred from the epoxide formed (reaction 3).

Compounds I and II were dehydrochlorinated with commercial sodium orthosilicate (a thick gummy paste) in dioxane solution.[8] With this method, 80% conversion to epoxide based on oxirane oxygen analyses was obtained. On distillation of the epoxides, however, these yields were greatly reduced owing to polymerization of the monomeric epoxide probably due to traces of dissolved alkali. A second distillation showed that the epoxides are thermally stable.

EXPERIMENTAL

When cyclohexylamine (0.2 mole) and epichlorohydrin (0.4 mole) were dissolved in 100 ml. of dioxane and kept at 8° overnight, a small amount (1.4 g.) of cyclohexylamine hydrochloride (m.p. 203°) precipitated and was filtered off. The dioxane solution was treated with sodium orthosilicate paste for 1 hr. at 45–50°. After the solution was filtered and stripped of dioxane, only 26.1 g. of product remained. The product was a pitch-like, reddish polymer. Therefore, the use of dioxane as a reaction medium was abandoned in favor of petroleum ether.

Preparation of N-(3-chloro-2-hydroxypropyl)cyclohexylamine I and its hydrochloride II. To 99 g. (1.0 mole) of distilled (b.p. 133°) Eastman[9] White Label cyclohexylamine in 500 ml. of petroleum ether (b.p. 62–69°) were added 185 g. (2.0 moles) of reagent grade epichlorohydrin. The agitated two-phase system was kept at 20–25° for 17 hr. and filtered. Approximately 137 g. of washed snow-white crystals was obtained (71.5% yield based on cyclohexylamine). The compound I after crystallization in hot petroleum ether melted at 79–80°.

Anal. Calcd. for $C_9H_{18}ClNO$: Cl, 18.0; N, 7.30. Found: Cl, 18.0; N, 7.25.

Another crystalline solid (1.8 g.) present was insoluble in hot petroleum ether and melted at 155° when purified (II). Compound I was unstable above its melting point, leading first to a clear liquid, and, finally, to a waxy white solid having a wide melting range 80–185°. Pure compound I was only very slightly soluble in water and gave no chloride ion test. After decomposition, the material was partially water-soluble and showed a strong chloride ion test. Note Reactions 3 and 4. With identical amounts of reagents but at 8–10° a much lower yield of monochlorohydrin I was obtained (38%). At the lower temperature, the dichlorohydrin III yield was approximately 40% and 4.5 g. of compound (II) were formed.

Compound II (m.p. 155°) was water-soluble and gave a test for chloride ions.

Anal. Calcd. for $C_9H_{19}Cl_2NO$: total Cl, 31.1; ionic Cl, 15.5; N, 6.2. Found: total Cl, 30.0; ionic Cl, 15.5; N, 6.1.

Compound II was synthesized, also, by passing dry HCl into an ether solution of I.

Preparation of N,N-bis(3-chloro-2-hydroxypropyl)cyclohexylamine (III) and its hydrochloride. When the 2 liquid phases formed in the preparation of I were separated, either

(7) A. Skita and W. Berendt, *Ber.*, **52**, 1519 (1919).

(8) N. V. de Bataafsche Petroleum Maatschappij, Brit. Patent 779,092 (July 17, 1957).

(9) Trade names have been used to identify materials used in the work, and such use does not imply endorsement or recommendation by the U. S. Department of Agriculture over other products not mentioned.

spontaneously or by the evaporation of some of the petroleum ether, the heavy viscous liquid was mainly compound III. A small quantity of II also was isolated from it by taking up the oil in chloroform and diluting with petroleum ether. Removal of the solvents led to product III.

Anal. Calcd. for $C_{12}H_{17}Cl_2NO_2$: Cl, 25.0; N, 4.93. Found: Cl, 24.85; N, 4.52.

Compound III was also prepared by reacting equimolar quantities of I and epichlorohydrin at room temperature in chloroform solution for 2 days.

Anal. Found: Cl, 26.2; N, 4.72.

Compound III was soluble in alcohol, chloroform, and dioxane, but insoluble in petroleum and ethyl ethers. Attempts to vacuum-distill compound III resulted in decomposition. A micro boiling point determination resulted in no definite b.p. up to 165° at 2.5 mm. pressure; and a solid brown resin resulted.

A *hydrochloride* (m.p. 174–175°) was formed when HCl gas was passed into a chloroform solution of III and allowed to cool. The solid was crystallized from chloroform or dioxane.

Anal. Calcd. for $C_{12}H_{23}Cl_2NO_2 \cdot HCl$: ionic Cl, 11.08. Found: ionic Cl, 11.13.

Dehydrochlorination of I. To 0.1 mole of I in dioxane were added 30 g. of commercial sodium orthosilicate paste. After the suspended silicate was stirred, the temperature rose to 40°, and was maintained for 1 hr. at 55–60°. The silicates and chlorides were removed by filtration and the solvent removed under vacuum. The yield of crude epoxide was 12.3 g. (79%) as determined by titration with hydrobromic acid.[10] Over 50% of the yield was lost during vacuum distillation due to polymer formation. The distilled epoxide, b.p. 90° (3.5 mm) was a clear mobile liquid (d_4^{26} 0.9934). The product was water-soluble (*p*H 8) and polymerized in water on standing to form a soft deformable solid. It self-polymerized on standing at room temperature in a few days to a clear, colorless resin, soluble in acetone.

Anal. Calcd. for *N*-(2,3-epoxypropyl)cyclohexylamine (IV): oxirane oxygen, 10.3; N, 8.92. Found: oxirane oxygen 10.6; N, 8.8.

When HCl was passed into an ether solution of IV, compound II was formed (m.p. 155°). It should be noted that an amine-epoxide such as IV requires two equivalents of HBr in Durbetaki's oxirane method.[10]

Dehydrochlorination of III. When 0.1 mole of III was dehydrochlorinated,[8] an 82% conversion to epoxide based on oxirane oxygen analyses was obtained. Vacuum distillation at 126–128° at 4 mm. resulted in the formation of *N,N*-bis(2,3-epoxypropyl)cyclohexylamine.

Anal. Calcd. for $C_{12}H_{21}NO_2$: oxirane oxygen, 15.1; N, 6.6. Found: oxirane oxygen, 14.9; N, 6.44.

The product was a colorless mobile liquid which yellowed slightly on exposure to air, but did not polymerize on standing. The distilled product (d_4^{24} 1.0403) was largely insoluble in water (*p*H 7). The polymers formed on distillation were acetone- and methanol-soluble.

Acknowledgment. We thank Messrs. Julian F. Jurgens and Voyce P. Whitley of the Analytical Laboratory (SURDD) for some of the chlorine and nitrogen analyses, and especially do we wish to thank Ruth Benerito of this laboratory for her advice in connection with this manuscript.

(10) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

NEW ORLEANS, LA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

Studies on 1-Phenylcycloalkyl Derivatives: A New Aldehyde Synthesis

JAMES W. WILT AND BROTHER HERBERT PHILIP, F.S.C.[1]

Received November 11, 1958

The synthesis and properties of some 1-phenylcycloalkyl derivatives in the three-, five- and six-membered ring systems are reported. These materials constitute intermediates in a useful conversion of acids with α-quaternary carbon centers into β-substituted acetaldehyde derivatives.

During our investigation of the synthesis and peroxide-induced, liquid-phase decarbonylation of some 1-phenylcycloalkylacetaldehydes[2] we have had occasion to prepare a number of 1-phenylcycloalkyl derivatives, heretofore unreported, which constitute intermediates in a new interesting aldehyde synthesis.

The sequence is illustrated in formulas I–VII. The transformation of the known 1-phenylcycloalkylcarbonitriles (I) into their corresponding acid chlorides III follows established routes.[3] In an effort to construct the aldehyde side chain *via* the acids II by the Rosenmund method, the attempted homologation of these acids by the Arndt-Eistert sequence[4] failed. The formation of the α-methoxy ketones (IV) by the catalyzed interaction of methanol and the diazo ketones derived from III proceeds quite satisfactorily.[5] In these reactions the customary[6] use of excess diazomethane is advisable. Otherwise, subsequent reaction of the diazo ketone with the methanol is immediate, with little or no boron trifluoride

(1) An Arthur Schmidt Pre-doctoral Fellow, 1957–58.

(2) Paper presented at the Fall Chemistry Conference of the *American Chemical Society*, Kansas City, Mo., November 14, 1958.

(3) Among many references to these substances are: (a) F. Case, *J. Am. Chem. Soc.*, **56**, 715 (1934); (b) A. W. Weston, *J. Am. Chem. Soc.*, **68**, 2345 (1946); and (c) R. E. Lyle and G. G. Lyle, *J. Am. Chem. Soc.*, **74**, 4061 (1952).

(4) W. E. Bachmann and W. S. Struve, *Org. Reactions*, 1, 38 (1942).

(5) The method of M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.*, **72**, 5161 (1950).

(6) W. J. Hickinbottom, *Reactions of Organic Compounds*, Second Edition, Longmans, Green and Co., London, 1948, p. 259.

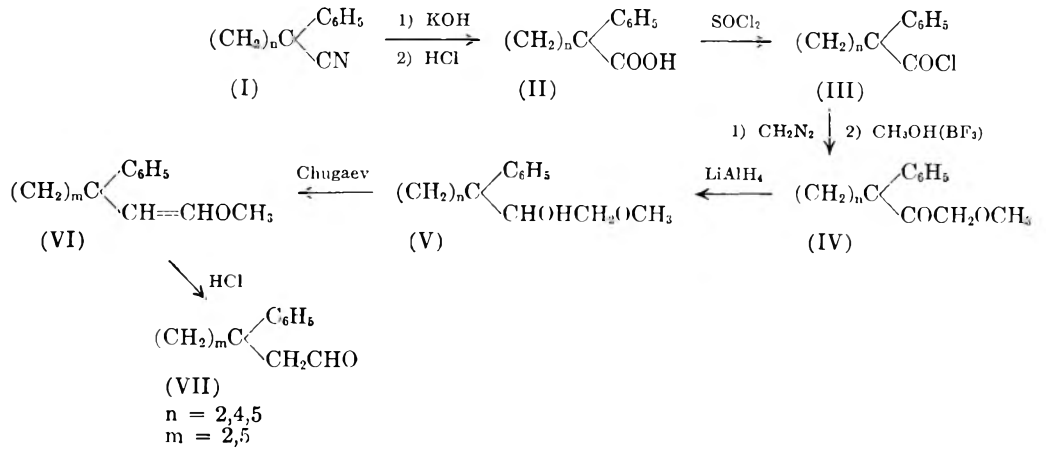
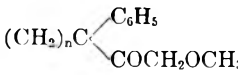


TABLE I

1-PHENYLCYCLOALKYL METHOXYMETHYL KETONES (IV)

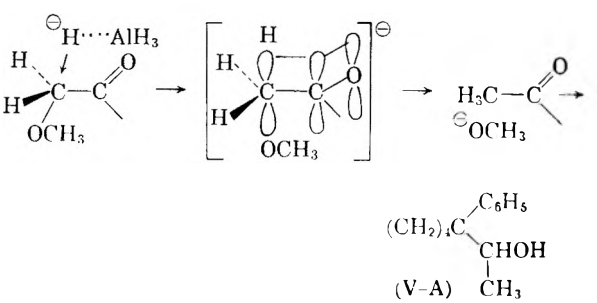


n	Yield (%)	B.P.(°C.)	Mm.	n_D^{20}	d_4^{20}	Analyses[a] Calcd. C	Calcd. H	Found C	Found H
2[b]	88	96–97	0.8	1.5290	1.103	75.76	7.41	75.56	7.32
4[c]	70	88–90	0.2	1.5310	1.070	77.03	8.31	76.90	8.13
5[d]	73	122–125	0.4	1.5364	1.078	77.57	8.68	77.48	8.66

[a] All combustion analyses by Galbraith Laboratories, Knoxville, Tenn. [b] 2,4-Dinitrophenylhydrazone, m.p. 178–179°. *Anal.* Calcd. for $C_{18}H_{18}N_4O_5$: N, 15.12. Found: N, 14.85. [c] 2,4-Dinitrophenylhydrazone, m.p. 145.5–146.5°. *Anal.* Calcd. for $C_{20}H_{22}N_4O_5$: N, 14.10. Found: N, 14.06. [d] 2,4-Dinitrophenylhydrazone m.p. 169.5–170.5°. *Anal.* Calcd. for $C_{21}H_{24}N_4O_5$: N, 13.59. Found: N, 13.60.

catalysis needed, and the α-methoxy ketone product is less pure.[7] The properties of these α-methoxy ketones are given in Table I.

The reduction of the α-methoxy ketones IV to the corresponding alcohols V by means of lithium aluminum hydride proceeds acceptably in the cyclopropyl and cyclohexyl compounds. The attempted reduction of IV (n = 4) in the normal fashion, however, leads to much recovered ketone. When longer reaction times are employed, an apparent reductive displacement of the methoxyl function occurs and a mixture of V (n = 4) with the *methyl* carbinol (V-A) results. Reduction of α-methoxy ketones to the corresponding alcohols with lithium aluminum hydride appears to be unreported previously. There are, therefore, no precedents for reductive displacement of the methoxyl function in such reactions.[8] The reactivity of these substances to such reductive displacement may be rationalized in that the transition state for such a process would be stabilized through the interaction of the developing *p*-orbital of the carbon atom undergoing attack with the pi-orbital of the adjacent carbonyl group, as shown in the following:



Analogous mechanisms have been proposed for the great reactivity of α-halo ketones in nucleophilic displacement reactions.[9] Various attempts to separate this mixture of alcohols failed and no analytical sample of V (n = 4) was obtained. For this reason, the investigation of the substituted cyclopentyl compound was not carried further in any detail (see Experimental Part). The properties of the alcohols V are given in Table II. The

(7) We have observed spectrophotometrically and by the Beilstein test that these products have a minor contaminant containing chlorine, presumably the α-chloro ketone. Such a substance may be methanolyzed subsequently to the slight extent sufficient for proton catalysis of the methanol-diazo ketone reaction.

(8) Similar displacements have been observed in the reduction of α-alkoxy acids and α-halo ketones with lithium aluminum hydride. See N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, 1956, p. 644 and pp. 904–7.

(9) See the discussion of E. L. Eliel with several references in *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, 1956, pp. 103–6.

TABLE II

(1-PHENYLCYCLOALKYL)METHOXYMETHYLCARBINOLS (V)

$$(CH_2)_nC\begin{matrix}C_6H_5\\ \diagup\\ \diagdown\\ CHOHCH_2OCH_3\end{matrix}$$

n	Yield (%)	B.P.(°C)	Mm.	n_D^{20}	d_4^{20}	Analyses Calcd. C	Calcd. H	Found C	Found H
2	93	94–96	1.0	1.5330	1.082	74.96	8.39	74.83	8.42
4	87[a]	95–96	0.5	1.5329	1.066	...	..	...	..
5	64	119–121	0.3	1.5431	1.070	76.88	9.47	76.99	9.62

[a] Crude.

formal dehydration step proceeding from the methoxycarbinols V to the vinyl (enol) ethers VI was achieved at length by the Chugaev method.[10] Because of the pinacolyl character of the carbinols, acid-catalyzed dehydration was not attempted since it was considered likely to involve phenyl group migration and to result in a mixture of rearranged unsaturated ethers. Similarly, conversion of the carbinols to halides in normal fashion (e. g., using the phosphorus halides), followed by dehydrohalogenation of the β-halo ethers[11] was also avoided because retropinacol rearrangements seemed probable in the halide-producing step. The new method for such reactions due to Sommer[12] was not successful. The transformation of the carbinols to *p*-toluenesulfonate derivatives was moderately successful, but detosylation or conversion to halides by nucleophilic displacement reactions failed under a variety of conditions. Pyrolysis of the V-acetates on glass helices at 500–525°, according to the technique of Bailey,[13] led to extensive charring with little acetic acid elimination, although enol ether is detectable in the pyrolysate. Relevant to this point is the fact that the methoxyl function does not activate adjacent methylene hydrogens (indeed it may *de*activate them) to elimination in acetate pyrolyses.[14] While the Chugaev method was carried through in a detailed manner only in the cyclohexyl (n = 5) substance the elimination succeeds in both the ring compounds used, as evidenced by the good yield of appropriate aldehyde 2,4-dinitrophenylhydrazone directly from the crude enol ether VI (see Table III). The Chugaev dehydrations on α-methoxycarbinols appear to be the first such reported and constitute a novel entry to substituted acetaldehydes when the elimination is prevented in the other direction by a quaternary carbon site. The acid-catalyzed hydrolysis of the enol ethers VI is inordinately slow, most likely for steric reasons.[15] Nonetheless, slow conversion to the aldehydes VII is shown by the development of the 5.8–5.9μ band (C=O stretch) in the infrared spectrum of the hydrolysis products. This production of carbonyl substances from the enol ethers incidentally affords evidence that the reactions in this sequence take place without rearrangement, as does the identity of the aldehyde 2,4-dinitrophenylhydrazone (VII, m = 5) produced *via* this route with that obtained in another way.[16] The value of the sequence reported here would be greater if a practical route for the regeneration of these aldehydes from their 2,4-dinitrophenylhydrazones were available. The technique given in the literature[17] for analogous ketone regeneration fails

TABLE III

1-PHENYLCYCLOALKYLACETALDEHYDE (VII) 2,4-DINITROPHENYLHYDRAZONES

$$(CH_2)_mC\begin{matrix}C_6H_5\\ \diagup\\ \diagdown\\ CH_2CH{=}NNHC_6H_3(NO_2)_2\end{matrix}$$

m	Yield (%)	M.P.(°C.)	Analyses Calcd. N	Found N
2[a]	51	115.5–116.5	16.46	16.41
5[b,c]	90	163–164	14.65	14.53

[a] Yield from crude enol ether. [b] Enol ether, b.p. 105–107° at 0.5 mm., n_D^{20} 1.5409, d_4^{20} 0.960. *Anal.* Calcd. for $C_{15}H_{20}O$: C, 83.26; H, 9.34. Found: C, 83.30; H, 9.11. [c] Aldehyde, obtained by a route soon to be reported, b.p. 112–113° at 0.5 mm., n_D^{20} 1.5395, d_4^{20} 1.080. *Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.14; H, 8.95. Found: C, 82.95; H, 9.09. Oxidizes readily in air to 1-phenylcyclohexylacetic acid (85%), m.p. 85–86°. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.36; H, 8.31. G. F. Woods, *et al.*, *J. Am. Chem. Soc.*, **74**, 5126 (1952), report m.p. 85–86°.

(10) D. J. Cram, ref. 9, pp. 305–9.

(11) (a) W. M. Lauer and M. A. Spielman, *J. Am. Chem. Soc.*, **53**, 1533 (1931); (b) W. H. Puterbaugh and M. S. Newman, *J. Am. Chem. Soc.*, **79**, 3469 (1957).

(12) L. H. Sommer, H. D. Blankman, and P. C. Miller, *J. Am. Chem. Soc.*, **76**, 803 (1954).

(13) W. J. Bailey and H. R. Golden, *J. Am. Chem. Soc.*, **75**, 4780 (1953).

(14) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 648 (1956).

(15) Essentially instantaneous hydrolysis of enol ethers under acidic conditions is usually observed. *Cf.* ref. 11(a). The use of the "rule of six" of M. S. Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950), although not directly applicable to these compounds, does indicate such structures to be hindered about the enol ether double bond.

(16) J. W. Wilt and H. Philip (Hogan), F. S. C., *J. Org. Chem.*, **24**, 441 (1959).

(17) J. Demaecker and R. H. Martin, *Nature*, **173**, 266 (1954).

here. Nevertheless, the synthesis does allow the construction of an acetaldehyde grouping from a "homologous" acid of lower carbon content.

EXPERIMENTAL

All melting points and boiling points are uncorrected. The former were determined on a Fisher-Johns block. Infrared spectra were obtained on a Perkin-Elmer Model 21 Infrared Spectrophotometer using sodium chloride optics. Since several preparations of most of the reported compounds were carried out, only representative procedures are described below. Individual preparations varied in slight detail in some cases.

1-Phenylcycloalkylcarbonitriles (I). The three nitriles were prepared by the method of Weston:[3b] *1-phenylcyclopropylcarbonitrile* (63%, b.p. 80° at 1 mm.); *1-phenylcyclopentylcarbonitrile* (45%, b.p. 127° at 3.5 mm.); *1-phenylcyclohexylcarbonitrile* (49%, b.p. 144–146° at 3.5 mm.).

1-Phenylcycloalkanecarboxylic acids (II). The three acids were obtained in nearly quantitative yield by the hydrolysis of the above nitriles with potassium hydroxide in diethylene glycol (190°, 3–4 days), followed by acidification:[3c] *1-phenylcyclopropanecarboxylic acid*, m.p. 87.5–88° (literature[3b] m.p. 86–87°); *1-phenylcyclopentanecarboxylic acid*, m.p. 155–156° (literature[3a] m.p. 158–159°); *1-phenylcyclohexanecarboxylic acid*, m.p. 121–122° (literature[3b] m.p. 121°).

1-Phenylcycloalkanecarboxylic acid chlorides (III). Treatment of the acids (II) with fresh thionyl chloride in the usual fashion gave the acid chlorides as follows: *1-phenylcyclopropanecarboxylic acid chloride* (93%, b.p. 96–97° at 0.8 mm.); *1-phenylcyclopentanecarboxylic acid chloride* (91%, b.p. 73–74° at 0.3 mm.); *1-phenylcyclohexanecarboxylic acid chloride* (85%, b.p. 126–127° at 2 mm.). While III (N = 2,5) are known compounds,[3b] III (n = 4) appears to be new. Because these materials decomposed readily on standing no analysis was attempted on III (n = 4).

1-Phenylcycloalkyl methoxymethyl ketones (IV). Into a cold (0–2°) solution of diazomethane (0.25–0.30 mole) in ether (250 ml.), prepared in the usual manner from nitrosomethylurea, was added dropwise with stirring a solution of the appropriate acid chloride (0.10 mole) in an equal volume of ether. The mixture was stirred in the cold until the evolution of nitrogen subsided (6–8 hr.). The yellow solution was washed with sodium bicarbonate solution (5%), dried over sodium sulfate and the ether removed. The crude diazo ketone was used directly in the next step.

Methanol (200 ml.) was added to the diazo ketone in one portion. Occasionally, if the diazo ketone had traces of acidic impurities present, nitrogen evolution occurred at this point. The purity and yield of the product in such instances suffered somewhat. Ordinarily, however, there was little reaction of the methanol with the diazo ketone on mixing. Boron trifluoride etherate (1.5 ml.) was next added and the mixture allowed to stand with stirring at room temperature overnight. Nitrogen evolution was normally 90–100% of theory. Excess methanol was removed by distillation and the crude methoxy ketone collected by a simple Claisen head vacuum distillation. The crude ketones were of excellent grade and were used subsequently as such, though the analytical samples were heart cuts of a column distillation. The materials exhibited normal C=O bands (5.75–5.85 μ) and O—CH_3 bands (6.86–6.90 μ) in their infrared spectra. The properties of the methoxy ketones are given in Table I, together with their readily prepared 2,4-dinitrophenylhydrazone derivatives.

(1-Phenylcycloalkyl)methoxymethylcarbinols (V). A solution of the appropriate methoxy ketone (IV) (0.25 mole) in dry ether (50–75 ml.) was added dropwise with stirring into a suspension of lithium aluminum hydride (2.66 g., 0.07 mole) in dry ether (100–150 ml.) held at 0°. Stirring was continued for an hour, followed by reflux for another 1–2 hr. Isolation of the carbinol was achieved in the customary manner using dilute hydrochloric acid (5%) in the work-up. The properties of the carbinols are given in Table II. The alcohols (V) showed a broad —O—H band (2.8–2.9 μ) and retained the methoxyl band in their infrared spectra. V (n = 4), as usually prepared, had a C=O (5.75 μ) peak present from unreduced ketone. Generally, however, the methoxy ketones could be entirely reduced in 3-hour reduction times. While the products V (n = 2,5) were blank in the C-methyl region (7.23–7.26 μ), V (n = 4) invariably showed a *moderately strong C-methyl peak* (7.24 μ) in addition to the aforementioned peaks. The appearance of this C-methyl absorption peak was evidence for the reductive displacement of the methoxyl function (see text of paper). The mixture of V (n = 4) with the C-methyl contaminant (assumed to be V-A) proved tenacious. Fractional distillation on available columns failed to separate the components. Various reduction times, periods of reflux, etc., gave mixtures of varying methylcarbinol contamination (C-methyl absorption intensity), but no method was found to remove V-A or to prevent its formation. Combustion analyses indicated 30–40% methylcarbinol (assuming a binary mixture). No derivatives of any of the alcohols (V) were obtained. Attempts to prepare various urethans, benzoates, and sulfonates gave oils. In the case of V (n = 2), rapid decomposition of the derivatives into dark tar was noticed.

1-Phenylcycloalkylacetaldehyde enol methyl ethers (VI). The S-methyl xanthate esters of the carbinols (V) were obtained by the method of Alexander and Mudrak,[18] with the excellent modification of using phenyllithium to obtain the alkoxide salt developed by Weinstock and Bordwell.[19] The xanthate esters were obtained as deep yellow-orange oils. Solidification of the xanthates did not occur. To establish the conditions for these eliminations, the pyrolysis of the cyclohexyl substance was investigated more thoroughly than the others. A typical pyrolysis is described. The crude S-methyl xanthate obtained from V (n = 5) (30 g., 0.127 mole) was heated at 190–195° (Wood's metal bath temperature) for 4.5 hr. vented into concentrated sodium hydroxide solution. Distillation under reduced pressure gave the crude enol ether (VI, m = 5) (17.5 g., 64%, b.p. 95–135° at 1 mm.). This material was taken up in ether, washed repeatedly with dilute (5%) sodium hydroxide, water, and then dried. The ether was removed from the dried extract and the enol ether distilled under vacuum. Its properties are given in Table III. The enol ethers (VI) so obtained were colorless to pale yellow oils with a faint odor. A strong C=C peak at 6.05 μ with no trace of carbonyl absorption (5.7–5.9 μ) characterized their infrared spectra. 2,4-Dinitrophenylhydrazone derivatives of their respective aldehydes (VII) were readily obtained in good yield upon treatment with the reagent in phosphoric acid-ethanol.[20] The yields and properties of these latter substances are given in Table III.

Attempted hydrolyses of the enol ethers (VI) *to the aldehydes* (VII). The rates of these hydrolyses were followed by the gradual diminution of the C=C peak of VI (6.05 μ) and the concomitant appearance of the C=O peak of the aldehydes (5.8–5.9 μ) as the time of reflux was lengthened. The hydrolyses were quite slow, considering the usually rapid hydrolysis of such ethers in acid.[11a] Thus, a mixture of VI (m = 5) (11.3 g., 0.052 mole), concentrated hydrochloric acid (1.8 ml.), water (12 ml.) and ethanol (95%, 25 ml.) was refluxed with stirring for 1 hr. The mixture was then poured over ice and extracted with ether. The extracts were

(18) E. R. Alexander and A. Mudrak, *J. Am. Chem. Soc.*, **72**, 1810 (1950).

(19) J. Weinstock and F. G. Bordwell, *J. Am. Chem. Soc.*, **77**, 6706 (1955).

(20) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

washed until neutral with dilute base and water, dried, and freed of ether. Distillation of the residual oil gave a series of fractions (8.1 g., b.p. 85–110° at 0.4 mm.), all of which showed both C=C and C=O bands in the infrared. Other hydrolyses involved reaction times as long as 12 hr. with Girard-T reagent work-up. While such measures decreased the enol ether content of VII, analytically pure samples of the aldehydes were not obtained. *1-Phenylcyclohexylacetaldehyde* (VII, m = 5) has been obtained pure, however, *via* another route[16] and its infrared spectrum was comparable to that of the aldehyde prepared in this work, with slight contamination by the enol ether evident.

CHICAGO 26, ILL.

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Catalytic Hydrogenation of 9,10-Epoxyoctadecanol and 9,10-Epoxyoctadecyl Acetate

SARA P. FORE AND W. G. BICKFORD

Received October 13, 1958

cis-9,10-Epoxyoctadecanol and *cis*-9,10-epoxyoctadecyl acetate have been hydrogenated in ethanolic solution employing palladium-carbon catalyst. Examination of the reaction products established the fact that nearly equal proportions of the 9- and 10-hydroxy isomers were formed in both cases. These results are in marked contrast to the preferential formation of methyl 10-hydroxyoctadecanoate encountered previously during the catalytic reduction of methyl 9,10-epoxyoctadecanoate. The difference in results obtained with the two esters is attributed to the relative position of the oxirane center with respect to the acyl and alkoxyl oxygen atoms of the ester.

Investigations conducted in this laboratory[2] and elsewhere[3,4] into the catalytic hydrogenation of the 9,10-epoxyoctadecaonates have shown that the reaction products consist principally of one positional isomer. Reduction of methyl *cis*-9,10-epoxyoctadecanoate, for instance, results in the formation of methyl 10-hydroxyoctadecanoate with little or no attendant formation of the 9-isomer.

The results obtained in our previous investigation suggested that the reaction proceeded by an ionic mechanism involving the preferential attack of a hydride ion on the ninth carbon-oxygen bond of an oxonium ion intermediate.[5] The specificity of the reaction was attributed to the influence exerted at both the oxirane center and the catalyst surface by the electrophilic —COO— group.

To obtain further information regarding the nature of this reaction we have now investigated the catalytic reduction of both *cis*-9,10-epoxyoctadecanol and *cis*-9,10-epoxyoctadecyl acetate. These epoxides were hydrogenated in ethanolic solution employing a palladium-carbon catalyst. The exact positions of the secondary alcohol groups thus formed were established by the following series of reactions: the diols obtained upon hydrolysis of the acetate, as well as those derived from the free alcohol, were oxidized to the corresponding keto acids; the oximes prepared from the keto acids were transformed by means of the Beckmann rearrangement; hydrolysis of the resultant amides and separation of the hydrolysis products were effected by the procedure of Bharucha and Gunstone[6]; the mixed dicarboxylic acid fraction was separated into its components by application of elution chromatography employing a modification[7] of the method of Higuchi *et al.*[8]

Application of the above described series of reactions to either *cis*-9,10-epoxyoctadecanol or *cis*-9,10-epoxyoctadecyl acetate resulted in the formation of azelaic and sebacic acids only, which were found to be present in nearly equimolar proportions. It may be concluded, therefore, that catalytic hydrogenation of either epoxide leads to the formation of equivalent amounts of the 9- and 10-hydroxy isomers. Apparently the acyl oxygen of the acetate exerted no greater directive influence on the course of the reaction than did the hydroxyl oxygen of the alcohol. These results are in marked contrast to those obtained by the catalytic hydrogenation of methyl *cis*-9,10-epoxyoctadecanoate and *cis*-9,10-epoxyoctadecanoic acid in which cases the 10-isomer was produced prefer-

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) C. H. Mack and W. G. Bickford, *J. Org. Chem.*, **18**, 686 (1953).

(3) I. G. V. Pigulevskiĭ and Z. Ya. Rubashko, *J. Gen. Chem. (U.S.S.R.)*, **9**, 829 (1939), *Chem. Abstr.*, **34**, 378 (1940).

(4) J. Ross, A. I. Gebhart, and J. F. Gerecht, *J. Am. Chem. Soc.*, **71**, 282 (1949).

(5) It was concluded that the ninth carbon atom of the epoxide was slightly positive with respect to the tenth carbon atom. Further support for this viewpoint is to be found in the observation of E. Jungermann and P. E. Spoerri, *J. Am. Chem. Soc.*, **75**, 4704 (1953), that hydrochlorination of methyl 9,10-epoxyoctadecanoate leads predominantly to the formation of methyl 9-chloro-10-hydroxyoctadecanoate.

(6) K. E. Bharucha and F. D. Gunstone, *J. Chem. Soc.*, 610 (1957).

(7) M. H. Chahine, E. R. Cousins, and R. O. Feuge, *J. Am. Oil Chemists' Soc.*, **35**, 396 (1958).

(8) T. Higuchi, N. C. Hill, and G. B. Corcoran, *Anal. Chem.*, **24**, 491 (1952).

entially. It is of interest to note in this connection that the —COOH group is much more electrophilic in nature than is either —OCOMe or —OH.[9] The essential structural difference between methyl 9,10-epxoyoctadecanoate and 9,10-epoxyoctadecyl acetate is the location of the oxirane group which is in the acid moiety of the former but in the alcohol moiety of the latter. It appears that the acyl oxygen does not exercise a directional influence on the hydrogenation when it is separated from the oxirane center by an alkoxyl oxygen. The origin of this effect can be traced to the low polarizability of the carbon-oxygen covalent bond as compared to that of the carbon-carbon covalent bond. That is, the alkoxyl oxygen of the ester interferes with the operation of the general inductive (field) effect in the case of the acetate. On the basis of the above observations, it may be concluded that the relative position of the oxirane center with respect to the acyl and alkoxyl oxygen atoms is an important factor in determining the course of the reaction.

EXPERIMENTAL

Since *cis*-9-octadecenol and *cis*-9-octadecenyl acetate were subjected to the same essential reactions, experimental details will be reported for the latter compound only.

Methyl oleate. Pecan oil was subjected to methanolysis employing sodium methylate as catalyst. The resultant mixed methyl esters were dissolved in acetone (1 g./10 ml.) and the saturated esters were removed by crystallization at −37°. Methyl oleate was isolated from the unsaturated fraction by means of two successive crystallizations from acetone (1 g./15 ml.) at −60°.

Anal. Calcd. for $C_{19}H_{36}O_2$: I.V., 85.6; diene, O. Found: I.V., 85.5; diene, 1.5; n_D^{20}, 1.4531.

cis-9-Octadecenol. This material was prepared by the sodium reduction of methyl oleate employing 1-butanol as the reducing alcohol.[10]

Anal. Calcd. for $C_{18}H_{36}O$: C, 80.52; H, 13.52; OH, 6.4; I.V., 94.5. Found: C, 80.62; H, 13.54; OH, 6.4; I.V., 94.0; n_D^{20}, 1.4620.

cis-9-Octadecenyl acetate. *cis*-9-Octadecenol was dissolved in a 200% excess of an acetic anhydride-pyridine reagent and stirred at 100° for 1 hr. The reaction mixture was drowned with water and extracted with ether. The ethereal solution was washed first with dilute hydrochloric acid, then with 5% sodium bicarbonate solution and finally with water. After the solution had been dried with sodium sulfate, the *cis*-9-octadecenyl acetate was recovered by evaporation of the ether.

Anal. Calcd. for $C_{20}H_{38}O_2$: I.V., 81.5; sap. equiv., 310.5. Found: I.V., 81.9; sap. equiv., 310.4; n_D^{20}, 1.4527.

cis-9,10-Epoxyoctadecyl acetate. *cis*-9-Octadecenyl acetate, 40.4 g. (0.13 mole), was dissolved in 100 ml. of chloroform and maintained at 15–20° during the dropwise addition of 249 ml. of a chloroform solution containing 0.143 mole of perbenzoic acid. Titration of aliquots showed that the theoretical quantity of oxygen had been absorbed after a reaction period of 2 hr. The reaction mixture was diluted with two volumes of ethyl ether, washed successively with 5% aqueous potassium hydroxide and distilled water and then dried over anhydrous sodium sulfate. After removal of the solvent, there was obtained 40.7 g. of *cis*-9,10-epoxyoctadecyl acetate.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73; oxirane O, 4.9. Found: C, 73.41; H, 11.63; oxirane O, 4.6.

1,9(10)-Octadecanediol. Epoxyoctadecyl acetate, 36.0 g., containing palladium-carbon catalyst, 7.2 g., was dissolved in 150 ml. of absolute ethanol. Hydrogenation at room temperature and an initial pressure of 27.5 p.s.i. was complete in 2.5 hr. After removal of the catalyst and addition of 14.5 g. of potassium hydroxide in 15 ml. of distilled water, the alcoholic solution was refluxed for 1 hr. to effect saponification of the ester. Recovery of the reaction product by the usual means yielded 30.1 g. of crude 1,9(10)-octadecanediol, m.p. 62–65°.

Anal. Calcd. for $C_{18}H_{38}O_2$: OH, 11.9. Found: OH, 10.6.

9(10)-Oxo-octadecanoic acid. Crude 1,9(10)-octadecanediol, 27.9 g. (0.097 mole), dissolved in 185 ml. of glacial acetic acid, was stirred and maintained at 30–35° during the dropwise addition of chromium trioxide, 26.3 g. (0.263 mole), dissolved in 18.5 ml. of distilled water and 273 ml. of glacial acetic acid. After addition of the reagent, which required 1 hr., the reaction mixture was maintained at the same temperature for another hour and then at 38–40° for 2 hr. The crystals which separated on dilution of the reaction mixture with water were boiled first with dilute hydrochloric acid and then with water. The resultant keto acids were dissolved in 826 ml. of 33% ethanol containing 12.0 g. of potassium hydroxide and extracted with ether for the removal of neutral materials. The keto acids, 20.6 g., were liberated from their potassium salts with dilute acid and recovered in the usual manner.

Anal. Calcd. for $C_{18}H_{34}O_3$: carbonyl O, 5.36; neut. equiv., 298.5. Found: carbonyl O, 4.51; neut. equiv., 298.0,

Oximes of oxo-octadecanoic acids. A solution of 12.4 g. (0.21 mole) of potassium hydroxide in 46 ml. of water was added to a mixture of 18.6 g. (0.062 mole) of the keto acid, 5.51 g. (0.077 mole) of hydroxylamine hydrochloride and 240 ml. of ethanol. The mixture was stirred and refluxed for a period of 6 hr. After removing most of the ethanol by vacuum distillation at room temperature employing nitrogen as a sweep gas, the product was treated with 100 ml. of 1.5*N* hydrochloric acid. Separation of the organic material by ether extraction yielded 17.9 g. of crude oximes.

Anal. Calcd. for $C_{18}H_{35}NO_2$: N, 4.5. Found: N, 3.9.

The Beckmann rearrangement. A 9.4 g. quantity of the oxime of 9(10)-oxo-octadecanoic acid was dissolved in 60 ml. of concentrated sulfuric acid and stirred at 100° for 1 hr. After addition of 74 ml. of distilled water, the sample was refluxed for 4 hr. in order to hydrolyze the amide.

Dicarboxylic acids. The hydrolysis mixture was diluted with 400 ml. of distilled water and subjected to steam distillation for the removal of monocarboxylic acids. Ether extraction of the distillation residue yielded 5.91 g. of a brown, waxy material containing the dicarboxylic acids. This fraction was extracted 10 times with 15-ml. portions of boiling water. The extract was concentrated to a volume of 40 ml. and upon standing at 5° deposited 0.835 g. of mixed dicarboxylic acids.

Anal. Calcd. for $C_9H_{16}O_4$: neut. equiv., 94.1. Calcd. for $C_{10}H_{18}O_4$: neut. equiv., 101.1. Found: neut. equiv., 97.1.

Chromatographic separation of the dicarboxylic acids. Duplicate samples of the mixed dicarboxylic acids, *ca.* 0.2 g., accurately weighed, were dissolved in 0.5 ml. of *t*-amyl alcohol and diluted to 10.0 ml. with chloroform. One-ml. aliquots of these solutions were added to a column prepared according to the procedure described by Higuchi *et al.*,[8] using 25.0 g. of dry silicic acid, 10.0 ml. of citrate buffer, *p*H 5.4, and 100 ml. of chloroform. The acids were eluted with successive 100 ml. portions of chloroform containing 0, 1.5, 3, 5, and 10% of 1-butanol, and 10.0 ml. portions of the eluate were titrated with 0.0255*N* sodium hydroxide solution. Only two fractions were encountered and these were

(9) H. J. Lucas, *J. Am. Chem. Soc.*, **48**, 1827 (1926).

(10) E. E. Reid, F. O. Cockerille, J. D. Meyer, W. M. Cox, Jr., and J. R. Ruhoff, *Org. Syntheses*, Coll. Vol. II, 468 (1943).

identified as azelaic and sebacic acids by chromatographing a sample of the mixed dicarboxylic acids to which known quantities of azelaic and sebacic acids had been added. The dicarboxylic acids obtained from *cis*-9,10-epoxyoctadecyl acetate consisted of 54.4 mole percent azelaic and 45.6 mole percent sebacic acids.

Application of the above described procedures to the dicarboxylic acids obtained from *cis*-9,10-epoxyoctadecanol showed the mixture to be 54.8 mole percent azelaic and 45.2 mole percent sebacic acids.

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NEW ORLEANS, LA.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF MARQUETTE UNIVERSITY AND IOWA STATE COLLEGE]

Studies in the Synthesis of Long-Chained Hydroxy Acids

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Four long-chained hydroxy acids have been prepared. Included in the group are 6-hydroxyhexacosanoic acid, 4-hydroxytetracosanoic acid, 10-hydroxydotriacontanoic acid, and 10-hydroxyhexacosanoic acid. In each preparation, thiophene was used as a chain extender, the thiophene sulfur ultimately being removed by desulfurization.

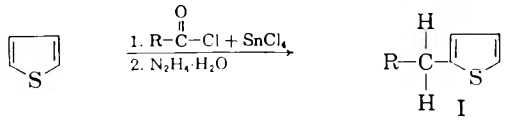
The preparation of hydroxy acids has generally been based upon hydrolysis of the halogenated acid or reduction of the keto acid. Because of the relative unavailability of the starting materials such syntheses have, of necessity, been limited. The present work was thus undertaken to investigate the synthesis of hydroxy acids by Raney nickel catalyzed reduction and desulfurization of selected acidic derivatives of thiophene.

While it has been known for about twenty years that Raney nickel easily and readily desulfurized sulfur-containing organic compounds,[1] it is only during the most recent years that the desulfurization reaction has been used in various synthetic applications. The preparation of an aldehyde from a thiolester[2] is an example.

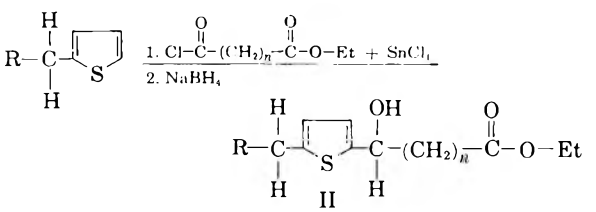
Of greater importance to the present study is the work which has been carried out on the desulfurization of thiophene derivatives.[3-5] During the past four years a number of investigators[6-10] have reported the synthesis of fatty acids by the desulfurization of substituted thiophenes.

Even more recently the work has been extended by the splendid studies of Wynberg and co-workers[11] to the preparation of long-chain mono- and dicarboxylic acids, ketones, alcohols and hydrocarbons.

The acylation of thiophene by an acyl chloride[9] using anhydrous stannic chloride as catalyst was followed by reduction of the resulting acylthiophene with hydrazine hydrate.[12] The resultant



n-alkylthiophene was then acylated with a selected ester-acid chloride, this acylation being followed by reduction of the keto compound to the corresponding hydroxy compound, employing sodium borohydride as the reducing agent.[13-15] Reduction



and desulfurization[9,10] of the acidic thiophenes obtained by hydrolysis of the corresponding thienyl esters yielded the desired hydroxy acids.

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(1) J. Bougault, B. Cattelain, and P. Chabrier, *Bull. soc. chim. France*, **5**, 1699 (1938); **7**, 781 (1940).
(2) E. Mossetig, *Org. Reactions*, VIII, 232 (1954).
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(5) F. Blicke and D. Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).
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(7) G. M. Badger, H. J. Rodda, and W. H. F. Sasse, *Chem. & Ind., (London)*, 308 (1954).
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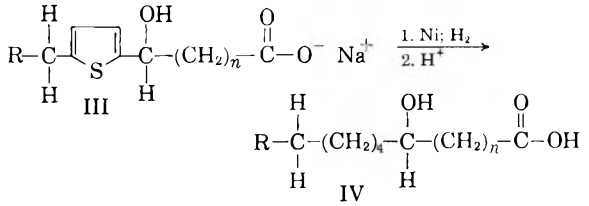

It can thus be seen that, while the total chain-length of the hydroxy acid will be dependent upon both the monobasic and dibasic acid used in the synthesis, the position of the hydroxyl group will be entirely dependent upon the chain-length of the dibasic acid.

EXPERIMENTAL[16]

Acyl and ester-acid chlorides. These were prepared by the action of thionyl chloride on fatty acids and methyl or ethyl hydrogen esters, respectively. In the case of the fatty acids, benzene was employed as solvent. The general procedure was that as described in *Organic Syntheses*.[17,18] All products were obtained in a pure state by vacuum distillation, the distillation being carried out under a nitrogen atmosphere.

Acylthiophenes. A mixture of 40.7 g. hexadecanoyl chloride, 12.5 g. thiophene and 175 ml. anhydrous thiophene-free benzene was cooled to −5° and 16.5 g. anhydrous stannic chloride was added dropwise, with stirring, during 45 min.[19] After removing the ice bath, the mixture was stirred for an additional 4 hr. Decomposition of the reaction mixture was then accomplished by the addition of 100 ml. of 10% hydrochloric acid. After separation, the benzene layer was washed with 10% hydrochloric acid, water, 5% sodium carbonate (aqueous), and water, then dried over calcium chloride. Removal of the solvent and unreacted thiophene afforded 41.0 g. of the product, 2-hexadecanoylthiophene (86.2%), melting at 42° (reported[11] m.p. 42°).

Anal. Calcd. for $C_{20}H_{34}OS$: S, 9.94. Found: S, 9.92.

In a similar manner, 2-octadecanoylthiophene was prepared from octadecanoyl chloride and thiophene in the presence of anhydrous stannic chloride. 2-Octadecanoylthiophene (87.5%) had m.p. 50–51° (reported[11] m.p. 51°).

Anal. Calcd. for $C_{22}H_{38}OS$: S, 9.11. Found: S, 9.00.

2-Dodecanoylthiophene was similarly prepared using dodecanoyl chloride and thiophene (stannic chloride). 2-Dodecanoylthiophene had b.p. 187–190° (1.4 mm.).

n-Alkylthiophenes. 2-Hexadecanoylthiophene (41.0 g.), 30 ml. 85% aqueous hydrazine hydrate and 375 ml. diethylene glycol were heated to 190° and maintained at that temperature until the water and excess hydrazine hydrate had distilled off. After cooling the mixture to 80°, 25 g. of potassium hydroxide was added, the temperature then being raised to, and maintained at, 180° for 2 hr. After cooling, the mixture was poured into cold water, acidified with hydrochloric acid and the aqueous solution extracted with benzene. Following drying of the benzene extracts (calcium chloride) and removal of the solvent, 2-*n*-hexadecylthiophene (30.0 g.; 81.3%) was obtained by vacuum distillation, the product boiling at 147–147.5° at 0.2 mm. (reported[11] b.p. 147° at 0.2 mm.).

Following the above procedure, reduction of 2-octadecanoylthiophene was accomplished with hydrazine hydrate. 2-*n*-Octadecylthiophene (88.3%) had b.p. 183° at 0.8 mm. (reported[11] b.p. 182° at 0.6 mm.) and crystallized very slowly to a solid of m.p. 30–31°.

2-Dodecanoylthiophene was similarly reduced to the corresponding *n*-alkylthiophene by using hydrazine hydrate. 2-*n*-Dodecylthiophene (87.2%) had b.p. 153–155° (2 mm.).

Anal. Calcd. for $C_{16}H_{28}S$: S, 12.75. Found: S, 12.69.

n-Alkylthenoyl esters. These were prepared by a method analogous to that used for the acylthiophenes described previously.

Thus, ethyl 5-(5-hexadecyl-2-thenoyl)valerate was prepared from 5-carbethoxyvaleryl chloride and 2-*n*-hexadecylthiophene. Recrystallization from methanol yielded the pure material (66%; m.p. 39–40°).

Anal. Calcd. for $C_{28}H_{48}O_3S$: C, 72.37; H, 10.41; S, 6.90. Found: C, 72.17; H, 10.58; S, 6.85.

Similarly, methyl 3-(5-hexadecyl-2-thenoyl)propionate was prepared from 3-carbomethoxypropionyl chloride and 2-*n*-hexadecylthiophene. Methanol recrystallization afforded the pure compound (80.0%; m.p. 30°).

Anal. Calcd. for $C_{26}H_{44}O_3S$: S, 7.34. Found: S, 7.36.

Using 2-*n*-octadecylthiophene and 9-carbethoxynonanoyl chloride, ethyl 9-(5-octadecyl-2-thenoyl)nonanoate was prepared in 79.5% yield. Recrystallization from methanol yielded the pure product, m.p. 58–59°.

Anal. Calcd. for $C_{34}H_{60}O_3S$: S, 5.85. Found: S, 5.79.

Ethyl 9-(5-dodecyl-2-thenoyl)nonanoate was obtained from 2-*n*-dodecylthiophene and 9-carbethoxynonanoyl chloride in 73.8% yield. The pure material, obtained by methanol recrystallization, had m.p. 44–45°.

Anal. Calcd. for $C_{28}H_{48}O_3S$: S, 6.90. Found: S, 6.92.

Reduction of the keto esters by sodium borohydride yielded the corresponding hydroxy esters (II). The following relative amounts were used: 0.0431 mole keto ester; 0.013 mole sodium borohydride (20% excess) and 150 ml. ethanol; the solution being stirred at 70–75° for 2 hr. After the addition of water and hydrochloric acid, the product was solvent-extracted, the extracts water-washed and dried, and the solvent evaporated. Recrystallization of the residue from dilute alcohol afforded the pure esters. The results are summarized in Table I.

TABLE I

PREPARATION OF HYDROXY ESTERS[a] (II)

Ester	% Yield	Sapon. Equiv. Calcd.	Found	M.P.
Ethyl 6-hydroxy-6-(5-hexadecyl-2-thienyl)hexanoate	92.5	466.7	465.9	28–29
Methyl 4-hydroxy-4-(5-hexadecyl-2-thienyl)butyrate	85.6	438.7	437.9	20–21
Ethyl 10-hydroxy-10-(5-octadecyl-2-thienyl)decanoate	79.5	549.9	549.1	44–45
Ethyl 10-hydroxy-10-(5-dodecyl-2-thienyl)-decanoate	86.4	465.7	464.8	...

[a] All esters prepared were negative toward phenylhydrazine, *p*-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine.

The free acids were obtained from the above esters by saponification with alcoholic potassium hydroxide followed by acidification with hydrochloric acid. After extraction with ether and drying (magnesium sulfate), the solvent was evaporated to afford the impure acid, which was then recrystallized from aqueous acetone to yield the pure material.

(16) All melting and boiling points are uncorrected.

(17) J. Cason, *Org. Syntheses*, **Coll. Vol. III**, 169 (1955).

(18) S. Swann, Jr., Rene Oehler, and R. J. Buswell, *Org. Syntheses*, **Coll. Vol. II**, 276 (1943).

(19) J. R. Johnson and G. E. May, *Org. Syntheses*, **Coll. Vol. II**, 8 (1943).

TABLE II

HYDROXY-THIO ACIDS

Acid	Neut. Equiv. Calcd.	Found	M.P.
6-Hydroxy-6-(5-hexadecyl-2-thienyl)hexanoic acid[a]	438.7	438.0	84–85
4-Hydroxy-4-(5-hexadecyl-2-thienyl)butyric acid[b]	410.7	410.1	78–79
10-Hydroxy-10-(5-octadecyl-2-thienyl)decanoic acid	522.9	523.1	68–69
10-Hydroxy-10-(5-dodecyl-2-thienyl)decanoic acid	437.7	438.9	31–32[c]

[a] *Anal.* Calcd. for $C_{26}H_{46}O_3S$: C, 71.18; H, 10.57; S, 7.29. Found: C, 71.30; H, 10.41; S, 7.13. [b] Product obtained as lactone which was converted to free acid. [c] Crystallized very slowly.

Desulfurization.[20]

TABLE III

DESULFURIZATION OF DERIVATIVES

Derivative III R	n	Product Acid	% Yield
n-pentadecyl	4	6-Hydroxyhexacosanoic	63.9
n-pentadecyl	2	4-Hydroxytetracosanoic	68.0
n-heptadecyl	8	10-Hydroxydotriacontanoic	75.0
n-undecyl	8	10-Hydroxyhexacosanoic	74.7

To a suspension of Raney nickel catalyst (dissolved and digested as described by Bilicka and Adkins)[21] in 900 ml. distilled water was added 5 g. 6-hydroxy-6-(5-hexadecyl-2-thienyl)hexanoic acid in 10% sodium carbonate (aqueous). The resultant mixture was stirred at 80 ± 3° for 3 hr., the catalyst was filtered off, the filtrate acidified (hydrochloric acid) and extracted with ether. The spent catalyst was dissolved in 15% hydrochloric acid and the solution extracted with ether. The ether extracts were combined, washed, dried (magnesium sulfate), and the solvent evaporated. Recrystallization of the residue (benzene-ethanol) gave pure 6-hydroxyhexacosanoic acid (63.9%), m.p. 89.5–90.5°.

Anal. Calcd. for $C_{26}H_{52}O_3$: C, 75.66; H, 12.65; OH, 4.12; Neut. Equiv., 412.7. Found: C, 75.53; H, 12.73; OH, 4.03; Neut. Equiv., 412.0.

Desulfurization of 4-hydroxy-4-(5-hexadecyl-2-thienyl)-butyric acid by the above procedure yielded 4-hydroxytetracosanoic acid (68.0%). The pure material, obtained from the lactone, had m.p. 80–82°.

Anal. Calcd. for $C_{24}H_{48}O_3$: OH, 4.42; Neut. Equiv., 384.6. Found: OH, 4.33; Neut. Equiv., 384.1.

In a similar manner, 10-hydroxydotriacontanoic acid was obtained by the desulfurization of 10-hydroxy-10-(5-octadecyl-2-thienyl)decanoic acid. Recrystallization from ethanol at −5° afforded the pure material (75%) of m.p. 81–83°.

Anal. Calcd. for $C_{32}H_{64}O_3$: OH, 3.42; Neut. Equiv., 496.6. Found: OH, 3.38; Neut. Equiv., 496.3.

10-Hydroxyhexacosanoic acid was likewise obtained by the desulfurization of 10-hydroxy-10-(5-dodecyl-2-thienyl)-decanoic acid. The pure product (74.7%), obtained by recrystallization from ethanol, had m.p. 93–95°.

Anal. Calcd. for $C_{26}H_{52}O_3$: OH, 4.12; Neut. Equiv., 412.7. Found: OH, 4.10; Neut. Equiv., 409.3.

The hydroxyl analysis mentioned in each of the above four desulfurizations was carried out according to the general procedure described by Smith and Shriner.[22]

Acknowledgment. The authors are indebted to the Sharples Chemicals Inc. for a generous sample of thiophene.

MILWAUKEE, WIS.

AMES, IOWA

(20) The weights of all thio-acids used were based on the introduction of 125 g. Raney nickel-aluminum alloy powder, the alloy being present in excess.

(21) H. R. Bilicka and H. Adkins, *Org. Syntheses*, Coll. Vol. III, 176 (1955).

(22) Walter T. Smith, Jr. and Ralph L. Shriner, *The Examination of New Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 112.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Reactions of Triphenylsilyllithium with Some Halides and Related Compounds of Group V Elements

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Whereas the reactions of triphenylsilyllithium with phosphorus trichloride, phosphorus tribromide, and phosphorus oxychloride give hexaphenyldisilane as the chief product, the reaction with tributyl phosphate gives *n*-butyltriphenylsilane. Arsenic trichloride, antimony trichloride, and bismuth trichloride give hexaphenyldisilane and the corresponding metals when allowed to react with triphenylsilyllithium. A possible explanation for the high yield of hexaphenyldisilane is given.

In the course of the past few years a study has been carried out in this Laboratory to ascertain the usefulness of triphenylsilyllithium as a synthetic tool for the preparation of various organosilicon compounds. Successful preparations of this reagent in a suitable solvent like tetrahydrofuran, by the lithium cleavage of hexaphenyldisilane[1] and by the direct reaction of chlorotriphenylsilane and lithium[2] have greatly increased the scope of this study.

The object of the present investigation was to study possible approaches to the synthesis of organosilylmetallic compounds containing some

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(2) H. Gilman, D. J. Peterson, and D. Wittenberg, *Chem. & Ind. (London)*, 1479 (1958). See, also, H. Gilman and T. C. Wu, *J. Org. Chem.*, 18, 753 (1953).

group V elements of the periodic table, P, As, Sb, and Bi, through the reaction of silyllithium compounds with halides of these elements.

Various instances of the reaction of organolithium compounds with phosphorus halides are reported in the literature. Phenyllithium, for example, reacts with phosphorus trichloride to give 61% of triphenylphosphine.[3] Similarly, reactions of arsenic, antimony, and bismuth trichloride with aryllithium compounds give the desired trisubstituted derivatives of these elements. Recently, Seyferth[4] has prepared tris(trimethylsilylmethyl) compounds of phosphorus, arsenic, antimony, and bismuth by the reaction of trimethylsilylmethylmagnesium chloride with the appropriate group V trichloride in tetrahydrofuran.

$$3\ Me_3SiCH_2MgCl + M^vCl_3 \longrightarrow (Me_3SiCH_2)_3M^v + 3\ MgCl_2\ (M^v = P, As, Sb, or Bi)$$

It seemed of interest to study some of the reactions of triphenylsilyllithium with group V trichlorides under conditions analogous to those of the reactions of organolithium and Grignard reagents, to prepare group V tris(triphenylsilyl) compounds.

The reaction in a 3:1 mole ratio, of triphenylsilyllithium and bismuth trichloride gave 78.8% of hexaphenyldisilane together with small amounts of triphenylsilane (3.4%), triphenylsilanol (7.6%), and hexaphenyldisiloxane (2.1%). Metallic bismuth was isolated in an 81.3% yield. The reaction of triphenylsilyllithium with bismuth trichloride seems to proceed through a route similar to that of the reaction of mercury salts.[5] For example, phenylmercuric bromide on treatment with triphenylsilyllithium gives mostly tetraphenylsilane (73%) and metallic mercury. The high yield of tetraphenylsilane in this reaction was explained on the basis of an unstable silicon-mercury intermediate. Similarly, reactions of mercury(II) chloride and of diphenylmercury with triphenylsilyllithium[5] gave products which could be explained satisfactorily only on the basis of such an unstable silicon-mercury intermediate. Bismuth trichloride may be reacting likewise with triphenylsilyllithium to give an unstable silicon-bismuth intermediate which decomposes to give hexaphenyldisilane and metallic bismuth.

$$(C_6H_5)_3SiLi + C_6H_5HgBr \longrightarrow [(C_6H_5)_3SiHgC_6H_5] + LiBr$$
$$[(C_6H_5)_3SiHgC_6H_5] \longrightarrow (C_6H_5)_4Si + Hg$$

$$(C_6H_5)_3SiLi + BiCl_3 \longrightarrow [(C_6H_5)_3SiBiCl_2] + LiCl$$
$$[(C_6H_5)_3SiBiCl_2] \longrightarrow (C_6H_5)_3SiCl + [BiCl]$$
$$(C_6H_5)_3SiCl + (C_6H_5)_3SiLi \longrightarrow (C_6H_5)_3SiSi(C_6H_5)_3 + LiCl$$
$$3\ [BiCl] \longrightarrow BiCl_3 + 2\ Bi$$

Another possibility is the formation of an unstable bis- or tris(triphenylsilyl)bismuth intermediate, which could decompose to give hexaphenyldisilane and bismuth.

$$3\ (C_6H_5)_3SiLi + BiCl_3 \longrightarrow [((C_6H_5)_3Si)_3Bi] + 3\ LiCl$$
$$2\ [((C_6H_5)_3Si)_3Bi] \longrightarrow 3\ (C_6H_5)_3SiSi(C_6H_5)_3 + 2\ Bi$$

When triphenylsilyllithium was treated with antimony trichloride, 50.1% of hexaphenyldisilane, 21.1% of triphenylsilanol, 6.2% of hexaphenyldisiloxane and 5.1% of triphenylsilane were isolated. A nearly quantitative amount (90.5%) of metallic antimony was obtained from this reaction. Similarly, from the reactions of arsenic trichloride, phosphorus trichloride and phosphorus tribromide with triphenylsilyllithium, 44%, 68.1%, and 80.5% of hexaphenyldisilane, respectively, were isolated. Smaller amounts of other products like triphenylsilanol and hexaphenyldisiloxane were also obtained from these runs. It is interesting to note that a substance like phosphorus oxychloride gives a nearly quantitative yield (90%) of hexaphenyldisilane and it appears that this reaction also proceeds through a route similar to those of the phosphorus trichloride and phosphorus tribromide reactions. As in the case of the bismuth trichloride reaction, the products formed in these experiments could be satisfactorily explained on the basis of transient silicon-antimony, silicon-arsenic, and silicon-phosphorus intermediates.

It is also conceivable that a halogen-metal interconversion reaction may be involved, particularly in the case of the more nonmetallic members of the series, and this mechanism should not be ignored. Although at least one compound containing the Si—P bond has been reported,[6] namely trimethylsilyldiphenylphosphine, no details of the preparation or work-up were given, so that no conclusions can be drawn as to the stability of such compounds to cleavage by reactive species such as triphenylsilyllithium. It is the opinion of the authors that such compounds would be cleaved readily under the conditions used in this investigation. This aspect is presently under investigation at this laboratory.

In order to study the reaction of a phosphate ester with a silyllithium compound, a reaction was carried out using a 1:1 mole ratio of tri-*n*-butyl phosphate and triphenylsilyllithium. From this run an 83.5% yield of *n*-butyltriphenylsilane was isolated. It would appear that triphenylsilyllithium is effecting a cleavage of one of the butyl groups from the phosphate ester. This reaction is analogous to the reaction of an organolithium or Grignard reagent with a sulfate ester like methyl sulfate. The applicability of this reaction as a general alkylation procedure is under investigation.

(3) E. M. Mikhailov, N. F. Kucherova, *Doklady Akad. Nauk S.S.S.R.*, **74**, 501 (1950).

(4) D. Seyferth, *J. Am. Chem. Soc.*, **80**, 1336 (1958).

(5) M. V. George, G. D. Lichtenwalter, and H. Gilman, *J. Am. Chem. Soc.*, **81**, 978 (1959).

(6) W. Kuchen and H. Buchwald, *Angew. Chem.*, **69**, 307 (1957).

EXPERIMENTAL

All melting points are uncorrected. Reactions were carried out under an atmosphere of dry, oxygen-free[7] nitrogen. Tetrahydrofuran, boiling at 65–66°, was freed from peroxides and moisture before use by refluxing over sodium, followed by distillation from lithium aluminum hydride. The halides and esters were anhydrous samples. Triphenylsilyllithium solutions were prepared in tetrahydrofuran by the cleavage of hexaphenyldisilane using lithium according to reported procedure.[1]

Triphenylsilyllithium and phosphorus trichloride. A solution of 0.09 mole of triphenylsilyllithium in 150 ml. of tetrahydrofuran was added, during 1.5 hr. to 4.6 g. (0.03 mole) of phosphorus trichloride, dissolved in 100 ml. of dry diethyl ether. The mixture was kept cooled in a bath of Dry Ice and acetone (−70°) during addition; the solution turned yellow at first and later brown. Color Test I[8] was negative when the addition was complete. The mixture was warmed to room temperature and the solvent was removed by distillation. The residue was successively extracted with 400 ml. of petroleum ether (b.p. 60–70°) and 600 ml. of benzene in a Soxhlet apparatus. The residue left in the Soxhlet thimble (17.6 g.) was then treated with hot tetralin to give 11.3 g. of hexaphenyldisilane, m.p. and mixed m.p. 362–364°. The tetralin-insoluble portion (4.9 g.) contained lithium chloride and a water-insoluble orange residue which gave a qualitative test for phosphorus.

The solvent from the petroleum ether extract was removed to give a solid with a wide melting range (145–200°) from which 1.7 g. (6.1%) of triphenylsilanol was isolated as the soluble fraction on treatment with methanol. It melted at 151–153° and did not depress the melting point of an authentic sample of triphenylsilanol. The methanol-insoluble fraction was mixed with the benzene extract of the original mixture and worked up.

The benzene extract when concentrated, deposited 6.8 g. of hexaphenyldisilane, m.p. and mixed m.p. 360–362°. Solvent from the mother liquor was removed and the residue was chromatographed on alumina. Elution of the column with chloroform gave 1.05 g. (2.0%) of hexaphenyldisiloxane, m.p. and mixed m.p. 226–228°. Further elution with methanol gave 0.85 g. (3.0%) of triphenylsilanol, which melted at 152–154° after crystallization from cyclohexane and did not depress the melting point of an authentic sample. The total yield of hexaphenyldisilane from various fractions was 18.2 g. (68.1%), and of triphenylsilanol, 2.6 g. (9.1%).

Triphenylsilyllithium and phosphorus tribromide. A solution of 0.06 mole of triphenylsilyllithium in 130 ml. of tetrahydrofuran was cooled to −50° in a Dry Ice–acetone bath. To this solution was added 5.4 g. (0.02 mole) of phosphorus tribromide dissolved in 50 ml. of tetrahydrofuran. When the addition was complete, the mixture gave a negative Color Test I. The solvent from the reaction mixture was removed by distillation under nitrogen and the residue was extracted with 400 ml. of benzene. The clear, amber-colored benzene extract was concentrated to about 300 ml. and filtered hot to deposit 3.7 g. of lithium bromide, identified by qualitative tests. Further concentration of the filtrate gave 2.1 g. of hexaphenyldisilane, m.p. 358–361°, identified by mixed melting point determination, and 1.6 g. (9.7%) of triphenylsilanol, m.p. 151–153° (mixed m.p.).

The original benzene-insoluble residue was extracted with hot tetralin to give 10.5 g. of hexaphenyldisilane, m.p. 362–364° (mixed m.p.). The total yield of hexaphenyldisilane was 80.5%. The tetralin insoluble portion contained lithium bromide and an orange-red solid (0.4 g.) which when dissolved in nitric acid gave a yellow precipitate with ammonium molybdate solution.

In a second run using the same quantities of reactants and solvent but with reverse addition, the products isolated were 12.7 g. (81.5%) of hexaphenyldisilane and 1.0 g. (6.0%) of triphenylsilanol, identified by mixed melting point determinations with authentic samples. In addition, 3.12 g. of lithium bromide and 0.45 g. of a residue which gave a positive test for phosphorus, were obtained.

Triphenylsilyllithium and phosphorus oxychloride. A solution of triphenylsilyllithium (0.09 mole, 103.5 ml.) was added, during one hour to 4.6 g. (0.03 mole) of phosphorus oxychloride dissolved in 25 ml. of tetrahydrofuran. The reaction was exothermic and the mixture became canary-yellow during the addition. The reaction mixture turned brown when all the triphenylsilyllithium had been added. Color Test I was negative. Tetrahydrofuran was removed from the mixture by distillation; the residue was treated with a mixture of 200 ml. of dry ether and 200 ml. of sodium-dried petroleum ether (b.p. 60–70°), and filtered under nitrogen. The filtrate was distilled to give a small amount of viscous material, which on treatment with cyclohexane gave 0.5 g. of an insoluble residue. It melted at 363–365° after crystallization from hot benzene and did not depress the melting point of an authentic sample of hexaphenyldisilane. The cyclohexane-soluble portion was chromatographed on alumina. Elution with carbon tetrachloride gave 0.2 g. (0.8%) of hexaphenyldisiloxane, m.p. and mixed m.p. 226–228°. Further elution with methanol gave 0.5 g. (2.0%) of triphenylsilanol, which melted at 152–153° after crystallization from cyclohexane, and did not depress the melting point of an authentic sample.

The residue obtained after treatment with the petroleum ether–ether mixture was hydrolyzed with water; a pronounced odor of phosphine was noticed. The mixture was filtered and the water-insoluble portion gave 21.0 g. (90.0%) of hexaphenyldisilane, m.p. and mixed m.p. 365–366°. The aqueous layer was worked up by extraction with ether, but no product could be isolated.

Triphenylsilyllithium and tri-n-butyl phosphate. To 23.0 g. (0.09 mole) of tri-*n*-butyl phosphate was added 0.09 mole of a solution of triphenylsilyllithium in 150 ml. of tetrahydrofuran, during one hour. Color Test I was negative at the end of the addition and the mixture was hydrolyzed by adding a half-saturated solution of ammonium chloride. It was extracted with ether and dried over anhydrous sodium sulfate. Partial evaporation of the solvent from the ether extract precipitated out a small quantity of hexaphenyldisilane (0.27 g., 1.2%) which melted at 360–362° and did not depress the melting point of an authentic sample. Complete removal of the solvent gave a residue which was chromatographed on alumina. Elution with petroleum ether (b.p. 60–70°) gave 23.7 g. (83.5%) of *n*-butyltriphenylsilane, m.p. 78–85°. Crystallization from methanol raised the melting point to 85–87°. The melting point was not depressed when the compound was admixed with an authentic sample of *n*-butyltriphenylsilane. Elution of the alumina column with benzene gave 0.3 g. (1.3%) of hexaphenyldisiloxane, m.p. and mixed m.p. 225–227°; and elution with methanol gave 1.2 g. (4.6%) of triphenylsilanol, which melted at 153–155° after crystallization from cyclohexane. No depression in melting point was observed when mixed with an authentic sample.

Triphenylsilyllithium and arsenic trichloride. To a solution of 5.4 g. (0.03 mole) of arsenic trichloride in 50 ml. of tetrahydrofuran was added 0.09 mole of a tetrahydrofuran solution of triphenylsilyllithium (150 ml.), during one hour. The reaction was strongly exothermic and the rate of addition was controlled to regulate the temperature. When the addition was complete the mixture gave a negative Color Test I and it was then hydrolyzed by adding water. The insoluble residue (11.8 g.) was extracted with hot tetralin to give 10.0 g. of hexaphenyldisilane, m.p. and mixed m.p. 362–364°. The tetralin insoluble portion was a black solid (1.8 g.) which was identified as metallic arsenic by qualitative tests. A portion of this residue was dissolved in con-

(7) L. J. Brady, *Anal. Chem.*, **20**, 1034 (1948).

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

centrated nitric acid. The addition of ammonium molybdate solution followed by warming of the mixture gave a yellow precipitate, indicating the presence of arsenic.

The aqueous layer of the hydrolyzed reaction mixture was extracted with ether and removal of the solvent from the ether extract after drying over sodium sulfate, gave a residue which was successively extracted with petroleum ether (b.p. 60–70°), methanol and hot benzene. The methanol extract gave 5.7 g. of triphenylsilanol, which melted at 151–153°, after crystallization from cyclohexane. A mixed melting point with an authentic sample was not depressed.

From the benzene extract, 0.3 g. of hexaphenyldisilane, m.p. and mixed m.p. 360–362° and 0.25 g. of hexaphenyldisiloxane, m.p. and mixed m.p. 224–226°, were isolated by fractional crystallization.

The petroleum ether extract was chromatographed on alumina. Elution with the same solvent gave 3.1 g. (13.2%) of triphenylsilane, identified by a comparison of the infrared spectrum in carbon tetrachloride with that of an authentic sample. The characteristic Si-H absorption band was observed at 2105 cm.$^{-1}$. Elution of the column with carbon tetrachloride gave 0.97 g. of hexaphenyldisiloxane, m.p. and mixed m.p. 224–226°. The column was finally eluted with methanol to give 1.1 g. of triphenylsilanol, m.p. and mixed m.p. 152–153°. The total yield of hexaphenyldisilane was 10.0 g. (44%), of triphenylsilanol was 6.8 g. (13.3%), and that of hexaphenyldisiloxane was 1.3 g. (5.1%).

Triphenylsilyllithium and antimony trichloride. A solution of 0.06 mole (140 ml.) of triphenylsilyllithium was slowly added to 4.6 g. (0.02 mole) of antimony trichloride dissolved in 25 ml. of tetrahydrofuran, during one hour at room temperature. Color Test I was negative after all the triphenylsilyllithium had been added. The mixture was hydrolyzed by adding water, the insoluble residue was removed by filtration and the aqueous layer was extracted with ether. The brown residue was extracted with hot tetralin to give 7.8 g. (50.1%) of hexaphenyldisilane, m.p. and mixed m.p. 364–365°. The tetralin-insoluble portion (2.2 g., 90.5%) was identified as metallic antimony by qualitative tests.

The ether extract was dried over sodium sulfate and removal of the solvent gave a viscous liquid, which was chromatographed on alumina. Elution with petroleum ether (b.p. 60–70°) gave 0.8 g. (5.1%) of triphenylsilane, identified by a comparison of the infrared spectrum with that of an authentic sample. Elution with benzene gave 1.0 g. (6.2%) of hexaphenyldisiloxane, m.p. and mixed m.p. 227–228°; and final elution of the column with methanol resulted in the isolation of 3.5 g. (21.1%) of triphenylsilanol, m.p. and mixed m.p. 154–155°.

Triphenylsilyllithium and bismuth trichloride. Addition of 0.09 mole (103.5 ml.) of triphenylsilyllithium to 9.5 g. (0.03 mole) of bismuth trichloride (dissolved in 50 ml. of tetrahydrofuran) was carried out, at room temperature, during 1 hr. The reaction was exothermic to give a black mixture and Color Test I was negative at the end of the addition. The mixture was hydrolyzed with water. The insoluble residue on extraction with tetralin gave 18.4 g. (78.8%) of hexaphenyldisilane, m.p. and mixed m.p. 365–366°, and 5.1 g. (81.3%) of metallic bismuth, identified by qualitative tests. The aqueous layer obtained after hydrolysis was extracted with ether and work-up as in the previous case by chromatography, gave 0.8 g. (3.4%) of triphenylsilane, 0.5 g. (2.1%) of hexaphenyldisiloxane and 1.9 g. (7.6%) of triphenylsilanol. These compounds were characterized by mixed melting point determinations with authentic samples.

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Reductions with Dialkylaluminum Hydrides

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Dialkylaluminum hydrides, such as diisobutylaluminum hydride and diethylaluminum hydride, effectively reduced cyclohexanone to cyclohexanol, benzoic acid to benzyl alcohol, benzonitrile to benzaldehyde, *n*-butyl caproate to *n*-butanol and *n*-hexanol, methyl benzoate to benzyl alcohol and diethyl fumarate to *trans*-2-butene-1,4-diol. No selectivity in reduction of the acetylenic bond of 2-butyne-1,4-diol was obtained but some selectivity was found with 1-ethynylcyclohexanol. The stoichiometries involved in the reductions with dialkylaluminum hydrides are very similar to those observed with lithium aluminum hydride.

Dialkylaluminum hydrides, *i.e.*, diisobutylaluminum hydride, are effective reducing agents and are similar to lithium aluminum hydride in their reactivities. The dialkylaluminum hydrides are liquids and are conveniently handled under nitrogen. Although the equivalent reducing weight of lithium aluminum hydride is lower than that of the dialkylaluminum hydrides, the latter appear to be more selective in certain reactions. Moreover, the ease of preparation and the relatively low cost of the dialkylaluminum hydrides offer certain advantages over lithium aluminum hydride.

The reduction of cyclohexanone with diisobutylaluminum hydride in a 1:1 mole ratio gave 83% yields of cyclohexanol.

Meerwein[1] reported that triethylaluminum and triethylboron could be used to reduce aldehydes,

(1) H. Meerwein, G. Hinz, H. Majert, and H. Sonke, *J. Prakt. Chem.*, 147, 226 (1937).

ketones, α,β-unsaturated aldehydes and halogenated aldehydes and ketones to the corresponding alcohols. We view this reaction as a particular case of the *Meerwein-Ponndorf-Verley reduction*[2] in which the alkyl groups act as hydrogen donors to give the corresponding aluminum alkoxide with the evolution of an olefin. However, the exact analogy cannot be drawn since the reduction with triethylaluminum is not reversible.

$$3\ RCHO + Al(C_2H_5)_3 \longrightarrow Al(OCH_2R)_3 + 3\ C_2H_4$$

Ziegler[3] repeated Meerwein's work and also noted the use of diisobutylaluminum hydride as a reducing agent but failed to report his experimental results.

Benzoic acid was reduced with diisobutylaluminum hydride to give 72% yields of benzyl alcohol. Gas was evolved upon the addition of the hydride to benzoic acid until one mole of the reducing agent had reacted with three moles of benzoic acid; thereafter, the addition gave no gas. Therefore, the isobutyl groups on the diisobutylaluminum hydride react quantitatively with active hydrogens, but, as we will try to indicate in this paper, these alkyl groups are not involved in the reduction of compounds other than aldehydes and ketones. Moreover, the stoichiometry of the reduction, as based on hydrogen evolved from excess reagent, seems to be six equivalents of hydride per mole of aluminum benzoate. This stoichiometry corresponds to that observed with lithium aluminum hydride.

The reduction of benzonitrile with diisobutylaluminum hydride gave no benzylamine, as such, instead only benzaldehyde and benzalbenzylamine were obtained. Using a 4:1 mole ratio of hydride to nitrile, 68% of benzaldehyde and 31% of benzylamine (based on hydrolysis products) were obtained, whereas a 2:1 mole ratio of hydride to nitrile gave 82% benzaldehyde and 13% benzylamine (based on hydrolysis products). When this reaction was repeated with a 1:1 mole ratio of hydride to nitrile 90% yields of benzaldehyde were obtained with only a trace of benzalbenzylamine. Moreover the gas obtained from the decomposition of the reduction complex consisted of only isobutane with no hydrogen or isobutylene. This indicates that a 1:1 mole ratio of hydride to nitrile is most efficient for reduction to the aldehyde and that the isobutyl groups do not participate in the reduction.

Benzonitrile has been reduced to benzylamine in 72% yield using a 2:1 mole ratio of nitrile to lithium aluminum hydride and in 93% yield with a 1:1 mole ratio.[4] Benzalaniline has been reduced to *N*-benzylaniline in 93% yield with a 4:1 mole ratio of benzalaniline to lithium aluminum hydride.

Friedman[5] reported the reduction of nitriles to aldehydes with lithium aluminum hydride by the very careful addition of one mole of hydride to four moles of nitrile.

Therefore it appears that diisobutylaluminum hydride is a more selective reagent than lithium aluminum hydride in the reduction of nitriles to aldehydes.

n-Butyl caproate was reduced with diisobutylaluminum hydride in varying mole ratios. With a 1:1 mole ratio of hydride to ester very poor yields of 1-hexanol were obtained. This is evidence that the residual alkyl groups on the hydride are not involved in the reduction of esters. Good yields of 1-hexanol were obtained with mole ratios of 3:1 and 4:1 of hydride to ester, but in each case the gases evolved upon decomposition of the complex indicated the proper stoichiometry to be a 2:1 mole ratio of hydride to ester. Therefore, methyl benzoate was reduced with a 2:1 mole ratio of diisobutylaluminum hydride to ester and a 90% yield of benzyl alcohol was obtained. Moreover, the off gas from this experiment contained 4 moles of isobutane and no hydrogen.

Lithium aluminum hydride has been reported[6] to reduce α,β-unsaturated esters to the corresponding α,β-unsaturated alcohols in excellent yields. We were unable to reduce diethyl fumarate to *trans*-2-butene-1,4-diol with lithium aluminum hydride although many different reaction conditions were tried. However, both diisobutylaluminum hydride and diethylaluminum hydride reacted with diethyl fumarate to produce *trans*-2-butene-1,4-diol in 55–70% yields. In each case a 4:1 mole ratio of reducing agent to diester was required. Since the olefin was obtained in good yields and since no gaseous olefin was obtained in the off-gas, it seems apparent that the residual alkyl groups on the hydrides are not involved in the reduction.

Wilke and Mueller[7] reported the reduction of disubstituted acetylenic hydrocarbons, *i.e.*, 3-hexyne, to the corresponding cis olefins with diisobutylaluminum hydride. It has also been shown that[8] lithium aluminum hydride reduced acetylenes to trans olefins in excellent yields if the triple bond is flanked by a propargylic hydroxyl group. Therefore, the reductions of 1-ethynylcyclohexanol and 2-butyne-1,4-diol were tried with diisobutylaluminum hydride. In the case of 2-butyne-1,4-diol the reduction was not selective and a very poor material balance was obtained. The reduction of 2-butyne-1,4-diol with lithium aluminum hydride

(2) A. L. Wilds, *Org. Reactions*, II, 178 (1944).

(3) K. Ziegler, K. Schneider, and J. Schneider, *Angew. Chem.*, **67**, 425 (1955).

(4) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948). L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(5) L. Friedman, Abstracts of Papers, 116th Meeting American Chemical Society, September 18–23, 1949, p. 5 M.

(6) C. J. Martin, A. I. Schepartz, and B. F. Daubert, *J. Am. Chem. Soc.*, **79**, 2601 (1948).

(7) J. Wilke and H. Mueller, *Chem. Ber.*, **89**, 444 (1956).

(8) A. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954).

gave *trans*-2-butene-1,4-diol in very poor yields. The reduction of 1-ethynylcyclohexanol with diisobutylaluminum hydride gave a product which contained 48% of 1-vinylcyclohexanol and 52% of unreacted 1-ethynylcyclohexanol.

EXPERIMENTAL

Koppers Co. diisobutylaluminum hydride and diethylaluminum hydride were used in this investigation.

All melting points and boiling points are uncorrected.

Hydrogen numbers were determined by reduction of the compounds in 95% ethanol with 0.1 g. Adams' platinum catalyst at 25° and one atmosphere of hydrogen.

Reduction of cyclohexanone. Cyclohexanone (21.6 g., 0.22 m.) in benzene (28 ml.) was added under nitrogen over 1.5 hr. to a stirred solution of diisobutylaluminum hydride (0.22 m.) in benzene (100 ml.). The temperature rose to 45° during the addition and was maintained at this temperature during an 8-hr. stirring period. The cooled reaction mixture was decomposed by the addition of methanol (22.8 g., 0.71 m.) in 25 ml. benzene followed by the addition of water (12.0 g., 0.66 m.) in 25 ml. methanol. The gas evolved during the decomposition contained isobutane but no isobutylene. The decomposed reaction mixture was filtered and distilled to give 18.3 g. (83% yield) of cyclohexanol; b.p. 82.5–83.0°/40 mm., n_D^{23} 1.4655.

The 3,5-dinitrobenzoate of cyclohexanol was prepared in the usual manner and after recrystallization from aqueous ethanol melted at 111° and gave no melting point depression when admixed with an authentic sample.

Similarly the phenylurethane of cyclohexanol was prepared (m.p. 82° from petroleum ether) and gave no melting point depression when admixed with an authentic sample.

Reduction of benzoic acid. Diisobutylaluminum hydride (0.45 m.) was added under nitrogen over 3 hr. to a stirred mixture of benzoic acid (18.3 g., 0.15 m.) in 200 ml. of benzene. Gas evolution stopped after 0.05 m. of diisobutylaluminum hydride had been added. The reaction temperature rose to 45° and stirring was continued at this temperature for 8 hr. The cooled reaction mixture was decomposed by the addition of methanol (44.8 g., 1.4 m.) in 45 ml. of benzene, followed by water (24.3 g., 1.35 m.) in 25 ml. of methanol. The gas evolved during decomposition contained 0.18 m. hydrogen and 0.69 m. of isobutane. The reaction mixture was filtered and distilled to give 11.7 g. (72% yield) of benzyl alcohol; b.p. 100°/18.5 mm., n_D^{23} 1.5390.

The phenylurethane was prepared in the usual manner and after recrystallization from petroleum ether melted at 77.5° and gave no melting point depression in admixture with an authentic sample of the phenylurethane of benzyl alcohol.

Reduction of benzonitrile. Diisobutylaluminum hydride (0.4 m.) was added under nitrogen over 1.5 hr. to a solution of benzonitrile (10.3 g., 0.1 m.) in 140 ml. of benzene. No gas evolution was observed and the temperature rose to 45°. Stirring was continued at 45° for 8 hr. The cooled reaction mixture was decomposed by the addition of methanol (38.4 g., 1.2 m.) in 45 ml. of benzene followed by water (21.6 g., 1.2 m.) in 50 ml. of methanol. The gas evolved during decomposition contained 0.32 m. hydrogen, 0.60 m. of isobutane and no isobutylene. The solid aluminum salts were filtered and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in ether (300 ml.) and extracted with 5% hydrochloric acid (2 × 100 ml.). The ether layer was dried and distilled to give 3.9 g. (37% yield) of benzaldehyde boiling at 50–60°/5 mm. The 2,4-dinitrophenylhydrazone of benzaldehyde (m.p. 237° from ethanol) was prepared in the usual manner and gave no melting point depression when admixed with an authentic sample.

The acid extract was made alkaline with aqueous sodium hydroxide, the organic amine extracted with ether and dried over anhydrous magnesium sulfate. Distillation of the dry ether solution gave 6.1 g. of product boiling at 168–170°/5 mm.; n_D^{24} 1.5962. Quantitative hydrogenation of this material over a palladium catalyst gave a hydrogen number of 0.98 assuming the compound to be benzalbenzylamine. The hydrogenated product was converted to the benzamide[10] melting at 112.5–113.5° and to the benzenesulfonamide[11] melting at 66–67°.

In a subsequent experiment run under identical conditions benzonitrile (17 g., 0.165 m.) was reduced with diisobutylaluminum hydride (0.33 m.). However, the decomposed reaction mixture was acidified with 300 ml. of 20% sulfuric acid and steam distilled. The steam distillate gave 12.2 g. of benzaldehyde and 4 g. of benzylamine was isolated from the residue by making it alkaline and extracting with ether. The gas evolved during decomposition contained 0.14 m. hydrogen, 0.51 m. of isobutane and no isobutylene.

This experiment was repeated with 22.8 g. (0.22 m.) of benzonitrile and 31.9 g. (0.22 m.) of diisobutylaluminum hydride and a 90% yield (20.9 g.) of benzaldehyde was obtained. Also only a trace of benzalbenzylamine was obtained and the gas evolved (0.44 m.) upon decomposition was entirely isobutane.

Reduction of n-butyl caproate. Diisobutylaluminum hydride (0.33 m.) was added under nitrogen over 2.5 hr. to a stirred solution of *n*-butyl caproate (18.4 g., 0.11 m.) in 150 ml. of benzene. The temperature rose to 45° during the addition and was maintained at this temperature for another 8 hr. The cooled reaction mixture was decomposed by the addition of methanol (32.0 g., 1.0 m.) in benzene (55 ml.) followed by water (18.0 g., 1.0 m.) in methanol (30 ml.). The gas evolved during decomposition contained 0.19 m. of hydrogen, 0.62 m. of isobutane, and no isobutylene. The decomposed reaction mixture was filtered, concentrated, and distilled to give 4.7 g. (58% yield) of 1-butanol boiling at 116°, n_D^{22} 1.3970, and 8.2 g. (73% yield) of 1-hexanol boiling at 155°, n_D^{22} 1.4174.

The α-naphthyl urethane of the 1-hexanol was prepared in the usual manner and after recrystallization from petroleum ether melted at 58.5–59.0°. No mixed melting point depression was observed when admixed with an authentic sample.

This experiment was repeated in petroleum ether and the ester was added to the diisobutylaluminum hydride; 1-hexanol was obtained in 77% yield. With a 1:1 mole ratio of diisobutylaluminum hydride to ester a very poor yield of 1-hexanol was obtained; a 4:1 mole ratio gave 82% yields of 1-hexanol. The gases obtained from decomposition of the reaction mixtures contained very little isobutylene and therefore the isobutyl groups could not be greatly involved in the reductions.

Reduction of methyl benzoate. Diisobutylaluminum hydride (30.6 g., 0.22 m.) was added under nitrogen over 1 hr. to a stirred solution of methyl benzoate (14.6 g., 0.11 m.) in 250 ml. of benzene. The temperature rose to 45° during the addition and was maintained at this temperature for another 2 hr. The product was decomposed in the usual manner to give 0.44 m. of gas which consisted entirely of isobutane with no hydrogen or isobutylene. Distillation of the organic product gave 10.4 g. (90% yield) of benzyl alcohol; b.p. 90–91°/7 mm., n_D^{25} 1.5386.

Reduction of diethyl fumarate. Diisobutylaluminum hydride (0.85 m.) was added under nitrogen over 10 hr. to a stirred solution of diethyl fumarate (34.4 g., 0.2 m.) and benzene (160 ml.). The maximum temperature during the addition was 50°. After standing overnight at room temperature, the reaction mixture was decomposed by the addition of methanol (76.8 g., 2.4 m.) in benzene (150 ml.) followed by water (45 g., 2.5 m.). The gas evolved during the de-

(10) H. Franzen, *Ber.*, **42**, 2465 (1909) reported a melting point of 112° for dibenzylamine benzamide.

(11) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, p. 194, John Wiley & Sons, New York, 1946, reports the melting point of dibenzylamine benzenesulfonamide to be 68°.

composition contained 0.09 m. of hydrogen, 1.60 m. of isobutane, and 0.03 m. of isobutylene. The reaction mixture was filtered and the aluminum salts were washed several times with methanol. The filtrate was distilled to give 12.3 g. (70% yield) of *trans*-2-butene-1,4-diol boiling at 86–88°/0.5 mm.; n_D^{25} 1.4758.

Bromine (12.2 g., 0.076 m.) was added dropwise over 4 hr. to a stirred mixture of *trans*-2-butene-1,4-diol (6.6 g., 0.075 m.) in chloroform maintained at 5–10°. The product was filtered and recrystallized from chloroform to give 14.2 g. of *meso*-2,3-dibromo-1,4-butanediol[12] melting at 130.0–130.6°.

Anal. Calcd. for $C_4H_8O_2Br_2$: Br, 64.5. Found: Br, 64.5.

Reduction of diethyl fumarate. Diethylaluminum hydride (0.2 m.) was added under nitrogen over 1 hour to a stirred solution of diethyl fumarate (8.6 g., 0.05 m.) in benzene (300 ml.). The temperature rose to 45° during the reaction. After stirring an additional 2 hr., the reaction mixture was decomposed at room temperature by the slow addition of methanol (25.6 g., 0.8 m.) in benzene (55 ml.) followed by water (15 g., 0.8 m.). The gas evolved during the decomposition contained 0.39 m. of ethane and 0.02 m. of ethylene. The decomposed reaction mixture was filtered and the aluminum salts were washed several times with methanol. The filtrates were combined and distilled to give 2.9 g. (66% yield) of *trans*-2-butene-1,4-diol boiling at 86–88°/0.5 mm.; n_D^{25} 1.4752.

Reduction of 2-butyne-1,4-diol with lithium aluminum hydride. 2-Butyne-1,4-diol (43.2 g., 0.5 m.) in tetrahydrofuran (300 ml.) was added dropwise to lithium aluminum hydride (39.0 g., 1.0 m.) in anhydrous ether (1 l.). The reaction mixture was refluxed for 18 hr., cooled, and decomposed by the addition of water (72 g., 4.0 m.). The resulting slurry was filtered, the ether dried and concentrated. Distillation of the residue (6.1 g.) gave 2-butene-1,4-diol (3.3 g., 7.5% yield) boiling at 112–114°/3 mm.

Anal. Calcd. for $C_4H_8O_2$: Hydrogen No., 1.00; Hydroxyl No.,[13] 2.0. Found: Hydrogen No., 1.05; Hydroxyl No., 1.9.

This was confirmed as the *trans* isomer by its infrared spectrum and dibromo derivative (m.p. 129–130°).

Reduction of 2-butyne-1,4-diol with diisobutylaluminum hydride. Diisobutylaluminum hydride (0.2 m.) was added over 4 hr. to a stirred slurry of 2-butyne-1,4-diol (25.8 g., 0.3 m.) in benzene (160 ml.). The volume of gas evolved during this addition indicated that the reaction of the diisobutylaluminum hydride with the hydroxyl groups of 2-butyne-1,4-diol was practically quantitative. After stirring at 45° for 6 hr., a second portion of diisobutylaluminum hydride (0.3 m.) was added over 0.5 hr. The mixture was stirred for 8 hr. at 45° and then was decomposed by the addition of methanol (32.0 g., 1.0 m.) in benzene (35 m.) followed by water (27.0 g., 1.5 m.) in methanol (30 ml.). The reaction mixture was filtered and concentrated under reduced pressure leaving 19.7 g. of solid residue. Recrystallization from ethyl acetate produced unreacted 2-butyne-1,4-diol (15.0 g.) melting at 55–56°.

Reduction of 1-ethynylcyclohexanol. Diisobutylaluminum hydride (0.2 m.) was added under nitrogen to a stirred solution of 1-ethynylcyclohexanol (12.4 g., 0.1 m.) in 150 ml. of benzene over 1.1 hr. The temperature rose to 40° during the addition. The reaction mixture was stirred at 60° for 8 hr., cooled and decomposed by the addition of methanol (19.2 g., 0.6 m.) in benzene (50 ml.) followed by water (10.8 g., 0.6 m.) in methanol (25 ml.). The product was filtered and concentrated to give 9.7 g. of residue which gave a hydrogen number of 1.52 and a methynyl hydrogen number[14] of 0.51. Therefore, this crude product contained 52% of unreacted 1-ethynylcyclohexanol and 48% of 1-vinylcyclohexanol.

Acknowledgment. The authors are indebted to Dr. E. H. Dobratz for the generous supply of diisobutyl- and diethylaluminum hydrides.

PITTSBURGH, PA.

(12) C. Prevost, *Compt. rend.*, **183**, 1292 (1926).

(13) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, p. 9, John Wiley & Sons, New York, 1954.

(14) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, p. 86, John Wiley & Sons, New York, 1954.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN COMPANY, DIVISION OF EASTMAN KODAK COMPANY]

Phosphorus-Containing Derivatives of 2,2-Dimethyl-1,3-propanediol

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A number of phosphorus-containing esters were made from 2,2-dimethyl-1,3-propanediol. Phosphoryl chloride gave a cyclic phosphorochloridate which could be treated with an alcohol or phenol to produce a neutral ester. Phosphonic dichlorides gave cyclic neutral esters directly. When phosphorus trichloride was used, a cyclic bisphosphite was produced; however, when this reaction was carried out in the presence of an alcohol, a cyclic hydrogen phosphite was formed. Treatment of 2,2-dimethyl-1,3-propanediol with diethyl phosphorochloridate gave a neutral bisphosphate which on pyrolysis liberated triethyl phosphate to yield a cyclic neutral ester. In general, these derivatives of 2,2-dimethyl-1,3-propanediol are stable, white, crystalline compounds.

This investigation was undertaken to study the preparation and properties of phosphorus-containing esters derived from 2,2-dimethyl-1,3-propanediol, a derivative of isobutyraldehyde. These esters were made using phosphoryl chloride, phosphonic dichlorides, phosphorus trichloride, and diethyl phosphorochloridate. Treatment of a 1,2- or 1,3-glycol with a phosphorus dihalide or trihalide usually results in the formation of cyclic esters.[1-13]

(1) A. D. F. Toy (to Victor Chemical Works), U. S. Patent 2,382,622 (1945).

(2) A. E. Arbuzov and M. M. Azanovskaya, *Izvest. Akad. Nauk S. S. S. R.*, 473 (1949); *Chem. Abstr.*, **44**, 1905b (1950).

2,2-Dimethyl-1,3-propanediol is particularly prone to form cyclic derivatives. These new phosphorus-containing heterocyclic compounds are usually much more stable than the analogous alkyl esters. In general, these products are white, crystalline solids.

When 2,2-dimethyl-1,3-propanediol was treated with phosphoryl chloride, the cyclic phosphorochloridate I was produced. I does not hydrolyze

$$POCl_3 + HOCH_2C(CH_3)_2CH_2OH \longrightarrow (CH_3)_2C(CH_2O)_2P(O)Cl$$

I

very readily since it is insoluble in water; however, it may be hydrolyzed to 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate by dissolving it in a moist organic solvent.

I is less reactive toward alcohols than a typical dialkyl phosphorochloridate; for example, diethyl phosphorochloridate reacts readily with an alcohol at 75–80° in the presence of pyridine to form the neutral phosphate, whereas only a negligible amount of I reacted with ethyl alcohol when refluxed for 6 hr. in benzene in the presence of pyridine. The reaction was also incomplete when I was dissolved in pyridine and treated with a large excess of ethyl alcohol at 80° for 16 hr. 2,2-Dimethyl-1,3-propanediol cyclic phosphorochloridate does react with alcohols in the presence of tertiary amines at higher temperatures; for example, treatment of I with an alcohol or phenol in the presence of pyridine in refluxing toluene gave the neutral ester II.

$$I + ROH \xrightarrow[110°]{\text{tertiary amine}} (CH_3)_2C(CH_2O)_2P(O)OR$$

II

IIa. R = C_2H_5—
IIb. R = $(CH_3)_2CHCH(C_2H_5)CH_2$—
IIc. R = C_6H_5—

It was also possible to prepare esters of type II by treating phosphoryl chloride with one mole of an alcohol or a phenol to produce the alkyl or aryl phosphorodichloridate. The crude intermediate phosphorodichloridate was subsequently treated with 2,2-dimethyl-1,3-propanediol to produce II. These reactions could be effected without using a tertiary base to absorb the liberated hydrogen chloride.

$$ROH + POCl_3 \xrightarrow{-HCl} ROP(O)Cl_2 \xrightarrow[-2\ HCl]{HOCH_2C(CH_3)_2CH_2OH} II$$

Phenylphosphonic and chloromethylphosphonic dichlorides reacted as expected when treated with 2,2-dimethyl-1,3-propanediol to produce the cyclic phosphonates III.

$$RP(O)Cl_2 + HOCH_2C(CH_3)_2CH_2OH \longrightarrow (CH_3)_2C(CH_2O)_2P(O)R$$

III

IIIa. R = C_6H_5—
IIIb. R = $ClCH_2$—

2,2-Dimethyl-1,3-propanediol reacted with diethyl phosphorochloridate to form 2.2-dimethyl-1,3-propanediol bis(diethyl phosphate) IV. IV

$$HOCH_2C(CH_3)_2CO_2OH + 2(C_2H_5O)_2P(O)Cl \longrightarrow (C_2H_5O)_2P(O)OCH_2C(CH_3)_2CH_2OP(O)(OC_2H_5)_2$$

IV

could be successfully distilled at low pressures (3 mm.). However, attempts to distill IV at higher pressures (64 mm.) led to pyrolysis. Under these conditions, triethyl phosphate was liberated and 2,2-dimethyl-1,3-propanediol cyclic ethyl phosphate was liberated and 2,2-dimethyl-1,3-propanediol cyclic ethyl phosphate was formed. This again illustrates the great tendency for these 2,2-dimethyl-1,3-propanediol derivatives to cyclize.

$$IV \xrightarrow{\Delta} (C_2H_5O)_3P(O) + (CH_3)_2C(CH_2O)_2P(O)OC_2H_5$$

IIa

This pyrolysis reaction represents an alternative path for the preparation of esters of type II.

Somewhat unusual results were obtained when 2,2-dimethyl-1,3-propanediol was treated with phosphorus trichloride. The predominant product was 2,2-dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphite) V whether or not a tertiary base was used.

$$HOCH_2C(CH_3)_2CH_2OH + PCl_3 \longrightarrow (CH_3)_2C(CH_2O)_2POCH_2C(CH_3)_2CH_2OP(OCH_2)_2C(CH_3)_2$$

V

and

$$(CH_3)_2C(CH_2O)_2P(O)H$$

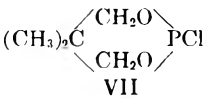
VI

(3) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).
(4) A. E. Arbuzov and M. M. Azanovskaya, *Izvest. Akad. Nauk S. S. S. R.*, 544 (1951); *Chem. Abstr.*, **47**, 98c (1953).
(5) A. F. McKay, R. O. Braun, and G. R. Vavasour, *J. Am. Chem. Soc.*, **74**, 5540 (1952).
(6) A. E. Arbuzov and V. M. Zoroastrova, *Bull. Acad Sci. U. S. S. R., Div. Chem. Sci. S. S. R.* (*Eng. Translation*), 697 (1952); *Chem. Abstr.*, **48**, 4496a (1954).
(7) A. E. Arbuzov and V. M. Zoroastrova, *Bull. Acad. Sci. U. S. S. R., Div. Chem. Sci. S. S. R.* (*Eng. Translation*), 705 (1952); *Chem. Abstr.*, **48**, 4495a (1954).
(8) H. R. Gamrath and R. E. Hatton (*to Monsanto Chemical Co.*), U. S. Patent **2,661,365** (1953).
(9) A. F. McKay, R. A. B. Bannard, R. O. Braun, and R. L. Benness, *J. Am. Chem. Soc.*, **76**, 3546 (1954).
(10) R. C. Morris and J. L. Van Winkle (to Shell Development Co.), U. S. Patent **2,744,128** (1956).
(11) W. M. Lanham (to Union Carbide and Carbon Corp.), British Patent **762,125** (1956).
(12) E. L. Gefter, *J. Gen. Chem. U. S. S. R.* (*Eng. Translation*), **26**, 1619 (1956).
(13) T. Ukita, K. Nagasawa, and M. Irie, *Pharm. Bull. Tokyo*, **5**, 121 (1957); *Chem. Abstr.*, **51**, 17735b (1957).

VI was probably formed by hydrolysis of VII, a likely intermediate, when traces of moisture were present in the reaction mixture. In one experiment without a tertiary base and when moisture was apparently absent, only V was obtained. It should be pointed out that 2,2-dimethyl-1,3-propanediol is extremely hygroscopic. The presence of moisture can be minimized by mixing this glycol with toluene or benzene and removing the water present as the azeotrope before beginning the reaction.

It seems likely that V may form by the following mechanism. 2,2-Dimethyl-1,3-propanediol cyclic phosphorochloridite VII could form rapidly and subsequently react with another molecule of VII and 2,2-dimethyl-1,3-propanediol. The pro-

$$HOCH_2C(CH_3)_2CH_2OH + PCl_3 \longrightarrow$$

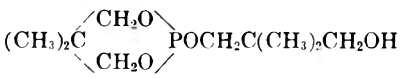


VII

$$VII + HOCH_2C(CH_3)_2CH_2OH + VII \longrightarrow V$$

duction of V appeared to be independent of the molar ratio of phosphorus trichloride to 2,2-dimethyl-1,3-propanediol.

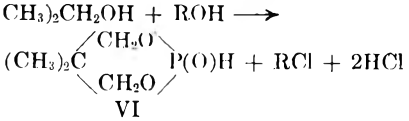
The difficulty in forming 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphite VI from the interaction of phosphorus trichloride and 2,2-dimethyl-1,3-propanediol may possibly be explained by the blocking effect of the two methyl groups adjacent to the carbon-oxygen bond. This blocking would tend to prevent dealkylation of V or 2,2-dimethyl-1,3-propanediol cyclic 3-



hydroxy-2,2-dimethylpropyl phosphite, by the liberated hydrogen chloride to form the cyclic hydrogen phosphite VI.

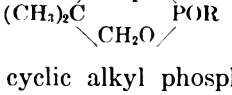
It was found that good yields of VI could be obtained by treating phosphorus trichloride with an equimolar mixture of 2,2-dimethyl-1,3-propanediol and an alcohol. Ethyl alcohol, isobutyl alcohol, and

$$PCl_3 + HOCH_2C(CH_3)_2CH_2OH + ROH \longrightarrow$$



VI

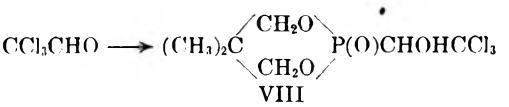
2-ethyl-1-hexanol were used successfully in this reaction. The reaction was not successful when cetyl alcohol was used. It is probable that a 2,2-dimethyl-



1,3-propanediol cyclic alkyl phosphite, is an intermediate which is dealkylated by the liberated hydrogen chloride. The cetyl radical may prevent the dealkylation to the cyclic hydrogen phosphite by a blocking effect similar to that proposed above for the 3-hydroxy-2,2-dimethylpropyl radical.

VI reacts as a typical hydrogen phosphite with chloral or chlorine. Treatment of VI with chloral forms 2,2-dimethyl-1,3-propanediol cyclic 2,2,2-trichloro-1-hydroxyethylphosphonate VIII. Treat-

$$VI + CCl_3CHO \longrightarrow$$

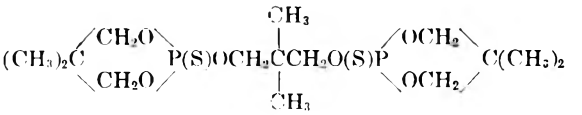


VIII

ment of VI with chlorine results in the formation of the cyclic phosphorochloridate I.

A cyclic bis(phosphorothionate) IX was obtained when V was treated with sulfur.

$$V + S \longrightarrow$$



IX

Thus, this investigation demonstrated the ease with which 2,2-dimethyl-1,3-propanediol forms cyclic esters. In general, these derivatives are stable, white, crystalline materials that undergo reactions typical of organophosphorus esters.

EXPERIMENTAL

2,2-Dimethyl-1,3-propanediol cyclic phosphorochloridate (I). *Method A.* 2,2-Dimethyl-1,3-propanediol (104 g., 1.0 mole) was dissolved in 400 ml. of anhydrous dioxane, and phosphoryl chloride (153 g., 1.0 mole) was added dropwise with vigorous stirring. After a short induction period, the temperature of the reaction mixture rose to about 80°. The temperature was not allowed to exceed 80°, and it was controlled by occasional external cooling using chilled water. After all the phosphoryl chloride had been added and the mixture had cooled to room temperature, stirring was continued for 8 hr. while dry nitrogen was bubbled in through a fritted glass disk to sweep out the liberated hydrogen chloride. The dioxane was removed by distillation at atmospheric pressure, leaving an oil which crystallized as it cooled. This material was washed with cold cyclohexane and then recrystallized from a 50/50 mixture of cyclohexane and benzene. It could also be recrystallized from a 75/25 mixture of cyclohexane and 1,2-dichloroethane. The purified material was obtained as white crystals (115 g., 62.4%), m.p. 102–103°. The product was soluble in acetone, benzene, and 1,2-dichloroethane and insoluble in water, ether, and cyclohexane.

Anal. Calcd. for $C_5H_{10}ClO_3P$: C, 32.54; H, 5.46; Cl, 19.21. Found: C, 32.60; H, 5.53; Cl, 19.20.

This compound was also prepared using 1,2-dichloroethane as the solvent rather than dioxane. In this case, the yield of recrystallized product was 65%.

Method B. 2,2-Dimethyl-1,3-propanediol cyclic hydrogen phosphite VI (15 g., 0.1 mole) was dissolved in 100 ml. of chloroform, and chlorine was bubbled in through a fritted glass disk with stirring. The solution became warm and the chlorine was absorbed rapidly. The reaction mixture was cooled externally with cold water while the chlorine was added. After 30 min., the yellow color of chlorine persisted. The flow of chlorine was stopped and the solution was stirred for 1 hr. at 25°. Next, nitrogen was bubbled through the solution for 4 hr. to remove excess chlorine and the liberated hydrogen chloride. The solvent was removed under reduced pressure, leaving the product as a white mass. Recrystallization of a small sample of crude material from a mixture of cyclohexane and benzene gave white crystals,

m.p. 102–103°. The melting point of a mixture with product obtained by Method A was not depressed.

A small sample of the 2,2-dimethyl-1,3-propanediol cyclic phosphorochloridate was dissolved in a 50/50 mixture of acetone and water. After the mixture had stood for 2 days, some of the solvent had evaporated and a white, crystalline material had deposited, m.p. 170–173°. Recrystallization of this compound from a mixture of benzene and ethyl alcohol gave long, slender needles, m.p. 174–176°. Analysis of this product indicated it to be the monohydrate of 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate.

Anal. Calcd. for $C_5H_{11}O_4P \cdot H_2O$: P, 16.82; neut. equiv., 184.1. Found: P, 16.87; neut. equiv., 174.1.

2,2-Dimethyl-1,3-propanediol cyclic ethyl phosphate (IIa). *Method A.* 2,2-Dimethyl-1,3-propanediol (31.2 g., 0.3 mole) was treated with diethyl phosphorochloridate (103.0 g., 0.6 mole) in the presence of pyridine (55.3 g., 0.7 mole) in 200 ml. of dioxane according to the procedure used for the preparation of IV. After the pyridine hydrochloride and solvent had been removed, the crude 2,2-dimethyl-1,3-propanediol bis(diethyl phosphate) was heated at 150–175° (64 mm.) for 8 hr. Distillation through an 18-in. Vigreux column gave two fractions: (1) 27.5 g., b.p. 97–136° (4.0–3.0 mm.), n_D^{20} 1.4101; and (2) 38 g., b.p. 136–145° (3.0–2.7 mm.), n_D^{20} 1.4242.

Fraction 2 was redistilled to give the following fractions: (1) 17.8 g., b.p. 77–78° (5.3 mm.), n_D^{20} 1.4055 (n_D^{20} of triethyl phosphate is 1.4053); (2) 10.0 g., b.p. 112–139° (5.3 mm.), n_D^{20} 1.4410; and (3) 3.4 g., b.p. 139–146° (5.3 mm.), n_D^{20} 1.4434. The infrared spectrum of Fraction 1 was identical with that of an authentic sample of triethyl phosphate. Analyses of Fractions 2 and 3 indicated the material to be 2,2-dimethyl-1,3-propanediol cyclic ethyl phosphate.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79. Found: C, 43.19; H, 7.75.

Method B. Ethyl alcohol (23 g., 0.5 mole) was added dropwise with stirring to phosphoryl chloride (76.6 g., 0.5 mole) dissolved in 250 ml. of dioxane while the reaction flask was cooled in an ice bath. The reaction mixture was stirred for 30 min. with cooling, then 2,2-dimethyl-1,3-propanediol (52 g., 0.5 mole) dissolved in 150 ml. of dioxane was added dropwise with stirring. The reaction mixture was stirred at 25° for 4 hr., and then it was allowed to stand overnight. Most of the solvent was removed by distillation at atmospheric pressure, and then a small amount of 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate precipitated. This material was filtered off and recrystallized from benzene and ethyl alcohol to obtain long, slender, white needles, m.p. 175–176°. There was no depression in the melting point of a mixture with material obtained from hydrolysis of the 2,2-dimethyl-1,3-propanediol cyclic phosphorochloridate as described above.

Anal. Calcd. for $C_5H_{11}O_4P \cdot H_2O$: P, 16.82; neut. equiv., 184.1. Found: P, 16.90; neut. equiv., 186.5.

The oil obtained after removal of the cyclic hydrogen phosphate impurity was fractionated *in vacuo* through a short Vigreux column. When the forerun had been removed, 21 g. (22%) of product was obtained, b.p. 129–137° (3.2 mm.), n_D^{20} 1.4388.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.95. Found: C, 43.59; H, 8.05; P, 15.98.

2,2-Dimethyl-1,3-propanediol cyclic 2-ethyl-4-methylpentyl phosphate (IIb). *Method A.* Pyridine (47.4 g., 0.6 mole) and 2,2-dimethyl-1,3-propanediol cyclic phosphorochloridate (50.3 g., 0.3 mole) were placed in 400 ml. of toluene and stirred while 2-ethyl-4-methyl-1-pentanol (39 g., 0.3 mole) dissolved in 100 ml. of toluene was added dropwise with stirring. No temperature rise was noted. The reaction mixture was stirred at 25° for 5 hr., then heated to reflux for 5 hr. After the mixture had stood overnight, the precipitated pyridine hydrochloride (29.8 g.; theor., 34.7 g.) was removed by filtration. The toluene solution was washed twice with water and dried over sodium sulfate. The toluene was removed, and then 1 g. of anhydrous sodium carbonate was added to the oil which remained. The crude product was distilled through an 8-in. Vigreux column to obtain 31.8 g. (38%) of a clear, colorless oil, b.p. 153–159° (1.3 mm.), n_D^{20} 1.4483.

Anal. Calcd. for $C_{13}H_{27}O_4P$: C, 56.09; H, 9.78; P, 11.13. Found: C, 56.03; H, 9.95; P, 11.41.

Method B. Phosphoryl chloride (76.6 g., 0.5 mole) was placed in a flask and cooled externally to 5°. 2-Ethyl-4-methyl-1-pentanol (65 g., 0.5 mole) was added dropwise over a 1-hr. period with stirring and cooling so that the temperature remained at 5°. The reaction mixture was stirred for 30 min. at 5° and then for 1.5 hr. at 25°. The mixture was allowed to stand overnight, and then was stirred for 2 hr. while nitrogen was passed through the product to remove the liberated hydrogen chloride. At this point, 2,2-dimethyl-1,3-propanediol (52 g., 0.5 mole) was added, and the mixture was stirred at 25° for several hours. Then it was heated gently on the steam bath while nitrogen was passed through the reaction mixture to remove hydrogen chloride. When no more could be detected emerging from the condenser, the reaction mixture was distilled *in vacuo* through a 6-in. Vigreux column. After the forerun had been removed up to a temperature of 159° at 1.2 mm., the product was cooled and 0.5 g. of anhydrous sodium carbonate was added. Vacuum distillation was then resumed, and 33.4 g. (24%) of product was collected at 159–161° (1.2–1.9 mm.), n_D^{20} 1.4485.

Anal. Calcd. for $C_{13}H_{27}O_4P$: C, 56.09; H, 9.78. Found: C, 56.08; H, 9.85.

When cooled, the distillation residue deposited a white, crystalline solid. This material, when recrystallized from a mixture of benzene and absolute ethyl alcohol, gave large, transparent prisms, m.p. 170–174°. This product was the monohydrate of 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate which was probably formed by the loss of 2-ethyl-4-methylpentene from the above product.

Anal. Calcd. for $C_5H_{11}O_4P \cdot H_2O$: P, 16.82. Found: P, 16.82.

2,2-Dimethyl-1,3-propanediol cyclic phenyl phosphate (IIc). *Method A.* Phenol (56.6 g., 0.6 mole), 2,2-dimethyl-1,3-propanediol cyclic phosphorochloridate (11 g., 0.6 mole), pyridine (95 g., 1.2 moles), and toluene (500 ml.) were mixed and heated to reflux with stirring for 16 hr. After the mixture had stood overnight, the precipitated pyridine hydrochloride was removed by filtration. The toluene solution was washed with water and then distilled *in vacuo*. After much of the toluene solution had been removed, a crystalline precipitate formed and was removed by filtration. This product was crude 2,2-dimethyl-1,3-propanediol cyclic phenyl phosphate containing 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate as an impurity. A small portion of this material was stirred in a hot mixture of benzene and cyclohexane. The insoluble part was removed by filtration, and analysis of this white, crystalline material indicated it to be 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphate, m.p. 189–192°.

Anal. Calcd. for $C_5H_{11}O_4P$: P, 18.65. Found: P, 19.07.

When crystallization had occurred in the benzene-cyclohexane solution, the crystals were removed by filtration and recrystallized from cyclohexane containing a small amount of ethyl alcohol. The product was obtained as short, white fluffy needles, m.p. 130–131°. The melting point of a mixture of the product with material obtained by Method B was not depressed.

Method B. Phenol (18.8 g., 0.2 mole), phosphoryl chloride (30.6 g., 0.2 mole), and anhydrous magnesium chloride (0.1 g.) were mixed with stirring and heated to approximately 125° over a 9-hr. period. The crude phenyl phosphorodichloridate was a yellow liquid. 2,2-Dimethyl-1,3-propanediol (20.8 g., 0.2 mole) was added to this crude product with stirring. The reaction was weakly exothermic. The mixture was stirred for 5 hr., and then heated on a steam bath with stirring for 3 additional hours. The steam bath was then removed and nitrogen was passed through

the reaction mixture. The reaction mixture solidified immediately to a white, crystalline mass, which was recrystallized from a mixture of benzene and cyclohexane. An analytical sample, m.p. 133–135°, was obtained by recrystallization of a small amount of this material from a 75/25 mixture of benzene and cyclohexane.

Anal. Calcd. for $C_{11}H_{15}O_4P$: C, 54.54; H, 6.24; P, 12.79. Found: C, 54.53; H, 6.44; P, 12.89.

2,2-Dimethyl-1,3-propanediol cyclic phenylphosphonate (IIIa). 2,2-Dimethyl-1,3-propanediol (31.2 g., 0.3 mole) and pyridine (55.3 g., 0.7 mole) were dissolved in 250 ml. of dry dioxane. Phenylphosphonic dichloride (58.5 g., 0.3 mole) was added dropwise with stirring while the reaction vessel was cooled externally with ice water. Then the reaction mixture was stirred at 25° for 1.5 hr. After the precipitated pyridine hydrochloride had been filtered off, the dioxane was removed under reduced pressure. The residual white, crystalline solid was washed well with water. The yield was 31 g. (46%) of product, m.p. 103–105°, that was soluble in acetone and methanol but insoluble in water.

Anal. Calcd. for $C_{11}H_{15}O_3P$: C, 58.40; H, 6.68. Found: C, 57.93; H, 6.66.

2,2-Dimethyl-1,3-propanediol cyclic chloromethylphosphonate (IIIb). This compound was prepared from 2,2-dimethyl-1,3-propanediol (31.2 g., 0.3 mole), pyridine (47.5 g., 0.6 mole), and chloromethylphosphonic dichloride (50.3 g., 0.3 mole) using 240 ml. of dioxane as the solvent. The procedure used was that described for preparation of 2,2-dimethyl-1,3-propanediol cyclic phenylphosphonate, except that the reaction mixture was stirred for 6 hr. instead of 1.5 hr. After the pyridine hydrochloride and the solvent had been removed, a crystalline residue was obtained. The residue was recrystallized from a 50/50 mixture of benzene and cyclohexane to yield 25 g. (42%) of snow-white crystals, m.p. 115–116°. The product was soluble in benzene, acetone, ethyl alcohol, and water but insoluble in cyclohexane.

Anal. Calcd. for $C_6H_{12}ClO_3P$: C, 36.28; H, 6.09. Found: C, 36.47; H, 6.32.

2,2-Dimethyl-1,3-propanediol bis(diethyl phosphate) (IV). 2,2-Dimethyl-1,3-propanediol (31.2 g., 0.3 mole) and pyridine (55.3 g., 0.7 mole) were dissolved in 300 ml. of dioxane. The mixture was stirred and cooled externally with ice water while diethyl phosphorochloridate (103 g., 0.6 mole) was added dropwise over a period of 30 min. The mixture was stirred for 2 hr. at 25°, and the precipitated pyridine hydrochloride was removed by filtration. The filtrate was distilled *in vacuo* through a short Vigreux column. A forerun of 42.5 g., b.p. 90–182° (3.0 mm.), was removed and then 43.6 g. (38.6%) of colorless oil was collected at 183–188° (3.1 mm.), n_D^{20} 1.4278.

Anal. Calcd. for $C_{13}H_{30}O_8P_2$: C, 41.49; H, 8.04. Found: C, 41.31; H, 8.00.

2,2-Dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphite) (V). 2,2-Dimethyl-1,3-propanediol (364 g., 3.5 moles) was dissolved in 1500 ml. of anhydrous dioxane. Pyridine (474 g., 6.0 moles) was added, and then phosphorus trichloride (274 g., 2.0 moles) was added dropwise with stirring while the reaction vessel was cooled externally with an ice bath. After all of the phosphorus trichloride had been added, the reaction mixture was stirred at room temperature for 5 hr. The pyridine hydrochloride was filtered off and the filtrate was fractionated *in vacuo* using a short Vigreux column. After a small amount of unreacted 2,2-dimethyl-1,3-propanediol had been removed, 45 g. (15% based on phosphorus trichloride) of 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphite, b.p. 140–145° (2.2–2.5 mm.), was obtained. When cooled, this material formed white crystals, m.p. 48–50°. The infrared spectrum of this material was identical with that of the product prepared as described below (see VI).

After an intermediate fraction of 38 g., b.p. 153–167° (2.5 mm.), had been removed, 98 g. (27% based on phosphorus trichloride) of 2,2-dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphite) was obtained, b.p. 167–177° (2.6 mm.), n_D^{20} 1.4689. This material solidified into large, transparent crystals after standing for several days. The product was low-melting and insoluble in water.

Anal. Calcd. for $C_{15}H_{30}O_6P_2$: C, 48.91; H, 8.21. Found: C, 48.66; H, 8.23.

When the above reaction was repeated using 0.4 mole of 2,2-dimethyl-1,3-propanediol and 0.2 mole of phosphorus trichloride without pyridine, no cyclic hydrogen phosphite was found. A small amount of 2,2-dimethyl-1,3-propanediol was recovered, and a 72% yield of 2,2-dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphite), n_D^{20} 1.4687, was obtained. The distillate solidified to a low-melting solid after standing for 2 days.

Anal. Calcd. for $C_{15}H_{30}O_6P_2$: C, 48.91; H, 8.21. Found: C, 48.61; H, 8.06.

In a separate reaction in which 3.0 moles of 2,2-dimethyl-1,3-propanediol dissolved in 700 ml. of 1,1,2,2-tetrachloroethane was treated with 2.0 moles of phosphorus trichloride, both V and VI were isolated. The presence of moisture in the reaction mixture probably accounted for the formation of VI.

2,2-Dimethyl-1,3-propanediol cyclic hydrogen phosphite (VI). Ethyl alcohol (13.8 g., 0.3 mole) and 2,2-dimethyl-1,3-propanediol (31.2 g., 0.3 mole) were mixed and stirred while phosphorus trichloride (41.3 g., 0.3 mole) was added dropwise. The reaction flask was cooled externally so that the temperature did not rise above 25°. After all the phosphorus trichloride had been added and the exothermic reaction had subsided, the reaction mixture was stirred at 25° while nitrogen was passed through to remove the liberated hydrogen chloride and ethyl chloride. Finally, the reaction mixture was warmed on the steam bath to complete the removal of the by-products. The evolved ethyl chloride (14 g., theor. = 19.4 g.) was collected in a Dry Ice trap. After a forerun of 2.5 g. had been removed, 28 g. (62%) of product was collected at 142–145° (2.9 mm.) through a short Vigreux column. This distillate solidified to a white, crystalline solid, m.p. 48–50°. The infrared spectrum of this compound was in agreement with the cyclic hydrogen phosphite structure. It had a P—H absorption band at 4.2 μ. The compound discolored both bromine and potassium permanganate solutions. The molecular weight, as determined by treatment of a sample with excess alkali followed by back titration with acid, was 153.7 (calculated molecular weight = 150.12).

Anal. Calcd. for $C_5H_{11}O_3P$: C, 40.00; H, 7.39; P, 20.64. Found: C, 39.62; H, 7.44; P, 20.57.

When the above reaction was repeated using isobutyl alcohol and 2-ethyl-1-hexanol instead of ethyl alcohol, the yields of 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphite were 68.5% [b.p. 117–119° (1.3 mm.)] and 75% [b.p. 117–120° (0.8 mm.)], respectively. In these two cases the reaction mixture was not cooled during the addition of the phosphorus trichloride; however, the temperature of the reaction mixture was moderated by the rate of addition of the phosphorus trichloride so that the temperature never exceeded 70°. None of the cyclic hydrogen phosphite was obtained when cetyl alcohol was used instead of ethyl alcohol.

2,2-Dimethyl-1,3-propanediol cyclic 2,2,2-trichloro-1-hydroxyethylphosphonate (VIII). Chloral (14.7 g., 0.1 mole) and 2,2-dimethyl-1,3-propanediol cyclic hydrogen phosphite (15.0 g., 0.1 mole) were mixed with stirring. Even though the flask was cooled in an ice bath, the temperature of the reaction mixture rose to 120°. At this temperature the system solidified to a white solid. A small sample of this material was recrystallized from ethyl alcohol to obtain transparent, square platelets, m.p. 209–210°. The compound was insoluble in cyclohexane, benzene, chloroform, and water. The infrared spectrum was compatible with the proposed structure and indicated that the —OH group present was hydrogen-bonded.

Anal. Calcd. for $C_7H_{12}Cl_3O_4P$: C, 28.25; H, 4.07; P, 10.41. Found: C, 28.25; H, 4.09; P, 10.30.

2,2-Dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphorothionate) (IX). 2,2-Dimethyl-1,3-propanediol bis(cyclic 2,2-dimethyltrimethylene phosphite) (18.4 g., 0.05 mole), sulfur (3.2 g., 0.1 mole), and 70 ml. of benzene were mixed with stirring. A weakly exothermic reaction occurred. The reaction mixture was stirred at 25° for 48 hr., refluxed for 8 hr., and then cooled. A cream-colored solid (3.3 g.) crystallized from the benzene solution. Recrystallization of this material from benzene gave white crystals, m.p. 163–164°.

Anal. Calcd. for $C_{15}H_{30}O_6P_2S_2$: P, 14.33; S, 14.83. Found: P, 14.13; S, 14.74.

KINGSPORT, TENN.

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Preparation and Characterization of Vinyldichlorophosphine, Vinyldimethylphosphine, and Ethyldimethylphosphine[1,2]

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The air and moisture sensitive compound vinyldichlorophosphine (b.p. 104°/760 mm.) is readily obtained by heating a mixture of phosphorus trichloride and divinylmercury. Treatment of methylmagnesium chloride in diglyme with vinyldichlorophosphine afforded vinyldimethylphosphine (b.p. 69.0°/760 mm.) Ethyldimethylphosphine (b.p. 73.3°/760 mm.) was similarly prepared from ethyldichlorophosphine. The vapor tensions of four phosphines are reported.

As part of a study[5] on the relative electron-pair donor power of several organophosphines it was necessary to prepare and characterize vinyldimethylphosphine and ethyldimethylphosphine. The latter compound has been reported by Collie,[6] but has not been mentioned in the chemical literature since its discovery in 1888. Ethyldimethylphosphine was prepared by us by the sequence of reactions:

$$3PCl_3 + PbEt_4 \longrightarrow 3EtPCl_2 + PbCl_2 + EtCl \quad (a)$$

$$EtPCl_2 + 2MeMgCl \xrightarrow[\text{diglyme}^7]{} EtPMe_2 + 2MgCl_2 \quad (b)$$

Reaction (a) was carried out exactly as described by Kharasch *et al.*[8] The normal boiling point of ethyldimethylphosphine is 11° less than that reported earlier.[6] The hitherto unreported compound vinyldimethylphosphine was obtained from the reaction between vinyldichlorophosphine and methylmagnesium chloride. Before this reaction could be carried out, however, it was necessary to prepare a vinyldihalophosphine. Although trivinylarsine and trivinylstibine undergo redistribution to the vinylhalo derivatives when mixed with the trichlorides or tribromides of the respective elements, trivinylphosphine and phosphorus trihalides yield only black solids.[9] Similarly, excellent yields of vinylhaloarsines were obtained by Seyferth[9,10] by treating arsenic trihalides with dibutyldivinyltin, but when the "mixed" redistribution method was applied to phosphorus trihalides the desired vinylhalophosphines were not obtained. It is still possible that vinyldihalophosphines could be obtained from these reactions by empirically varying the experimental techniques until the correct conditions are found, but meanwhile, as described in the experimental section, the recently discovered divinylmercury[11] provides a ready route to such compounds.

$$(CH_2{:}CH)_2Hg + PCl_3 \xrightarrow{\text{heat}} CH_2{:}CHPCl_2 + CH_2{:}CHHgCl$$

Vinyldichlorophosphine (b.p. 104°/760 mm.) is very sensitive to air and to moisture. Even when sealed in evacuated ampoules it will decompose unless the ampoules have been thoroughly baked during evacuation. The gas-phase infrared spectrum of vinyldichlorophosphine has been studied[3] over the region 650–3500 cm.$^{-1}$. It shows the typical absorption C—H stretches at 3050 and 3110 cm.$^{-1}$; an overtone of a 968 cm.$^{-1}$ band at 1930 cm.$^{-1}$; C—H deformations at 1400, 1324 and 968 cm.$^{-1}$; and the P—C stretch frequency at 728 and 671

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(2) Presented at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

(3) Taken from the thesis of H. D. Kaesz submitted to the Graduate School of Arts and Sciences, Harvard University, in partial fulfillment of the requirements of the Ph.D. degree. Other parts of the dissertation are published elsewhere.

(4) Public Health Predoctoral Fellow of the National Heart Institute.

(5) H. F. Kaesz and F. G. A. Stone, abstracts of papers presented at the 135th Meeting of the American Chemical Society held in Boston, Mass., April 1959, p. 11M.

(6) N. Collie, *Trans. Chem. Soc.*, **53**, 714 (1888).

(7) Diglyme is the commercial name for diethyleneglycol dimethyl ether (Ansul Chemical Co.).

(8) M. S. Kharasch, E. V. Jensen, and S. Weinhouse, *J. Org. Chem.*, **14**, 429 (1949).

(9) L. Maier, D. Seyferth, F. G. A. Stone, and E. G. Rochow, *J. Am. Chem. Soc.*, 79, 5884 (1957).

(10) D. Seyferth, Technical Report, Office of Naval Research Contract No. Nonr-1866(13), February, 1957.

(11) B. Bartocha, F. E. Brinckman, H. D. Kaesz, and F. G. A. Stone, *Proc. Chem. Soc.*, 116 (1958); B. Bartocha and F. G. A. Stone, *Z. Naturforsch.*, **13b**, 347 (1958); G. F. Reynolds, R. E. Dessy, and H. H. Jaffé, *J. Org. Chem.*, **23**, 1217 (1958).

TABLE I

PHYSICAL CONSTANTS OF THE PHOSPHINES

Compound	$Log_{10}P(mm.) = -A/T + B$ A	B	ΔH Vap. at B.P., Kcal. Mole^{-1}	Trouton Constant, E.U.	Boiling Point[a]
(Et)(Me)$_2$P	1712	7.850	7.83	22.4	71.2[b]
(CH$_2$:CH)(Me)$_2$P	1693	7.846	7.75	22.7	67.9[c]
Et$_3$P	2065	8.035	9.45	23.6	127.5[d]
(CH$_2$:CH)$_3$P	1944	7.868	8.90	22.8	116.6[e]

[a] By extrapolation of vapor pressure equation. [b] Reference (6) reports a normal boiling point of 84°. Observed in this work 73.3°. [c] Observed in this work 69.0°. [d] Observed 127.5°, by F. G. Mann and D. Purdie, *J. Chem. Soc.*, 1549 (1935). [e] Observed in this work, 58.1°/100 mm. Calcd. 58.1°/100 mm.

cm.$^{-1}$. The P—Cl stretch normally occurs at 430 to 585 cm.$^{-1}$ and would not be seen on this spectrum. The infrared spectra of a variety of phosphorus compounds have been correlated in a review by Daasch and Smith.[12]

Vapor tensions of ethyldimethylphosphine and vinyldimethylphosphine are listed in Table II. The vapor tensions of triethylphosphine do not appear to have been reported previously, so these are also given in Table II. Vapor tensions of trivinylphosphine have been reinvestigated by us (Table II) because those previously obtained by Stone[9] are incorrect. Trivinylphosphine was first reported by Maier[9] who obtained it, after some difficulty, from vinylmagnesium bromide and phosphorus trichloride. Unfortunately unknown to Maier *et al.*[9] the vinyl bromide obtained commercially and used to make the vinyl Grignard contained appreciable quantities (*circa* 20%) of ethyl bromide with the result that the trivinylphosphine prepared contained significant amounts of triethylphosphine and perhaps ethylvinylphosphines. It is of course impossible to detect triethylphosphine in trivinylphosphine by elemental analysis, or to separate effectively the two compounds by distillation. Infrared spectra differences, however, will detect as little as 3% ethyl contamination of vinyl-metal or -metalloid compounds.[13] The infrared spectrum of triethylphosphine has strong bands at 1468 cm.$^{-1}$, 1423 cm.$^{-1}$, and 1380 cm.$^{-1}$. Bands at these frequencies do not appear in the spectrum of trivinylphosphine.

The constants which may be derived from the results presented in Table II are listed in Table I.

It is interesting to note that a tetrahydrofuran solution of trivinylphosphine, unlike a tetrahydrofuran solution of trimethylphosphine, does not give an immediate red precipitate with carbon disulfide. Vinyldimethylphosphine is intermediate between trivinyl- and trimethylphosphine in its behavior toward carbon disulfide. Triphenylphosphine, on the other hand, gives no precipitate with carbon disulfide. Rate of formation of a red adduct from an organophosphine and carbon disulfide appears to correlate roughly with the Lewis base strength of the phosphine, even though the carbon disulfide adducts might not be simple molecular addition compounds.

(12) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

(13) H. D. Kaesz and F. G. A. Stone, *Spectrochimica Acta*, in press.

EXPERIMENTAL

Microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Vapor tensions of the phosphines. Representative vapor tensions were determined with a tensimeter[14] and are given in Table II. Temperature measurements were made with N.B.S. calibrated thermometers graduated in 1/10ths from 0° to 100°. For each temperature setting 0.5 hr. was allowed for thermal equilibration, the temperature being controlled to within ±0.1°. An oil bath was used to heat the tensimeter. The bath tank had windows of parallel plate glass. Pressure readings were taken with a George & Becker Co. (London) cathetometer with a vernier calibrated to 0.02 mm.

TABLE II

VAPOR TENSIONS OF SOME ORGANOPHOSPHINES

t	$P_{mm.}$ Obsd.	$P_{mm.}$ Calcd.	t	$P_{mm.}$ Obsd.	$P_{mm.}$ Calcd.
Ethyldimethylphosphine					
0.1	38.4	38.7	14.7	81.4	80.3
4.5	48.2	48.6	19.2	99.7	99.1
9.5	63.0	62.4	24.2	124.3	124.4
Vinyldimethylphosphine					
0.0	44.5	44.5	14.3	90.5	90.4
4.4	55.7	55.7	18.9	111.8	111.9
9.5	71.8	71.8			
Triethylphosphine					
41.8	30.0	30.2	62.5	76.6	76.5
48.8	42.0	41.9	70.5	106.3	106.4
50.1	44.5	44.4	80.0	154.0	154.3
Trivinylphosphine					
39.7	45.2	45.2	60.7	111.0	111.2
46.9	62.5	62.4	67.5	145.5	145.3
54.3	85.6	85.6			

Preparation of phosphines by the Grignard technique. In the preparation of organophosphines by reaction between phosphorus trichloride and Grignard reagents, best yields are obtained using a large excess of *chloro*-Grignards, and the two reagents should be brought together at as low

(14) A. B. Burg and H. I. Schlesinger, *J. Am. Chem. Soc.*, 59, 780 (1937).

a temperature[15] as is possible, down to −78°. Thus, the procedure described by Maier *et al.*[9] for the preparation of trivinylphosphine involving simultaneous addition of vinylmagnesium bromide and phosphorus trichloride is unnecessary when vinylmagnesium chloride is used instead of vinylmagnesium bromide. Normal Grignard procedures may be followed and yields are good. Vinylmagnesium chloride (1.11 mole in 1 liter tetrahydrofuran) with phosphorus trichloride (0.254 mole in 350 ml. tetrahydrofuran) gave, after hydrolysis with saturated ammonium chloride solution, a 55% yield of trivinylphosphine (b.p. 58.1°/100 mm.). Before the vinyl chloride was used to make the Grignard, its purity (better than 99%) was established by gas-phase chromatography.

Reaction between ethyldichlorophosphine and methylmagnesium chloride. Methylmagnesium chloride (2.75 mole) was formed in tetrahydrofuran, and this solvent subsequently exchanged for 1 l. of diglyme.[16] This was done by removing the tetrahydrofuran *in vacuo*, with stirring to avoid bumping. A lubricated Tru-bore stirrer will withstand a pressure differential of one atmosphere. Prepurified nitrogen was readmitted to the system and 500 ml. of the new solvent added. Solvent removal was continued. This process of taking the Grignard down almost to dryness was repeated twice, using fresh increments of diglyme, until the infrared spectrum of the distillate showed the absence of tetrahydrofuran. The Grignard in diglyme was then cooled at about −60° and treated with ethyldichlorophosphine[8] (60 g., 0.458 mole) dissolved in 350 ml. of thoroughly dried and degassed diglyme. The mixture was not hydrolyzed. Liquid was removed from the reaction flask under reduced pressure and collected at −78°. Treatment with dry hydrogen chloride gave a white solid[17] which was washed with diethyl ether, and dried by pumping *in vacuo*. Free dimethylethylphosphine was released from its phosphonium salt by treatment with dimethylamine. The phosphine was treated for several days with resublimed P_2O_5 to remove traces of moisture and dimethylamine. The dimethylethylphosphine was carefully fractionated (b.p. 73.3 ± 0.1/760 mm.). Yield, 32 g. (78%).

Anal. Calcd. for $C_4H_{11}P$: C, 53.31; H, 12.31. Found: C, 53.49; H, 12.49.

Reaction between divinylmercury and phosphorus trichloride. Freshly distilled phosphorus trichloride (420 g., 3.06 mole), together with 60 ml. of dry degassed mineral oil, were placed under nitrogen in the flat bottomed flask, suitable for magnetic stirring, and equipped with a thermometer well, dropping funnel, and reflux condenser. A 145 g. (0.57 mole) sample of divinylmercury[11] was placed in the pressure-equalized addition funnel, and the flask was warmed by a heating mantle until gentle reflux took place. Divinylmercury was then slowly added, and stirring begun. The temperature of the reaction flask was maintained between 65° and 85° during addition of divinylmercury, and the reflux was continued for 1 hr. after all the mercury compound had been added. The contents of the flask turned dark brown. On cooling, the reaction flask was attached to a distillation apparatus, and about 250 ml. of excess phosphorus trichloride carefully removed at 200 mm. pressure. Previous experience had shown that if distillation is completed in the presence of the brown solids, only a small quantity of desired material is obtained. Therefore, the remaining liquid was transferred *in vacuo* at room temperature to a 100 ml. distillation flask cooled to −78°, and containing 15–25 ml. of degassed mineral oil. Toward the end of the transfer, the reaction flask was heated to 100° to ensure complete transfer of liquid product. The contents of the 100 ml. distillation flask were carefully fractionated, yielding vinyldichlorophosphine (36 g.) (b.p. 63.4 ± 0.2/200 ± 1 mm.) in 50% yield.

Anal. Calcd. for $C_2H_3PCl_2$: C, 18.63; H, 2.34; Cl, 55.00. Found: C, 18.45; H, 2.22; Cl, 54.80.

Reaction between vinyldichlorophosphine and methylmagnesium chloride. This reaction was carried out in a manner similar to that described above for the preparation of ethyldimethylphosphine. Methylmagnesium chloride (1.12 mole in 1250 ml. of diglyme) was treated with vinyldichlorophosphine (36 g., 0.28 mole) in 300 ml. of thoroughly dried and degassed diglyme. The mixture was not hydrolyzed, crude vinyldimethylphosphine being removed *in vacuo* and condensed at −78°. This material was fractionated giving pure vinyldimethylphosphine (8.7 g.) (b.p. 69.0°/760 mm.) in 35% yield.

Anal. Calcd. for C_4H_9P: C, 54.53; H, 10.30. Found: C, 54.30; H, 10.30.

Acknowledgment. We are indebted to the Ethyl Corp. for providing us with a sample of tetraethyllead which was used to prepare the ethyldichlorophosphine mentioned in this paper.

CAMBRIDGE, MASS.

(15) We are indebted to Dr. J. Chatt for emphasizing the importance of low temperature, although our own studies on trivinylphosphine led us tentatively to the same conclusion.

(16) Solvent exchange was carried out in order that the synthesis could be continued in a solvent whose boiling point was very different from that of the phosphine being prepared.

(17) Due to the extreme hygroscopic nature of phosphonium salts, the HCl must be rigorously dry. Traces of moisture will form a water solution of the phosphonium salt, which must then be dried by heating near 100°, under reduced pressure. It is necessary that the product at this point be a crystalline salt to permit ether washing and filtration.

[CONTRIBUTION FROM THE VENEREAL DISEASE EXPERIMENTAL LABORATORY, COMMUNICABLE DISEASE CENTER, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

Preparation and Ultraviolet Absorption Spectra of Some Derivatives of Phosphafluorinic Acid[1]

LEON D. FREEDMAN AND G. O. DOAK

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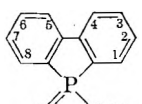
The Busch reaction, which involves the formation of carbon-carbon bonds through the reduction of aryl or alkyl halides, was used to prepare 3,6-dimethyl- and 2,7-dimethylphosphafluorinic acid. Three other derivatives were prepared by the nitration of phosphafluorinic acid, the reduction of 2,7-dinitrophosphafluorinic acid, and the oxidation of 3,6-dimethylphosphafluorinic acid. The ultraviolet absorption spectra of these compounds exhibit the intensity characteristic of the phosphafluorinic acid ring system. Hydrogenation of phosphafluorinic acid over rhodium-on-alumina yielded a dodecahydro derivative which showed no absorption in the ultraviolet.

Only five phosphinic acids have been reported in which the phosphorus atom is a member of a ring system. The first compound of this type was phenphosphazinic acid,[2] the heterocyclic ring of which contains nitrogen as well as phosphorus. More recently Kosolapoff[3] has used the Grignard reaction to prepare cyclopentamethylene-, cyclotetramethylene-, and cyclotrimethylenephosphinic acids, and we[4] have reported the synthesis of phosphafluorinic acid (I) by means of the Busch reaction.[5] The present paper is concerned with the preparation and properties of several derivatives of phosphafluorinic acid.



I

3,6-Dimethylphosphafluorinic acid was readily prepared from bis(2-bromo-4-tolyl)phosphinic acid[6] under the same conditions used for preparing phosphafluorinic acid itself. As indicated in Table I, the spectrum of the 3,6-dimethyl derivative exhibits the intensity and fine structure characteristic of the spectrum of the parent compound. There is a slight bathochromic shift such as one usually observes for alkyl substituted aromatic systems.[7] The spectrum of di-*p*-tolylphosphinic acid (which is formed as a by-product in the preparation of 3,6-dimethylphosphafluorinic acid) is included in Table I for comparison with the phosphafluorinic acid derivatives.

Application of the Busch reaction to bis(2-chloro-5-tolyl)phosphinic acid was not successful under the conditions used with the *o*-bromo derivatives. Even after a reaction period of eleven days, only 60% of the chlorine was split from the ring, and the ultraviolet absorption spectrum of the reaction mixture indicated that little or none of the desired phosphafluorinic acid derivative was present. However, when the amount of palladium used was doubled and the concentration of potassium hydroxide was increased from 1.25*N* to 3*N*, over 90% of the chlorine was cleaved from the ring in six days; and a small yield of 2,7-dimethylphosphafluorinic acid was obtained from the reaction mixture. As might be expected, the spectrum of this compound is similar to that of the 3,6-dimethyl derivative. The main product of the reduction was di-*m*-tolylphosphinic acid, the spectrum of which is also given in Table I.

3,6-Dicarboxyphosphafluorinic acid was prepared from the 3,6-dimethylphosphafluorinic acid by means of the pyridine-permanganate oxidation procedure recently used by Morgan and Herr[8] for preparing carboxylic acids containing the phosphine oxide group. The spectrum of 3,6-dicarboxyphosphafluorinic acid is devoid of fine structure and includes a low intensity long wave length band. Diminished fine structure is often produced by carboxy groups in polynuclear hydrocarbons.[9] It is seen also that the spectrum of

(1) The nomenclature and numbering system employed in this paper are in accord with the usage of F. G. Mann, *The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth, and Silicon*, Interscience Publishers, Inc., New York, 1950.

(2) P. G. Sergeev and D. G. Kudryashov, *Zhur. Obshchet Khim.*, **8**, 266 (1938).

(3) (a) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **77**, 6658 (1955); (b) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 3739 (1957).

(4) L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **21**, 238 (1956).

(5) The formation of carbon-carbon bonds by the reaction of an alkyl or aryl halide with palladium-on-calcium carbonate and a reducing agent has been thoroughly investigated by M. Busch and his coworkers; *cf.* M. Busch and W. Weber, *J. prakt. Chem.*, **146**, 1 (1936). In the present paper this reaction is termed the "Busch reaction."

(6) The preparation of bis(2-bromo-4-tolyl)phosphinic acid was described in ref. 18, but was erroneously called "(2-Br-5-$CH_3C_6H_3$)$_2PO_2H$."

(7) B. Pullman and A. Pullman, *Les Theories Electroniques de la Chimie Organique*, Masson & Cie, Paris, 1952, p. 515.

(8) P. W. Morgan and B. C. Herr, *J. Am. Chem. Soc.*, **74**, 4526 (1952).

(9) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley & Sons, Inc., New York, 1951, p. 20.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compound	λ_{max}, mμ	ϵ_{max}
Phosphafluorinic acid[b]	226	26,200
	232.5	30,200
	239.5	27,500
	278	10,100
	289.5	8,370
	320	1,060
3,6-Dimethylphosphafluorinic acid	232	32,900
	237.5	38,800
	244.5	31,900
	282	7,180
	293	5,920
	324[c]	656
Di-*p*-tolylphosphinic acid	231	19,000
	263	993
2,7-Dimethylphosphafluorinic acid	227	28,800
	235	31,200
	241.5	28,600
	283	15,400
	295	14,600
	331	1,170
Di-*m*-tolylphosphinic acid	226.5	12,900
	270	1,880
	277	1,620
3,6-Dicarboxyphosphafluorinic acid	249	70,000
	336	626
Bis(*p*-carboxyphenyl)phosphinic acid	246.5	27,900
	277	3,290
2,7-Dinitroarsafluorinic acid[d]	255.5	10,600
	325	21,200
2,7-Dinitrophosphafluorinic acid	261.5	11,600
	326	21,400
	335	20,900
2,7-Diaminophosphafluorinic acid	223.5	30,800
	229.5	35,200
	236.5	33,700
	276.5	11,800
	288	10,200
Bis(*m*-aminophenyl)phosphinic acid[e]	221	14,600
	260[c]	784
	264	885
	271	784
Diphenylphosphinic acid[f]	224	13,100
	259.5	956
	265	1,200
	271.5	917
Phosphanilic acid[e]	257	528
	262.5	544
	268.5	431
Phenylphosphonic acid[f]	258	391
	263.5	524
	270	432

[a] Spectra of amino-substituted compounds were determined in 0.1*N* hydrochloric acid solution. Ethyl alcohol (95%) was used as the solvent for all other compounds. [b] The spectrum of this compound is described in ref. 4, but the low intensity peak at 320 mμ was not previously noted. [c] Shoulder. [d] Prepared as described in ref. 10. [e] Prepared as described by G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, 74, 753 (1952). [f] Taken from H. H. Jaffé and L. D. Freedman, *J. Am. Chem. Soc.*, 74, 1069 (1952).

the phosphafluorinic acid derivative is similar to, but more intense than, its non-heterocyclic analog, bis(*p*-carboxyphenyl)phosphinic acid.

Nitration of phosphafluorinic acid to give a dinitro derivative was accomplished by a procedure very similar to that described by Feitelson and Petrow[10] for the dinitration of arsafluorinic acid. The structure of the dinitro derivative of phosphafluorinic acid was not established unequivocally, but it almost certainly is the 2,7-derivative by analogy with the results obtained in the nitration of arsafluorinic acid. It is seen in Table I that the spectrum of the dinitrophosphafluorinic acid is quite like the spectrum of 2,7-dinitroarsafluorinic acid. Reduction of the dinitrophosphafluorinic acid with Raney nickel and hydrogen yielded diaminophosphafluorinic acid; by contrast, the reduction of 2,7-dinitroarsafluorinic acid with Raney nickel yields benzidine.[10] The spectrum of diaminophosphafluorinic acid in 0.1*N* hydrochloric acid solution resembles the spectrum of phosphafluorinic acid itself. It has often been observed that the ammonio (NH_3^+) group has little effect on ultraviolet absorption.[11] As shown in Table I, the spectrum of bis(*m*-aminophenyl)phosphinic acid in acid solution is remarkably similar to the spectrum of diphenylphosphinic acid; and the spectrum of phosphanilic (*p*-aminophenylphosphonic) acid in acid solution is almost identical with the spectrum of phenylphosphonic acid.

An attempt was made to prepare 2,7-diaminophosphafluorinic acid by the Busch reaction on bis(2-bromo-5-aminophenyl)phosphinic acid. The theoretical amount of bromine was cleaved from the ring, and the spectrum of the reaction mixture indicated that the phosphafluorinic acid ring system had been formed. However, the crude product contained only 5.79% nitrogen (theoretical nitrogen is 11.38%); and the properties of this material did not become constant even after repeated reprecipitations from alkaline solution. We have been unable to isolate any pure compound from the reaction mixture.

Hydrogenation of phosphafluorinic acid over rhodium-on-alumina[12] yielded a phosphinic acid which exhibited no ultraviolet absorption. This compound was shown not to be dicyclohexylphosphinic acid[12] and is therefore, presumably, a dodecahydrophosphafluorinic acid. No attempt was made to investigate the stereochemistry of this compound.

EXPERIMENTAL[13]

3,6-Dimethylphosphafluorinic acid. Bis(2-bromo-4-tolyl)-phosphinic acid[6] (10.1 g.) was treated with palladium-on-

(10) B. N. Feitelson and V. Petrow, *J. Chem. Soc.*, 2279 (1951).

(11) See, for example, L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947).

(12) L. D. Freedman, G. O. Doak, and E. L. Petit, *J. Am. Chem. Soc.*, 77, 4262 (1955).

(13) Melting points under 300° were taken as previously described; *cf.* ref. 15a. M.p.'s over 300° were determined in capillary tubes on a copper block and are uncorrected. Phosphorus was determined by the method of B. C. Stanley. S. H. Vannier, L. D. Freedman, and G. O. Doak, *Anal. Chem.*, 27, 474 (1955).

calcium carbonate and methanolic potassium hydroxide by the same procedure previously used for converting bis(*o*-bromophenyl)phosphinic acid to phosphafluorinic acid.[4] The solid obtained upon acidification of the reaction mixture was dissolved in 65 ml. of hot 4% sodium hydroxide soluton. When the solution was cooled, the sodium salt of 3,6-dimethylphosphafluorinic acid crystallized. This salt was removed by filtration and washed with 20 ml. of 5% sodium hydroxide solution. In order to obtain the free phosphinic acid, the sodium salt was dissolved in 75 ml. of hot water, and the solution was filtered from a trace of undissolved material; acidification of the filtrate yielded 3.5 g., 57%, of pure 3,6-dimethylphosphafluorinic acid, m.p. 303–305°. Recrystallization of the acid from 95% ethanol did not appreciably change the analysis, m.p., or ultraviolet absorption.

Anal. Calcd. for $C_{14}H_{13}O_2P$: P, 12.68; neut. equiv., 244.2. Found: P, 12.61; neut. equiv., 240.4.

When the alkaline filtrate from the sodium salt of 3,6-dimethylphosphafluorinic acid was acidified to Congo red, a sticky precipitate was obtained which was dried and recrystallized from ether to yield 0.7 g. of di-*p*-tolylphosphinic acid, m.p. 133.5–135.5° (lit.[14] 131–132°). The identity of this material was confirmed by analysis, by ultraviolet absorption, and by mixed m.p. with an authentic sample of di-*p*-tolylphosphinic acid, the synthesis of which is described below.

p-Tolylphosphonic acid and di-p-tolylphosphinic acid. Dry *p*-toluenediazonium fluoborate was suspended in isopropyl acetate and treated with phosphorus tribromide and cuprous bromide; these conditions have been shown to increase the yield of phosphinic acid.[15] After the reaction was steam distilled, the residual liquid in the distilling flask was transferred to a beaker and cooled. The phosphinic acid, which separated out of the solution, was removed by filtration and dissolved in sodium carbonate solution. The alkaline solution was treated with charcoal, filtered, and the acid reprecipitated by the addition of hydrochloric acid. After recrystallization from ether, the yield of di-*p*-tolylphosphinic acid was 11%; m.p. 132–135°.

The usual treatment of the original filtrate from the crude phosphinic acid resulted in the isolation of *p*-tolylphosphonic acid, which was purified by procedure A as previously described.[15a] The yield was 20%; m.p. 192–194.5° (lit.[15a] 198–199°).

2-Chloro-5-tolylphosphonic acid and bis(2-chloro-5-tolyl)-phosphinic acid. 2-Chloro-5-methylaniline (Eastman P7406) was purified by distillation and then converted to the corresponding diazonium fluoborate by the method designated by Roe as II A.[16] The dried diazonium salt was suspended in isopropyl acetate and treated with phosphorus trichloride and cuprous bromide.[15] After the steam distillation, the residual liquid in the distilling flask was filtered hot. The crude phosphinic acid, which remained on the filter paper, was washed several times with hot water and then purified by reprecipitation from 2% sodium hydroxide solution and subsequent recrystallization from aqueous alcohol. The yield of pure bis(2-chloro-5-tolyl)phosphinic acid was 9%; m.p. 235–237.5°.

Anal. Calcd. for $C_{14}H_{13}Cl_2O_2P$: Cl, 22.50; P, 9.83; neut. equiv., 315.1. Found: Cl, 22.37; P, 9.50; neut. equiv., 308.7.

The original filtrate from the crude phosphinic acid was evaporated on the steam bath to incipient crystallization, cooled, and filtered. The resulting crude phosphonic acid was dissolved in an excess of 5% sodium hydroxide solution, and, after the solution was treated with charcoal, was reprecipitated by the addition of hydrochloric acid. The precipitate obtained was recrystallized from 6*N* hydrochloric acid. The yield was 36%; m.p. 185–190°.

Anal. Calcd. for $C_7H_8ClO_3P \cdot H_2O$: P, 13.79, neut. equiv., 112.3; H_2O, 8.02. Found: P, 13.80, neut. equiv., 112.5; wt. loss at 120°, 7.80.

When phosphorus tribromide was used in place of phosphorus trichloride in the above reaction, the yield of phosphinic acid was increased to 14% while the yield of phosphonic acid decreased to 23%.

2,7-Dimethylphosphafluorinic acid. Bis(2-chloro-5-tolyl)-phosphinic acid (7.90 g.) was dissolved in a mixture of 80 ml. of 3.0*N* aqueous potassium hydroxide and 90 ml. of methanol and heated under reflux with 6.0 g. of 2% palladium-on-calcium carbonate for 6 days. The mixture of phosphinic acids was isolated from the reaction mixture by the procedure previously described[4] and then dissolved in 35 ml. of hot 5% sodium hydroxide solution. When this solution was cooled, the sodium salt of 2,7-dimethylphosphafluorinic acid crystallized. The salt was removed by filtration and washed with 10 ml. of 5% sodium hydroxide solution. A second crop of the sodium salt was obtained by evaporating the combined filtrate and washings to 25 ml., cooling to room temperature, and washing the resulting crystals with 10 ml. of 5% sodium hydroxide solution. Both crops of sodium salt were combined and converted to the free phosphinic acid by the same procedure used for the 3,6-isomer. The yield was 0.34 g., 5.5%, m.p. 320–323°. Recrystallization of the acid from 95% ethanol changed the m.p. to 325–328° but did not affect the analysis or ultraviolet absorption.

Anal. Calcd. for $C_{14}H_{13}O_2P$: P, 12.68; neut. equiv., 244.2. Found: P, 12.53; neut. equiv., 241.2.

When the alkaline filtrate from the second crop of sodium 2,7-dimethylphosphafluorinate was acidified to Congo red, a sticky precipitate was obtained which was recrystallized from aqueous acetone to yield 1.9 g. of slightly impure di-*m*-tolyl-phosphinic acid, m.p. 165–167.5°. The ultraviolet absorption of this material was identical with that of authentic di-*m*-tolylphosphinic acid, the synthesis of which is described below.

m-Tolylphosphonic acid and di-m-tolylphosphinic acid. Dry *m*-toluenediazonium fluoborate[17] was suspended in isopropyl acetate and treated with phosphorus tribromide and cuprous bromide in the usual manner.[15] The phosphinic acid was isolated from the reaction mixture by the procedure described above for the *p*-isomer and was then recrystallized from aqueous acetone. The yield of pure di-*m*-tolylphosphinic acid was 8.5%, m.p. 173.5–175° (lit.[17a] 166–168°).

Anal. Calcd. for $C_{14}H_{15}O_2P$: P, 12.58; neut. equiv., 246.2. Found: P, 12.25; neut. equiv., 242.8.

The original filtrate from the crude phosphonic acid was extracted with ether (three 25-ml. portions for preparations on a 0.1-mole scale), the ethereal extracts were combined, and the ether was removed by evaporation. The oily residue was dissolved in an excess of 10% sodium carbonate solution and treated with charcoal. On acidifying the decolorized solution, *m*-tolylphosphonic acid separated as an oil. The mixture was then extracted with ether (three 25-ml. portions for preparations on a 0.1-mole scale); evaporation of the combined ethereal extracts yielded a white solid which was recrystallized from a mixture of benzene and chloroform. The yield of pure *m*-tolylphosphonic acid was 16%; m.p. 121–122.5° (lit.[17] 121°).

3,6-Dicarboxyphosphafluorinic acid. 3,6-Dimethylphosphafluorinic acid (2.20 g.), dissolved in a mixture of 15 ml. of pyridine and 15 ml. of water, was treated with 25 g. of potassium permanganate according to the procedure of Morgan and Herr.[3] After steam distillation to remove pyridine, the

(14) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **71**, 369 (1949).

(15) (a) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951); (b) **75**, 683 (1953).

(16) A. Roe in *Org. Reactions*, V, 204 (1949).

(17) E. C. Ashby and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 4903 (1953).

(17a) J. M. Denham and R. K. Ingham, *J. Org. Chem.* **23**, 1298 (1958). This paper appeared subsequent to the completion of our work.

reaction mixture was filtered, decolorized with charcoal, and then added slowly, with good stirring, to 100 ml. of 10% hydrochloric acid. The precipitated phosphinic acid was removed by filtration and recrystallized from aqueous acetone. The yield was 1.21 g. (44%); m.p. >300°.

Anal. Calcd. for $C_{14}H_9O_5P$: P, 10.18; neut. equiv., 101.4. Found: P, 9.97; neut. equiv., 101.6.

Bis(p-carboxyphenyl)phosphinic acid. Di-*p*-tolylphosphinic acid (2.46 g.) was oxidized with 25 g. of potassium permanganate by the procedure described above. The yield of bis(*p*-carboxyphenyl)phosphinic acid, after recrystallization from aqueous acetone, was 2.39 g. (78%) m.p. > 300°.

Anal. Calcd. for $C_{14}H_{11}O_6P$: P, 10.12, neut. equiv., 102.1. Found: P, 10.11, neut. equiv., 102.1.

2,7-Dinitrophosphafluorinic acid. Phosphafluorinic acid was nitrated by the procedure used for the arsenic analog.[10] The yield of dinitrophosphafluorinic acid was 93%, decomposition point above 260°. The sample used for analysis and for determination of the ultraviolet absorption spectrum was recrystallized from a mixture of 95% ethanol and acetone.

Anal. Calcd. for $C_{12}H_7N_2O_6P$: N, 9.15, P, 10.12. Found: N, 9.05, P, 9.95.

2,7-Diaminophosphafluorinic acid. 2,7-Dinitrophosphafluorinic acid (1.90 g.) was dissolved in a mixture of 150 ml. of 0.2% sodium hydroxide solution and 100 ml. of 95% ethanol, and the *p*H adjusted to 6.9 with acetic acid. Reduction was effected with Raney nickel and hydrogen at 30 lb. pressure. After the catalyst was removed, the solution was acidified to *p*H 4.0 with acetic acid whereupon 2,7-diaminophosphafluorinic acid separated from solution. The yield was 0.96 g. (63%), m.p. > 300°.

Anal. Calcd. for $C_{12}H_{11}N_2O_2P$: N, 11.38, P, 12.58. Found: N, 11.32; P, 12.42.

Bis(2-bromo-5-aminophenyl)phosphinic acid. Bis(2-bromo-5-nitrophenyl)phosphinic acid[18] (4.66 g.), dissolved in a mixture of 150 ml. of 0.3% sodium hydroxide and 75 ml. of 95% ethanol, was reduced by the method described above. The *p*H of the solution before reduction should be 6.9. Some bromine was split from the ring at this *p*H; however, the amount of splitting increased at higher *p*H's. The reduction product was purified by reprecipitation from alkaline solution. The yield was 2.16 g. (53%), decomposition point about 300°.

Anal. Calcd. for $C_{12}H_{11}Br_2N_2O_2P$: Br, 39.36; N, 6.90; P, 7.63. Found: Br, 39.25; N, 6.90; P, 7.53.

Dodecahydrophosphafluorinic acid. Phosphafluorinic acid (1.0 g.) was dissolved in 125 ml. of absolute ethanol and shaken for 4 hr. at 50° with 3.0 g. of rhodium-on-alumina and hydrogen at an initial gage pressure of 50 lb. After the catalyst was removed, the filtrate was evaporated to dryness on a boiling water bath. The residue, which consisted of a colorless oil, was dissolved in warm aqueous alcohol. On cooling, 0.16 g. (15%) of white crystals, m.p. 153–154.5°, separated from solution. Mixed m.p. with dicyclohexylphosphinic acid was 78–82°.

Anal. Calcd. for $C_{12}H_{21}O_2P$: C, 63.14; H, 9.27; P, 13.57. Found: C, 62.87; H, 9.22; P, 13.36.

The mother liquors gave an oily material, which presumably consists of a mixture of stereoisomers. We have been unable to obtain any additional crystalline material from this mixture.

CHAPEL HILL, N. C.

(18) L. D. Freedman, H. Tauber, G. O. Doak, and H. J. Magnuson, *J. Am. Chem. Soc.*, **75**, 1379 (1953).

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

Pyrolysis of Cyclic Sulfites of 1,3-Glycols

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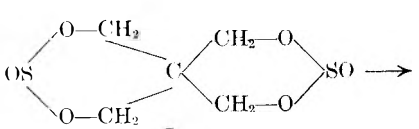
The pyrolysis of the cyclic sulfites of pentaerythritol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, and 2-hydroxymethyl-2-methyl-1,3-propanediol was studied at various temperatures. The disulfite of pentaerythritol gave 2,4,8-trioxa-3-thiaspiro[5,3]nonane-3-oxide. The sulfite of 2,2-dimethyl-1,3-propanediol was stable at 500°. The corresponding derivatives of 2-hydroxymethyl-2-methyl-1,3-propanediol and 1,3-propanediol gave no oxetanes.

The pyrolysis of cyclic sulfites of glycols has been of interest since the first report[2] that 2,3-butylene oxide was formed from the sulfite of 2,3-butylene glycol. Extension of the reaction to other 1,2-glycols, however, has been found to yield only aldehydes or ketones.[3]

In the 1,3-glycol series the pyrolysis has been carried out only for the cyclic sulfite of 2,2-bis-(chloromethyl)-1,3-propanediol.[4] No oxetane was formed but decomposition occurred to 3-chloro-2-chloromethyl-1-propene, sulfur dioxide, and formaldehyde.

In the present work the pyrolysis of the cyclic sulfites of pentaerythritol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, and 2-hydroxymethyl-2-methyl-1,3-propanediol was studied under various conditions in an attempt to prepare oxetanes. The reaction was successful only for the disulfite of pentaerythritol (I); 2,4,8-trioxa-3-thiaspiro-[5,3]-nonane-3-oxide (II) was formed.



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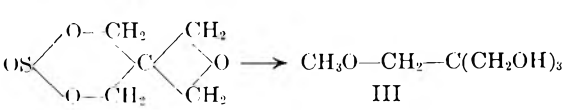

II III

(1) Abstracted in part from the Ph.D. Thesis of J. T. Loft, August 1959.

(2) L. Denivelle, *Compt. rend.*, **208**, 1024 (1939).

(3) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1211 (1954).

(4) A. S. Matlack and D. S. Breslow, *J. Org. Chem.*, **22**, 1723 (1957).

The structure of this compound (II) was demonstrated by its conversion with methanol and sulfuric acid to pentaerythritol monomethyl ether (III). The pyrolysis was followed by measuring the evolution of sulfur dioxide and gave the best yield when only about 25% of the theoretical amount of sulfur dioxide was evolved. Heating beyond this point produced mainly polymeric materials. No dioxaspiroheptane was produced.

The sulfite of 2,2-dimethyl-1,3-propanediol was stable up to temperatures of 500°. The corresponding derivative of 2-hydroxymethyl-2-methyl-1,3-propanediol was stable at 450°. At 600–625° a small amount of a compound analyzing approximately for methallyl alcohol was obtained but the amount was too small to investigate further. No attempt was made to identify the formaldehyde which was probably also formed in this reaction. This behavior is markedly different from that reported for the cyclic carbonate[5] in which 3-hydroxymethyl-3-methyloxetane was produced by heating at 180–200°.

Pyrolysis of the sulfite of 1,3-propanediol at 230° gave sulfur dioxide and tars and no oxetane. The same reaction at 300° using a tube packed with glass wool gave a small amount of a polymer derived from formaldehyde. No attempt was made to collect the ethylene which was probably formed in this decomposition.

The course of the decomposition for the sulfites of 1,3-propanediol and 2-hydroxymethyl-2-methyl-1,3-propanediol follows that observed for the sulfite of 2,2-bis(chloromethyl)-1,3-propanediol[4] and probably goes by the mechanism suggested for the latter compound. The possibility that an oxetane is formed as an intermediate cannot be completely excluded since trimethylene oxide is reported to decompose at 420–460° in a similar way into formaldehyde and ethylene.[6]

EXPERIMENTAL[7]

Pyrolysis of pentaerythrityl disulfite(2,4,8,10-tetraoxa-3,9-dithia[5,5]undecane-3,9-dioxide (I). Pentaerythrityl disulfite (I) (45.6 g.) was heated at 260–270° until 2 l. of sulfur dioxide was evolved. The resulting liquid was cooled, triturated with methanol (50 ml.) in order to precipitate the unchanged disulfite (22 g.). Filtration of the solid was followed by evaporation of the methanol. The oil obtained, when crystallized from methylene chloride and petroleum ether (60–70°), gave more of the disulfite (3.25 g.). Removal of the solvent followed by extraction with cyclohexane gave 2,4,8-trioxa-3-thiaspiro[5,3]nonane-3-oxide (II) (8.0 g.) melting at 65–66°. Crystallization from cyclohexane followed by several sublimations at 60° (1 mm.) gave a sample melting at 74–75°.

Anal. Calcd. for $C_5H_8O_4S$: C, 36.61; H, 4.87. Found: C, 36.23; H, 4.75.

Continuing the heating beyond this point usually gave polymeric products from which only a small amount of 2,4,8-trioxa-3-thiaspiro[5,3]nonane-3-oxide (II) was isolated. No 2,6-dioxaspiro[3,3]heptane was produced in the pyrolysis.

Reaction of 2,4,8-trioxa-3-thiaspiro[5,3]nonane-3-oxide (II) *with methanol and sulfuric acid.* 2,4,8-Trioxa-3-thiaspiro-[5,3]nonane-3-oxide (II) (4.1 g.) in methanol (50 ml.) was treated with 3 drops of concentrated sulfuric acid and allowed to stand for 24 hr. at room temperature. The solution was refluxed for 2 hr. and then neutralized with solid sodium carbonate. Removal of the methanol gave an oil which upon crystallization from a mixture of chloroform and ethyl acetate gave pentaerythritol monomethyl ether (III) (1.35 g.) melting at 63–67°. One recrystallization from chloroform gave a sample melting at 70–73° which did not depress the melting point of an authentic sample.[9] The infrared spectra of the two samples were identical. A mixture with 2,4,8-trioxa-3-thiaspiro[5,3]nonane-3-oxide (II) melted at 58–65°.

Pyrolysis of trimethylene sulfite (1,3,2-dioxathiane-2-oxide). Pyrolysis of trimethylene sulfite[10] at 230° gave sulfur dioxide and tar but no trimethylene oxide. The same reaction using a glass tube at 300° packed with glass wool and 50 g. of the sulfite gave in addition to the tars a solid (4 g.) melting at 155°. The product was insoluble in acetone, dimethylformamide, and acetonitrile and melted after this treatment at 157–158°.

Anal. Calcd. for $(CH_2O)_x$: C, 40.00; H, 6.66. Found: C, 40.30; H, 6.66.

The infrared spectra for this compound resembled that of paraformaldehyde.

Pyrolysis of 5,5-dimethyl-1,3,2-dioxanthiane-2-oxide. This sulfite[11] was stable at 230° and was practically completely recovered unchanged when dropped on barium oxide at 350° and aluminum oxide at 400–500°.

5-Methyl-5-hydroxymethyl-1,3,2-dioxathiane-2-oxide. A mixture of 2-methyl-2-hydroxymethyl-1,3-propanediol (240 g.) suspended in 200 ml. of methylene chloride was treated slowly with thionyl chloride (236 g.) with stirring at 0–10°. After the addition the solution was allowed to stand at 25° for 48 hr. Removal of the solvent gave a liquid which boiled at 118° (3 mm.); yield 296 g.; n_D^{24} 1.4786; d_4^{25} 1.498.

Anal. Calcd. for $C_5H_{10}O_4S$: C, 36.13; H, 6.04. Found: C, 35.77; H, 5.94.

Passing this sulfite (40 g.) at 450° using nitrogen as a diluent through a glass tube packed with glass helices gave only unchanged sulfite. Using 600–625° a small amount of liquid (4 g.) boiling at 118° at atmospheric pressure and analyzing for approximately methallyl alcohol was formed. The literature[12] reports a value of 114°.

Anal. Calcd. for C_4H_8O: C, 66.7; H, 11.1. Found: C, 65.2; H, 11.24.

This fraction was not studied further.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Preparation of Some Sulfanilamide Derivatives of s-Triazine[1]

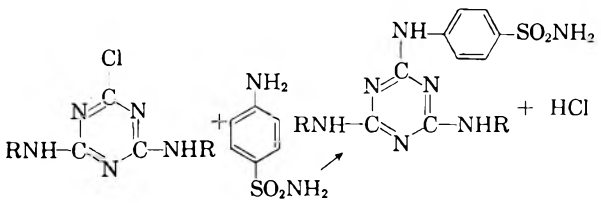
G. F. D'ALELIO AND HARRY J. WHITE, Jr.[2]

Received September 22, 1958

A general procedure for the synthesis of N^4-sulfanilamide derivatives of *s*-triazine from chloro-*s*-triazines and sulfanilamide is described. A series of new compounds was prepared using this method.

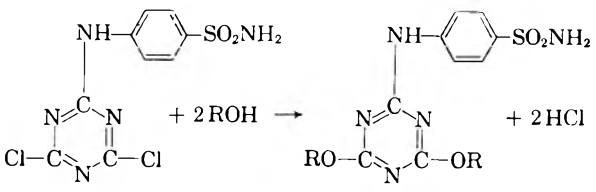
The reaction of cyanuric chloride with aliphatic[3] and aromatic[4] amines is well known. Thurston[5] used this method to prepare a number of amino-chloro-*s*-triazines. Kaiser[6] prepared a variety of substituted melamines by the reaction of chloro-*s*-triazines with amines. However, little attention has been given to the reaction of sulfanilamide with cyanuric chloride, and only two of these derivatives have been reported.[7] Since some of these sulfanilamide derivatives may have useful drug properties, it was considered worthwhile to prepare an assortment of these compounds for broad screening.[8]

It has been found in this work that the reaction of sulfanilamide with substituted chloro-*s*-triazines constitutes a good general method for the preparation of substituted (4-sulfamoylanilino)-*s*-triazines. Water is a convenient solvent for this reaction since sulfanilamide is soluble in hot water and the chloro-*s*-triazines are at least partially soluble in this solvent. There was no evidence of hydrolysis of the chloro-*s*-triazines in the aqueous medium. Since the (4-sulfamoylanilino)-*s*-triazines are insoluble in water, the products are isolated in good yields. Sodium hydroxide is the most efficient hydrogen chloride acceptor for these reactions.



Cyanuric chloride reacts with one mole of sulfanilamide at 0–5° to form 2,4-dichloro-6-(4-sulfamoylanilino)-*s*-triazine. The product is isolated in good yield from acetone solution.

2,4-Dichloro-6-(4-sulfamoylanilino)-*s*-triazine reacts with alcohols and amines to form 2,4-dialkoxy- and 2,4-diamino-6-(4-sulfamoylanilino)-*s*-triazines. The reaction with amines was found to run smoothly in water at 100°. Aqueous sodium hydroxide is the most suitable hydrogen chloride acceptor, although excess amine may be used. The reaction with alcohols was run at reflux temperature in the presence of sodium hydroxide using excess alcohol as the solvent.



The two chlorine atoms of 2,4-dichloro-6-(4-sulfamoylanilino)-*s*-triazine are readily hydrolyzed to yield 2,4-dihydroxy-6-(4-sulfamoylanilino)-*s*-triazine. The most satisfactory procedure is to reflux the chloro-*s*-triazine in glacial acetic acid. Since the product is insoluble in the reaction medium, a quantitative yield is obtained. The hydrolysis may also be carried out using aqueous sodium hydroxide, but this procedure was not preferred since the yield was lower.

Sulfanilamide replaces the three chlorine atoms of cyanuric chloride at 100°. The reaction is carried out in water using sodium hydroxide as the hydrogen chloride acceptor.

The sulfanilamide derivatives of *s*-triazine prepared in this work are described in Table I and the analytical data is given in Table II.[9]

EXPERIMENTAL

2,4-Dichloro-6-methoxy-s-triazine and 2-chloro-4,6-dimethoxy-6-triazine were prepared according to the method of Dudley.[10] 2-Chloro-4,6-diamino-*s*-triazine and 2,4-dichloro-6-(2-hydroxyethylamino)-*s*-triazine were prepared using the method described by Thurston.[5]

2,4-Dichloro-6-(4-sulfamoylanilino)-s-triazine(I). A solution of 17.2 g. (0.1 mole) of sulfanilamide in 100 ml. of ace-

(1) Abstracted from a portion of the Ph.D. dissertation of Harry J. White, Jr., University of Notre Dame, 1957.

(2) Miles Laboratories Fellow 1955–57.

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(9) Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. and Midwest Microlab, Indianapolis, Ind.

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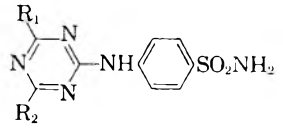
TABLE I

4-SULFAMOYLANILINO-*s*-TRIAZINES,



Compound	R_1	R_2	Yield, %	M.P., °C.
I	Cl	Cl	94	Infusible
II	NH_2	NH_2	89	308–309 (dec.)
III	OC_2H_5	OC_2H_5	71[a]	210–211
IV	OC_6H_5	OC_6H_5	93[a]	207–208
V	OCH_3	OCH_3	74	214–218 (dec.)
VI	NHC_6H_5	NHC_6H_5	57[a]	216–217
VII	*p*-$NHC_6H_4SO_2Na$	*p*-$NHC_6H_4SO_3Na$	56[a]	Infusible
VIII	$NHCH_2CO_2Na$	$NHCH_2CO_2Na$	68[a]	Infusible
IX	OH	OH	99[a]	295–296 (dec.)
X	*p*-$NHC_6H_4SO_2NH_2$	OCH_3	93	307 (dec.)
XI	*p*-$NHC_6H_4SO_2NH_2$	$NHCH_2CH_2OH$	90	297–298 (dec.)
XII	*p*-$NHC_6H_4SO_2NH_2$	*p*-$NHC_6H_4SO_2NH_2$	92	Infusible

[a] Prepared from I.

TABLE II

ANALYTICAL DATA

Compound	Formula	N Calculated	S Calculated	N Found	S Found
I	$C_9H_7Cl_2N_5O_2S$[a]		10.00		10.24
II	$C_9H_{11}N_7O_2S$		11.36		11.12
III	$C_{13}H_{17}N_5O_4S$	20.64	9.44	20.37	9.22
IV	$C_{21}H_{17}N_5O_4S$	16.08	7.36	15.82	7.14
V	$C_{11}H_{13}N_5O_4S$	22.43	10.28	22.11	10.62
VI	$C_{21}H_{17}N_7O_2S$	22.61	7.38	22.22	7.02
VII	$C_{21}H_{17}N_7O_8S_3Na_2.4H_2O$[b]				
VIII	$C_{13}H_{13}N_7O_6SNa_2.2H_2O$[c]				
IX	$C_9H_9N_5O_4S.2H_2O$	21.94	10.03	21.92	9.66
X	$C_{16}H_{17}N_7O_5S_2$	21.74	14.10	21.65	13.96
XI	$C_{17}H_{20}N_8O_5S_2$	23.36	13.32	23.14	12.87
XII	$C_{21}H_{21}N_9O_6S_3$	21.30	16.51	20.96	16.48

[a] *Anal.* Calcd.: Cl, 22.18. Found: Cl, 21.70. [b] *Anal.* Calcd: C, 35.55; H, 3.53. Found: C, 35.12; H, 3.90. [c] *Anal.* Calcd: C, 32.68; H, 3.55. Found: C, 32.44; H, 3.10.

tone was dropped into a solution of 18.5 g. (0.1 mole) of cyanuric chloride in 100 ml. of acetone. The temperature was maintained at 0–5°. The mixture was stirred for 0.5 hr. and then a solution of 4.0 g. (0.1 mole) of sodium hydroxide in 60 ml. of water was added dropwise. Stirring was continued for an additional 0.5 hr. Ice water (200 ml.) was added and the solid was filtered. The product was washed with ice water until free of chloride ion. The yield was 30 g. (94%) of an infusible white solid.

The product was purified by dissolving in hot acetone and precipitating with ice water.

Reaction of chloro-s-triazines with sulfanilamide. One mole of the chloro-s-triazine was added to a solution of sulfanilamide (1 mole for each chlorine atom to be replaced) in hot water. The mixture was heated to reflux and a stoichiometric amount of aqueous sodium hydroxide was dropped in over a period of 1 hr. Refluxing was continued for 2–3 hr. The mixture was cooled and the product was filtered and washed with water. The products were recrystallized from 50% aqueous acetone or 50% aqueous dioxane.

Reaction of I with amines. One mole of I was added to a solution or suspension of 2 moles of amine in water. The mixture was heated to reflux and 2 moles of aqueous sodium hydroxide was slowly added. Refluxing was continued for 2–4 hr. The insoluble products were easily isolated by filtration. In the case of sodium salts, the products were isolated by precipitation with ethanol.

Reaction of I with alcohols. One mole of I was added to a solution or suspension of 2 moles of sodium hydroxide in the appropriate alcohol. The mixture was refluxed for 4–5 hr. The products were isolated by precipitation with water.

2,4,6-Tris-(4-sulfamoylanilino)-s-triazine. Cyanuric chloride (9.5 g., 0.05 mole) was added to 29.3 g. (0.17 mole) of sulfanilamide in 100 ml. of water. The mixture was heated to reflux and a solution of 6.0 g. (0.15 mole) of sodium hydroxide in 50 ml. of water was added. Refluxing was continued for 10 hr. The mixture was cooled and the solid was filtered off and washed with water. Yield was 27 g. (92%). The infusible product was recrystallized from 50% aqueous acetone.

Acknowledgment. The authors wish to express their sincere thanks to Miles Laboratories, Inc., Elkhart, Ind., whose financial aid made this work possible.

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[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

2-Alkoxy-2-imidazolines and Related Compounds[1]

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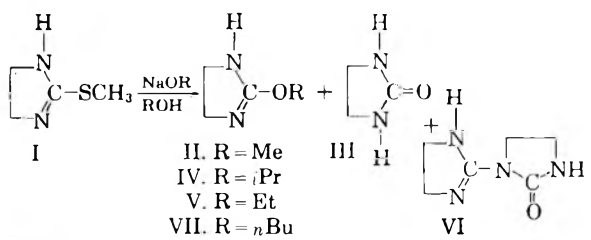
Received October 24, 1958

The preparation of several of 2-alkoxy-2-imidazolines by treating 2-methylmercapto-2-imidazoline with strong bases in the appropriate alcohol is described. A side-product, which was isolated in several cases, was shown to be 1-(2′-imidazolin-2′-yl)-2-imidazolidinone (VI). Further proof for the correct structure of Jaffe's base (IX, the thio analog of VI) is presented. Attempts to improve the yield of side-product VI or obtain it by an alternate method were unsuccessful.

The reaction of amines with 2-methylmercapto-2-imidazoline (I) hydroiodide gives 2-substituted amino-2-imidazolines.[2] In a study of this reaction using secondary amines and mercuric oxide in methanol solvent,[3] we isolated 2-methoxy-2-imidazoline (II) as the fumarate in very low yield. Since 2-alkoxy-2-imidazolines had not been previously reported,[4] we decided to investigate their preparation and properties. Although many examples are known of the replacement of the methylmercapto group in heterocycles by amino, substituted amino, and hydroxyl groups, we are unaware of any reports of replacement by alkoxyl.

The use of triethylamine with mercuric oxide, I-hydriodide, and methanol did not appreciably increase the yield of II despite the fact that the tertiary amine could not form a 2-amino-2-imidazoline. We then turned our attention to stronger bases. When heated under reflux with sodium methoxide in methanol, 2-methylmercapto-2-imidazoline slowly liberated methyl mercaptan. After 18 hours, mercaptan evolution had practically ceased. Work-up of the reaction gave a 75 to 80% recovery of organic material. This mixture of products was conveniently separated by differential ether solubility; the ether-insoluble part proved to be ethyleneurea (III) which was obtained in 5 to 20% yield. The ether-soluble product was crude 2-methoxy-2-imidazoline which was present in 50 to 70% yield. Conversion to a salt such as the fumarate or chromatography on alumina of the free base provided pure products in 40–50% yield.



As the free base, 2-methoxy-2-imidazoline proved to be a rather low-melting, fairly volatile crystalline solid. It tended to become oily on standing, which may have been due to the somewhat hygroscopic nature of II. When pressed into potassium bromide pellets for a study of the infrared spectrum, medium intensity bands appeared at 5.8 and 5.9 μ that were absent in solution or Nujol mull spectra and suggested that chemical changes occurred in the pelleting process. However, it was recovered unchanged after standing overnight in normal sodium hydroxide solution as well as 24 hours at 40° in normal hydrochloric acid.

A number of unsuccessful attempts were made to obtain a reasonable yield of II by other routes. Methods known to *O*-methylate caprolactam[5] and urea[6] when applied to ethyleneurea yielded only the *N*-methylated product (1-methyl-2-imidazolinone). Since the conversion of I to II by alkoxides bears some formal resemblance to ester interchange,[7] 2-methylmercapto-2-imidazoline was subjected to acid-catalyzed interchange conditions. With hydrogen chloride in dry methanol, I was recovered unchanged. When I was heated in methanol with a catalytic amount of *p*-toluenesulfonic acid hydrate, only ethyleneurea could be isolated. The appearance of a report by Behringer and Meier[8] describing several methods for converting cyclic thioureas and ureas to the corresponding methyl isoureas prompted our investigation of them in the five-membered ring case. We repeated Behringer and Meier's[8] attempted reaction of ethylenethiourea and mercuric oxide in methylene chloride–methanol in the hope of detecting a small amount of 2-methoxy-2-imidazoline but found only unchanged ethylenethiourea, confirming their result. However, heating ethyleneurea with methyl *p*-toluenesulfonate did give us about 1.5% of II, isolated and identified as the picrate. These results

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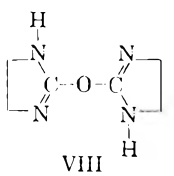
(8) H. Behringer and H. Meier, *Ann.*, **607**, 67 (1957).

made it apparent that the 2-alkoxy-2-imidazoline system is relatively difficult to form. We find its stability to acid and base somewhat surprising.

The behavior of 2-methylmercapto-2-imidazoline in several other alkanols with the sodium alkoxide was investigated. After 63 hours' heating of I in isopropanol with sodium isopropoxide, methyl mercaptan continued to evolve slowly. The reaction was worked up giving 66% of unchanged I and, after chromatography over alumina, 11% of 2-isopropoxy-2-imidazoline (IV). With sodium ethoxide in ethanol, about 45 hours under reflux was required to complete the reaction. In this case, 2-ethoxy-2-imidazoline (V) was obtained in crude yields of 30 to 85%. It was conveniently isolated as the fumarate which was obtained pure in yields up to 65%. In addition, this reaction gave up to 40% of a mixture from which up to 17% of a new base VI was isolated. The structure and formation of VI is discussed in greater detail below. When *N*-butyl alcohol was used, a 22-hour reflux period provided 47% of pure 2-*n*-butoxy-2-imidazoline (VII) and about 10% of product VI. With benzyl alcohol and sodium benzylate, 23 hours' heating at 100° completed the reaction. No 2-benzyloxy-2-imidazoline could be found in the mixture of products. Small amounts of ethyleneurea and compound VI were separated from this mixture.

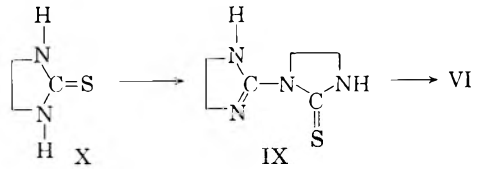
Microanalyses of compound VI and its normal fumarate showed the formula $C_6H_{10}N_4O$. Only two structures, VI and VIII, can be reasonably written for this formula. Since VI is a monoacidic base and VIII would have two basic nitrogens,



VIII

a potentiometric titration of compound VI which showed a single break in the curve (pK_a 6.0, neut. equiv. 160) allowed us to choose structure VI. This structure was supported by the infrared spectrum which showed an intense carbonyl absorption band at 5.82 μ. Although ethyleneurea itself shows its carbonyl absorption band at 6.0 μ, the proximity of the C=N function to the carbonyl group in VI would be expected to lead to a vibrational interaction between the two groups which would result in the observed lowering of the carbonyl absorption wave length.[9]

In seeking additional support for structure VI, we have prepared the known thioanalog IX [1 (2′-imidazolin-2′-yl)-2-imidazolidinethione; "Jaffé's base"] and converted it to VI by heating in aqueous ethanol with mercuric oxide. Since both



X IX

the original[10] and a subsequent[11] assignment of structure to Jaffé's base (IX) were in error,[12] we have provided additional evidence for the correctness of IX. Structure IX was first suggested by Lecher and Gubernator[13] by analogy to some of their results with *N*-alkylthioureas but without carrying out experimental work. Later Chase and Walker[14] prepared Jaffé's base, investigated its ultraviolet spectrum and concluded that Lecher and Gubernator were correct in assigning structure IX. Initially we prepared Jaffé's base by Johnson and Edens' method *via* ethylenethiourea disulfide hydroperiodide. Analysis of the base and its hydroiodide, potentiometric titration of the base and ultraviolet and infrared spectra of the base and its salts provided convincing evidence for assignment of the 1-(2′-imidazolin-2′-yl)-2-imidazolidinethione structure. These data together with the conversion of IX to VI mutually support both structures as written.

The reported conversion of 1,1,3-trimethyl-2-thiourea into 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea by reaction with mercuric oxide in benzene[13] prompted us to try the reaction with ethylenethiourea (X). With benzene as a solvent, we recovered only a trace of organic material. However, by heating ethylenethiourea with mercuric oxide in xylene, a 25% recovery of organic product was realized from which 9% of pure Jaffé's base IX was obtained by recrystallization.

An effort was made to determine the source of 1-(2′-imidazolin-2′-yl)-2-imidazolidinone (VI). Although many experiments designed to shed light on a logical pathway to VI were carried out, the results have been disappointing.

Particularly frustrating was the variability in the amount of this compound obtained from one run to the next. Variations in concentration of 2-methylmercapto-2-imidazoline or of the base, in the presence or absence of water, air, and peroxide, and in the methods of working up the reaction

(9) We have observed a 0.15 μ lowering of the carbonyl band in several 2-benzoxazolinones substituted on the nitrogen atom with a doubly bound carbon; see J. Sam, J. N. Plampin, and G. I. Poos, *J. Org. Chem.*, **23**, 1500 (1958).

(10) M. Jaffé and B. Kühn, *Ber.*, **27**, 1663 (1894).

(11) T. B. Johnson and C. O. Edens, *J. Am. Chem. Soc.*, **63**, 1058 (1941); T. B. Johnson and C. O. Edens, *J. Am. Chem. Soc.*, **64**, 2706 (1942).

(12) The second incorrect assignment persists in several authoritative books on heterocycles: (a) E. S. Schipper and A. R. Day in Elderfield, *Heterocyclic Compounds*, Vol. 5, John Wiley & Sons, Inc., New York, N. Y. (1957), p. 251. (b) K. Hofmann, *The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives (Part I)*, Interscience Publishers, Inc., New York, N. Y. (1953), p. 237.

(13) H. Z. Lecher and K. Gubernator, *J. Am. Chem. Soc.*, **75**, 1087 (1953).

(14) B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).

mixtures could not be correlated with variations in the yield of VI.

An attempt to react ethyleneurea (III) with 2-methylmercapto-2-imidazoline (I) in potassium *t*-butoxide/*t*-butyl alcohol led to the recovery of I and III. Equimolar quantities of I and III heated in methanolic sodium methoxide gave only II and III. Equal amounts of the S- and O-methyl compounds I and II were heated under reflux in toluene for many hours without reaction. When I and ethylenethiourea (X) with 0.5 mole of sodium hydroxide in ethanol were heated until methyl mercaptan evolution had ceased, an estimated 55% of X was recovered, Jaffé's base (IX) was formed in 45% yield (based on I and X), and 2-ethoxy-2-imidazoline (V) in 45% yield. No VI was found. The reaction of V and X under similar conditions gave a complex mixture but no VI could be detected by infrared. With sodium hydroxide in ethanol, III and X failed to react.

EXPERIMENTAL[15]

2-Methoxy-2-imidazoline (II). Freshly liberated 2-methylmercapto-2-imidazoline (I, 11.5 g., m.p. 102–107°, from 24.5 g., 0.1 mole, of the hydroiodide[16]) was added to a solution of 0.1 mole of sodium methoxide in 85 ml. of reagent grade methanol. The colorless solution was heated under reflux for 23 hr. Methyl mercaptan began to evolve after 1 hr. and appeared to have ceased after 20 hr. The solution was concentrated to dryness under vacuum, ice and water were added, and the resulting aqueous solution was continuously extracted for 6 hr. with methylene chloride. Evaporation of the extract provided 7.6 g. of a low-melting residue. Care had to be taken to prevent loss of product by volatilization. The residue was triturated with anhydrous ether and the insoluble part was separated by filtration; 0.46 g. (5.3%), m.p. 128–132°. After recrystallization from ethanol, this minor product melted at 132–134° and was shown to be ethyleneurea by mixed melting point and infrared spectrum (λ_{max} 3.03, 6.0, 6.61, 6.71 μ).

Evaporation of the ethereal filtrate provided 7.0 g. (70%) of crude crystalline product, m.p. 57–69°. Purification by recrystallization from heptane gave water-soluble, somewhat volatile, colorless crystals melting at 67–70°. When adsorbed on alumina, eluted with 1:4 ether–petroleum ether and then recrystallized from ether–petroleum ether, the resulting pure 2-methoxy-2-imidazoline showed m.p. 70–72°; λ_{max} 3.16, 6.11, 6.59 μ; pK_a 5.8 (neut. equiv. 101). Ultraviolet spectra in methanolic, acidic, and basic solution showed only end absorption. On standing in the atmosphere, 2-methoxyimidazoline became oily and liquefied. A single attempt at microanalysis gave low values for carbon, hydrogen, and nitrogen.

The *acid fumarate* from methanol had m.p. 136–139°; λ_{max} 3.23, 3.67, 5.90, 6.09, 6.33, 6.70 μ.

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 from methanol, 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.

2-Isopropoxy-2-imidazoline (IV). One-tenth mole quantities of sodium and then I were dissolved in 150 ml. of anhydrous 2-propanol and the solution heated under reflux. After 63 hr., methyl mercaptan continued to evolve slowly so the solution was concentrated *in vacuo*, the residue dissolved in ice water, and the resulting solution was extracted with ether and methylene chloride. From the combined extracts there was obtained 10 g. of an oily solid that appeared to be a mixture of I and IV by infrared.

Chromatography over 200 g. of alumina using ether–petroleum ether gave crude IV first followed by recovered I (7.3 g., 66%, m.p. 104–105°). Rechromatography of the product provided 1.3 g. (10%), m.p. 65–67°; λ_{max} 3.16, 6.16, 6.63, 6.74 μ.

Anal. Calcd. for $C_6H_{12}N_2O$: N, 21.87. Found: N, 21.20.

Picrate from methanol, m.p. 131–133°.

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.

2-Ethoxy-2-imidazoline (V) *and 1-(2′-imidazolin-2′-yl)-2-imidazolidinone* (VI). Absolute ethanol (75 ml.) containing sodium ethoxide (0.1 mole) and methylmercapto compound I (0.1 mole) was heated under reflux until the evolution of methyl mercaptan had ceased (47 hr.) and worked up as described for II. The total crude product amounted to 10.5 g. of oily solid which was separated into ether-insoluble [0.40 g. (5%), m.p. 145–160°] and ether-soluble [9.6 g. (84%), m.p. 30–40°] fractions. The amount of ether-insoluble material, which proved to be crude VI, varied in a series of experiments from a mere trace up to about 3 g. (40%).

Purification of the ether-soluble product by chromatography over alumina using ether–petroleum ether to elute the product gave pure 2-ethoxy-2-imidazoline, m.p. 50–51.5°; λ_{max} 3.23, 6.14, 6.57, 6.73 μ.

When the entire ether-soluble fraction was combined in methanol with an equimolar quantity of fumaric acid, the acid fumarate of V was precipitated with ether in 70% yield; m.p. 116–121°. Recrystallization from ethanol-ether gave the pure salt, m.p. 123–125°; λ_{max} 3.25, 3.70, 5.15–5.25, 5.88, 6.12, 6.20, 6.34, 6.68 μ.

Anal. Calcd. for $C_9H_{14}N_2O_5$: N, 12.17. Found: N, 12.16, 12.23.

Recrystallization of the ether-insoluble fraction from acetone-heptane and finally from benzene provided pure VI, m.p. 200–204° (dec.); λ_{max} 3.00, 3.18, 5.82, 6.22, 6.64, 6.70 μ, pK_a 6.0.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34; neut. equiv. 154. Found: C, 46.77; H, 6.51; N, 36.31; neut. equiv. 160.

The normal *fumarate* of VI was recrystallized from methanol-ether, melted at 232–234° (dec.) and showed λ_{max} 3.02, 3.65, 5.70, 6.14, 6.30, 6.65, 6.73 μ.

Anal. Calcd. for $C_{16}H_{24}N_8O_6$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.22; H, 5.70; N, 26.42.

2-n-Butoxy-2-imidazoline (VII). Tenth-molar quantities of sodium *n*-butoxide and I were heated under reflux in *n*-butyl alcohol for 22 hr. and the reaction mixture was worked up as described for II. From acetone-heptane, the total crude product yielded 1.0 g. (13%) of VI, m.p. 187–197°, identified by infrared spectrum. Chromatography on alumina of the remainder of the material provided 6.7 g. (47%) of pure VII, m.p. 56–58°; λ_{max} 3.16, 6.13, 6.58, 6.71 μ. The acid fumarate of VII was prepared, m.p. 126–128°; λ_{max} 3.26, 3.72, 5.20, 5.38, 6.01, 6.12, 6.39 μ.

Anal. Calcd. for $C_{11}H_{18}N_2O_5$: N, 10.85. Found (K): N, 10.73, 10.82.

1-(2′-Imidazolin-2′-yl)-2-imidazolidinethione (IX). *A. By the method of Johnson and Edens.*[11] Ethylenethiourea disulfide hydroperiodide was obtained in 80% yield from ethylenethiourea, iodine, and KI as purple crystals which decomposed at about 100°; λ_{max} 2.99, 3.07, 6.14, 6.23, 6.48, 6.55 μ. Boiling the hydroperiodide in water gave the hydroiodide of IX as white needles, m.p. 220–260° (dec.) in 50% yield. A sample recrystallized from water decomposed at 296–299° and showed λ_{max} 3.17, 6.15, 6.27, 6.52, 6.72 μ; λ_{max} 222 mμ, ϵ_{max} 25,000, λ_{max} 263 mμ, ϵ_{max} 11,700.

Anal. Calcd. for $C_6H_{11}IN_4S$: C, 24.17; H, 3.72; N, 18.95. Found: C, 24.14; H, 3.60; N, 18.90.

(15) Melting points were determined with a Kofler micro hot-stage. Infrared spectra were determined in mineral oil mull and ultraviolet spectra in methanol solution.

(16) W. Schacht, *Arch. Pharm.*, **235**, 441 (1897).

Liberation of the base from an aqueous solution of the hydroiodide with ammonia gave crude IX melting at 218–222° (dec.). Recrystallization from ethanol to constant melting point provided prisms, m.p. 236–238° (dec.); λ_{max} 3.05, 3.25, 6.21, 6.45–6.52, 6.60, 6.74 μ; λ_{max} 234 mμ, ϵ_{max} 11,600, λ_{max} 262 mμ, ϵ 12,600 (literature[14] 232 and 264 mμ in methanol, ϵ_{max} 13,500).

Anal. Calcd. for $C_6H_{10}N_4S$: C, 42.33; H, 5.92; N, 32.91; S, 18.83. Found: C, 42.46; H, 5.80; N, 33.07; S, 18.71.

B. From ethylenethiourea and mercuric oxide. A suspension of 10 g. of yellow mercuric oxide and 5.0 g. of ethylenethiourea in 50 ml. of xylene was heated under reflux for 4 hr. and filtered hot. The dark insolubles were continuously extracted with chloroform and the combined xylene filtrate and chloroform extract was concentrated to dryness providing 1.21 g. of yellow solid, m.p. 155–190°. Two recrystallizations from ethanol resulted in 0.37 g. (9%) of IX, identified by mixed melting point [236–238° (dec.)] and infrared spectrum.

Conversion of IX *to* VI. A mixture of 3.00 g. of IX, 9.0 g. of yellow mercuric oxide, and 55 ml. of 50% ethanol was heated under reflux for 4.5 hr., was then filtered hot, and the dark insoluble part was washed thoroughly with hot ethanol. The combined solution was concentrated to dryness and the gummy residue (1.15 g.) was dissolved in acetone and the solution was filtered. Concentration to low volume provided 0.14 g. (5%), m.p. 188–202°, which after recrystallization from acetone-benzene amounted to 0.11 g. of VI, m.p. and mixed m.p. 200–204° (dec.), further identified by infrared spectrum.

O-Methylation of ethyleneurea. A mixture of 8.6 g. (0.10 mole) of ethyleneurea and 18.6 g. (0.10 mole) of methyl *p*-toluenesulfonate was heated at 100° for 4 hr. by the method of Behringer and Meier.[8] The cooled mixture was distributed between ether and dilute hydrochloric acid and the acid layer was made basic and extracted with ether. From the dried ether extract there was obtained a small amount of oily solid which gave an infrared spectrum very similar to that of 2-methoxy-2-imidazoline (II). A picrate was obtained from methanol, which after one recrystallization amounted to 0.50 g. (1.5%) of II-picrate, m.p. 164–166°, identified by mixed melting point and infrared spectrum.

1-Methyl-2-imidazolinone. The procedure known to *O*-methylate caprolactam[5] was applied to ethyleneurea. In this case, a heterogeneous reaction mixture was obtained. From 17.2 g. (0.2 mole) of ethyleneurea and 25.2 g. (0.2 mole) of dimethylsulfate, there was obtained 15.9 g. of organic material after work-up. Fractional crystallization from ethyl acetate provided 2.8 g. (16%) of unchanged starting material, identified by melting point (128–131°) and infrared spectrum. The remainder was chromatographed over alumina. No 2-methoxy-2-imidazoline could be detected. The first material to be eluted (with mixtures of ether–petroleum ether and with ether) was crystalline 1-methyl-2-imidazolinone, melting first at 100–110° and then at 110–112° in later fractions. Purification by recrystallization from benzene and benzene-ether gave 2.3 g. (11%), m.p. 115–116°; λ_{max} 3.07, 3.22, 5.95, 6.60 μ.

Anal. Calcd. for $C_4H_8N_2O$: C, 47.98; H, 8.05; N, 27.98. Found: C, 48.14; H, 7.93; N, 27.60.

Heating ethyleneurea with methylsulfate by the method used to make methylisourea[6] gave very similar results.

PHILADELPHIA 32, PA.

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

1,3-Disubstituted Indeno[1,2-*c*]pyrazol-4-ones[1]

ROBERT A. BRAUN AND WILLIAM A. MOSHER[2]

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The reaction of hydrazine with 2-pivalyl, 2-benzoyl, and 2-*p*-methoxy-1,3-indandiones give the corresponding 3-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-ones in good yields. These compounds give *N*-sodium and potassium salts which react readily with active halogen compounds to give a new class of fluorescent compounds, 1,3-disubstituted indeno[1,2-*c*]pyrazol-4-ones. The infrared absorption spectra are discussed.

In connection with our earlier work on the Wolff-Kishner reduction of 2-acyl-1,3-indandiones,[3] we showed that 3-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-ones were intermediates in the reduction. The primary purpose of the investigation reported here was to study 3-substituted-indeno[1,2-*c*]-pyrazol-4(1*H*)-ones and their reactions, with emphasis on the new compounds, 1,3-disubstituted indeno[1,2-*c*]pyrazol-4-ones.

The cyclization of β-diketones with hydrazine to give pyrazoles has been studied extensively,[4] but prior to our work there has been no report of the cyclization reaction of 2-acyl(aroyl)-1,3-indandiones with hydrazine. A somewhat related reaction was studied by Ruhemann[5] and later by Leucks and Kowalski.[6] They found that ethyl-1-hydrindone-2-oxalate reacted with phenyl hydrazine to give ethyl-1-phenylindeno[1,2-*c*]pyrazole-3-carboxylate.

In our study of the monohydrazones of 2-acyl-(aroyl)-1,3-indandiones we observed that certain indandiones did not give monohydrazones, but cyclized very rapidly. 2-Pivalyl, 2-benzoyl, or 2-*p*-methoxybenzoyl-1,3-indandione reacts with one equivalent of hydrazine in refluxing alcohol to give white crystalline compounds resulting from the elimination of two moles of water, as shown by elemental analyses and molecular weight de-

(1) From the dissertation submitted by Robert A. Braun in partial fulfillment of the requirements for the Ph.D. degree, University of Delaware.

(2) To whom inquiries should be addressed.

(3) R. A. Braun and W. A. Mosher, *J. Am. Chem. Soc.*, **80**, 4919 (1958).

(4) H. Gilman, *Organic Chemistry, An Advanced Treatise*, John Wiley & Sons, Inc., New York, N. Y., 1953, Vol. IV, p. 774.

(5) S. Ruhemann, *J. Chem. Soc.*, **101**, 1731 (1912).

(6) H. Leucks and G. Kowalski, *Ber.*, **58B**, 2288 (1958).

TABLE I

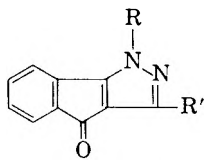
3-SUBSTITUTED INDENO[1,2-*c*]PYRAZOL-4(1*H*)-ONES (II)

R	Yield, %	M.P., °C.[a]	Empirical Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$C(CH_3)_3$	99.0[b]	191–192[d]	$C_{14}H_{14}N_2O$	75.31	75.02	6.18	6.27	12.40	12.38
C_6H_5	98.3[c]	254–255[e]	$C_{16}H_{10}N_2O$	78.04	77.84	4.09	4.10	11.36	11.48
p-$CH_3OC_6H_5$	84.8[b]	264–265[f]	$C_{17}H_{12}N_2O_2$	73.90	74.19	4.38	4.68	10.14	10.23

[a] All melting points are corrected. [b] Reaction time, 2 hr. [c] Reaction time, 24 hr. [d] Recrystallized from aqueous methanol. [e] Recrystallized from ethanol. [f] Recrystallized from methanol-dimethylformamide.

TABLE II

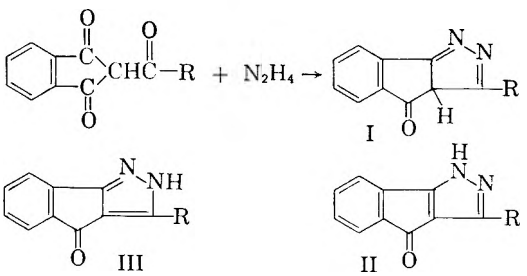
1,3-DISUBSTITUTED INDENO[1,2-*c*]PYRAZOL-4(1*H*)-ONES



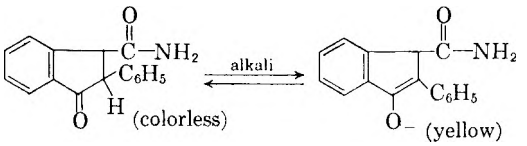
R	R′	Empirical Formula	Yield, %	M.P., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	p-$OCH_3C_6H_4$	$C_{19}H_{16}N_2O_2$	80.2	156–156.5	9.20	9.34[a]
C_2H_5	C_6H_5	$C_{18}H_{14}N_2O$	88.4	140.5–141	10.21	9.96
C_6H_5CO—	$C(CH_3)_3$	$C_{21}H_{18}N_2O_2$	92.3	101–102	8.48	8.43[b]
C_2H_5COO—	$C(CH_3)_3$	$C_{17}H_{18}N_2O_3$	78.0	147.5–148.5	9.39	9.24[c]
C_2H_5COO—	C_6H_5	$C_{19}H_{14}N_2O_3$	97.0	163–164	8.80	8.78
C_2H_5COO—	p-$OCH_3C_6H_4$	$C_{20}H_{16}N_2O_4$	97.4	174.5–175	8.04	7.83
$C_6H_5SO_2$—	p-$OCH_3C_6H_4$	$C_{25}H_{16}N_2O_4S$	81.9	224.5–225.5	6.73	6.71

[a] Carbon, calcd. 74.98, found 74.94. Hydrogen, Calcd. 5.30, found. 5.23. [b] Carbon, calcd. 76.34, found 76.35. Hydrogen, Calcd. 5.49, found 5.41. [c] Carbon, calcd. 68.44, found 68.55.

termination. Their infrared spectra showed strong carbonyl bands and they also formed 2,4-dinitrophenylhydrazones. From the above information it is evident that structures I–III must be considered.



Upon initial examination it was thought that I was the correct structure since these compounds reacted with base in the same way as IV which was studied by Coe *et al.*[7] Structure I, however, is not consistent with the infrared spectra of these compounds as each has a band in the 3.1μ region, due to a hydrogen bonded N—H group.[3] The correct structure (II) has been distinguished from the alternate structure (III) by spectral evidence. The proof of this type of structure has been presented in a previous paper.[3] The properties and analyses of the 3-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-ones are summarized in Table I.



The 3-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-

TABLE III

PRINCIPAL INFRARED ABSORPTION BANDS (μ)[a] OF 1,3-DISUBSTITUTED (INDENO[1,2-*c*]PYRAZOL-4(1*H*)-ONES)

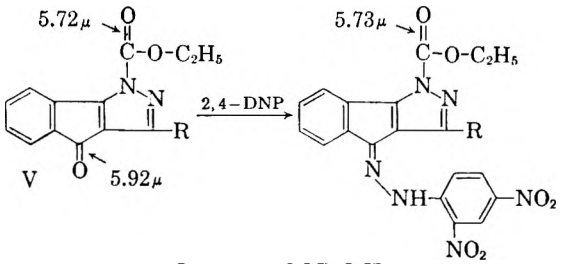
R	R′	C=O	N—H (Hydrogen Bonded)	(C=N, C=C)
H	$C(CH_3)_3$	5.88	3.4[b]	6.19
H	C_6H_5	5.96	3.4[b]	6.21
H	p-$OCH_3C_6H_4$	5.96	3.3[b]	6.21
C_2H_5	p-$OCH_3C_6H_4$	5.93	..	6.20
$COOC_2H_5$	$C(CH_3)_3$	5.67[c]	..	6.20
		5.87[d]		
$COOC_2H_5$	C_6H_5	5.72[c]	..	6.23
		5.91[d]		
$COOC_2H_5$	p-$OCH_3C_6H_4$	5.67[c]	..	6.18
		5.87[d]		
COC_6H_5	$C(CH_3)_3$	5.98[e]	..	6.29
		5.90[d]		

[a] Infrared recording spectrophotometer, Model B, Baird Associates, Inc., Cambridge, Mass. [b] Very wide and intense band. [c] Ester carbonyl. [d] Carbonyl on indan ring. [e] Amide carbonyl.

(7) D. G. Coe, M. M. Gale, R. P. Linstead, and C. J. Timmons, *J. Chem. Soc.*, 123 (1957).

ones reacted with hot alcoholic potassium hydroxide or hot aqueous sodium hydroxide to give insoluble yellow salts that were stable at room temperature although they could not be purified by recrystallization from water, alcohol, or dimethylformamide-ethanol. These were shown, by reaction with a series of active halogen compounds (ethyl bromide, ethyl chloroformate, benzoyl chloride, and benzenesulfonyl chloride), to be the *N*-alkali salts. Analytical data for these new compounds are shown in Table II and their spectral properties are summarized in Table III.

To establish further the carbonyl band assignment, the 2,4-dinitrophenylhydrazone of V was prepared and its spectrum shows only one carbonyl band at 5.73μ, because of the ester carbonyl.



R = *p* − $OCH_3C_6H_4$

All of the *N*-substituted indeno[1,2-*c*]pyrazol-4-(1*H*)-ones were yellow crystalline solids and were extremely fluorescent under ultraviolet light both in the solid state and in solution. This finding was unexpected as the parent 3-substituted indeno-[1,2-*c*]pyrazol-4(1*H*)-ones were not fluorescent. Although the 1,3-disubstituted indeno [1,2-*c*]-pyrazol-4(1*H*)-ones are similar in some respects to the fluorescent benzo-bispyrazolones,[8] they represent a new class of fluorescent compounds.

EXPERIMENTAL[9]

3-t-Butylindeno[1,2-c]pyrazol-4(1H)-one. Experimental details for the preparation of this compound from 2-pivalyl-1,3-indandione and hydrazine were given in an earlier paper.[3] The properties of the other 3-substituted indeno[1,2-*c*]-pyrazol-4(1*H*)-ones are shown in Table I. A yield of 99.0% of 3-*t*-butylindeno[1,2-*c*]pyrazol-4(1H)-one was obtained by using anhydrous ethanol as solvent and 95% pure hydrazine, while a 50% yield of the same product was obtained by running the reaction at 25° for 2 hr. The two other compounds of this type were prepared in the same way and their properties are summarized in Table I.

Sodium salt of 3-t-butylindeno[1,2-c]pyrazol-4(1H)-one. 3-*t*-Butylindeno[1,2-*c*]pyrazol-4(1*H*)-one (1.58 g., 0.007 mole) was mixed at room temperature with 50 ml. of 10% aqueous sodium hydroxide, but the white solid did not dissolve. After warming at 80° for 3 min. a clear yellow solution was obtained which was filtered through a fritted glass filter. The filtrate crystallized upon cooling. The yellow needles were collected and dried at 100°; yield, 1.70 g. (97.7%). Its melting point was greater than 350°. All attempts at recrystallization were unsuccessful.

High yields of the potassium salts could be obtained using hot alcoholic potassium hydroxide. The sodium and potassium salts of 3-phenyl- and 3-*p*-methoxyphenylindeno-[1,2-*c*]pyrazol-4(1*H*)-one are yellow high melting solids.

1-Ethyl-3-p-methoxyphenylindeno[1,2-c]pyrazol-4-one. A mixture of 1.00 g. (0.0033 mole) of the sodium salt of 3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-4(1*H*)-one and a large excess (5 ml.) of ethyl bromide in 20 ml. of ethanol was refluxed for 5 hr. The solvent and excess ethyl bromide were evaporated and the residue was dried at 70°. After recrystallization from methanol the yellow fluorescent crystals of 1-ethyl-3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-4-one melted at 156–156.5°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.94; H, 5.230 N, 9.34.

1-Benzenesulfonyl-3-methoxyphenylindeno[1,2-c]pyrazol-4-one. Benzenesulfonyl chloride (0.7 g., 0.004 mole) was added to a slurry of 1.00 g. (0.0033 mole) of the sodium salt of 3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-4(1*H*)-one in 30 ml. of ether and the mixture was warmed at reflux for 30 min. The resulting solid was filtered, washed with ether, and recrystallized from a mixture of dimethylformamide and ethanol to give strongly fluorescent, light yellow needles, m.p. 224.5–225.5°.

Anal. Calcd. for $C_{23}H_{16}N_2O_4S$: N, 6.73. Found: N, 6.71.

Ethyl 4-oxo-3-p-methoxyphenylindeno[1,2-c]pyrazol-1-carboxylate. Ethyl chloroformate (0.38 g., 0.0035 mole) was added to a slurry of the sodium salt of 3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-4(1*H*)one (1.00 g., 0.0033 mole) in 20 ml. of ether. There was an immediate exothermic reaction and the color changed from a nonfluorescent pale yellow to a bright, strongly fluorescent yellow color. After refluxing for 10 min. the solid was collected and washed with ether, yielding 1.12 g. (97.4%) ethyl 4-oxo-3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-1-carboxylate; m.p. 173–175.° After recrystallization from dimethylformamide-methanol the compound melted at 174.5–175°. This material fluoresced intensely with a yellow-green color under ultraviolet light.

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: N, 8.04. Found: N, 7.83.

The same procedure was used to prepare the other compounds of this type. Their properties are summarized in Table II.

These compounds can also be prepared by the reaction of excess ethyl chloroformate with 3-substituted indeno(1,2-*c*)-pyrazol-4(1*H*)-ones but the yields are much lower (5 to 20%).

The *2,4-dinitrophenylhydrazone* of ethyl 4-oxo-3-*p*-methoxyphenylindeno[1,2-*c*]pyrazol-1-carboxylate was recrystallized from ethyl acetate, m.p. 237–238°. The orange needles are not fluorescent. The infrared spectrum contains a N—H band at 3.05μ and a strong ester carbonyl band at 5.73μ.

1-Benzoyl-3-butylindeno[1,2-c]pyrazol-4-one. A 0.50 g. (0.002 mole) sample of the sodium salt of 3-*t*-butylindeno-[1,2-*c*]pyrazol-4(1*H*)-one was suspended in 10 ml. of anhydrous ether and excess (0.8 ml.) benzoyl chloride was added at room temperature. After warming in a hot water bath for 10 min. the yellow solid was filtered, dried, and crystallized from ethanol to give strongly fluorescent, yellow needles; yield, 0.52 g. (92.3%); m.p. 101–102°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found; C, 76.35; H, 5.41; N, 8.43.

NEWARK, DEL.

(8) S. Veibel and H. Lillelund, *Tetrahedron*, 1, 201 (1957).

(9) Microanalyses by the Geller Microanalytical Laboratories, West Englewood, N. J. All melting points are corrected.

[CONTRIBUTION FROM JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Reaction of Hydrazoic Acid with Cinnamic Acids

DONALD C. DITTMER, ALVIN SILVERSTEIN, AND LILLIAN P. LEMPKA

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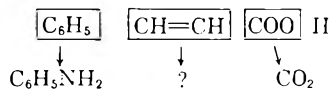
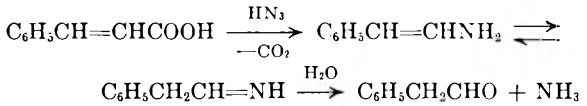
3-[*p*-Methoxyphenyl]-2-phenylacrylic acid yields *p*-anisidine, phenylacetaldehyde and *p*-methoxybenzyl phenyl ketone on treatment with hydrazoic acid. Cinnamylidene acetic acid under similar conditions gives aniline and benzaldehyde. These products may arise by addition of hydrazoic acid both to the olefinic bonds and to the carboxyl carbonyl group, followed by rearrangements.

Hydrazoic acid and cinnamic acid have been reported to react in a sulfuric acid–chloroform medium to give, after neutralization, aniline, phenylacetaldehyde, carbon dioxide, nitrogen, and ammonia.[1] The formation of aniline from cinnamic acid leaves two carbons unaccounted for in the isolated products, barring the unlikely possibility that they were oxidized to carbon dioxide.



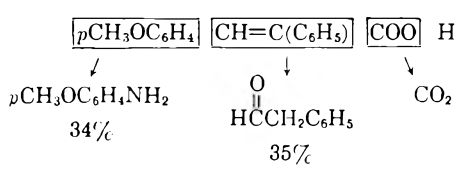
The phenylacetaldehyde has been suggested as being derived from styrylamine formed *via* the usual mechanism for the Schmidt reaction.[2]



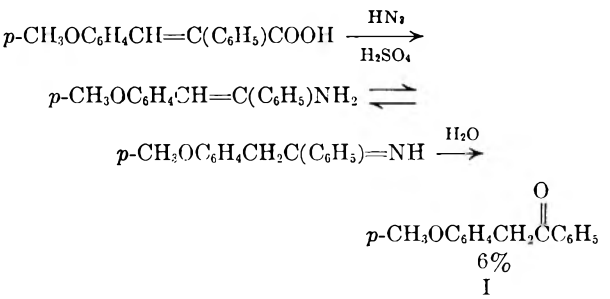
Our attempts to isolate a two-carbon fragment from the reaction were in vain. Under the reaction conditions the two-carbon fragment may have yielded the tar which was always found.

Finding a larger fragment than a two-carbon one might be more successful and, accordingly, the reaction of 3-[*p*-methoxyphenyl]-2-phenylacrylic acid with hydrazoic acid was studied. In this acid, an eight-carbon fragment (—CH=CC_6H_5—) corresponds to the two-carbon one (—CH=CH—) in cinnamic acid.

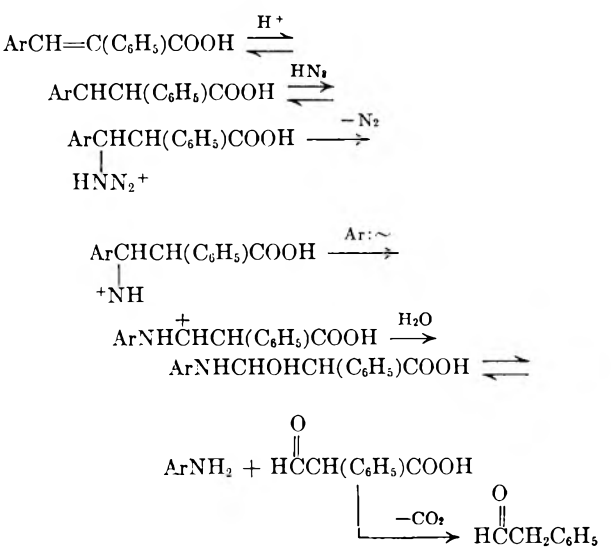
The reaction of this substituted acrylic acid with hydrazoic acid gave phenylacetaldehyde, an eight-carbon compound which could only have come from the cinnamic acid side chain. Other products were *p*-anisidine and *p*-methoxybenzyl phenyl ketone(I).



Average yields of *p*-anisidine and phenylacetaldehyde were roughly the same. The *p*-methoxybenzyl phenyl ketone apparently was formed in the same way as the phenylacetaldehyde from cinnamic acid itself.



The products (other than the *p*-methoxybenzy phenyl ketone) from 3-[*p*-methoxyphenyl]-2-phenylacrylic acid may be produced by addition of hydrazoic acid to the carbon-carbon double bond, followed by loss of nitrogen and a rearrangement of the *p*-methoxyphenyl group to positive nitrogen. The "missing" two-carbon fragment from cinnamic acid would be predicted to be acetaldehyde which polymerizes in the strong acid used for the reaction.



Nothing is known about when the decarboxylation step occurs. It may have occurred earlier than shown.

Addition of hydrazoic acid to the carbon-carbon double bond in cinnamic acids has an analogy in

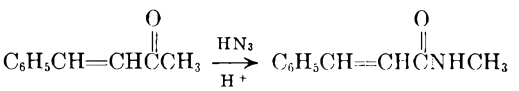
(1) M. Osterlin, *Angew. Chem.*, **45**, 536 (1932).
(2) H. Wolff, *Org. Reactions*, *III*, 307 (1947).

the addition of hydrazoic acid to olefins.[3] For example, 1,1-diphenylethylene gives acetophenone and aniline.[4]

The *p*-anisyl group has been shown to have a high migration aptitude in the Schmidt reaction of olefins.[5] Extensive rearrangements, presumably involving carbonium ions, have been observed with triethylacetic acid.[6]

In some cases, azides are formed from olefins or acetylenes and hydrazoic acid.[7] In strong acid azides are decomposed with loss of nitrogen and rearrangement.[8] It is possible that an azide could be a transient intermediate in our reaction.

It is interesting that cyclopropyl styryl ketone[9] and benzalacetone[10] apparently yield no products derived by addition of hydrazoic acid to the olefinic bond in strong acid.

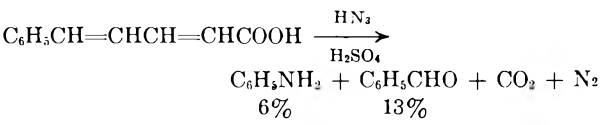


Perhaps in the acids a carboxyl group or a protonated carboxyl group is stabilized enough by resonance so that addition of hydrazoic acid may go elsewhere (*i.e.*, to a carbon-carbon double bond).

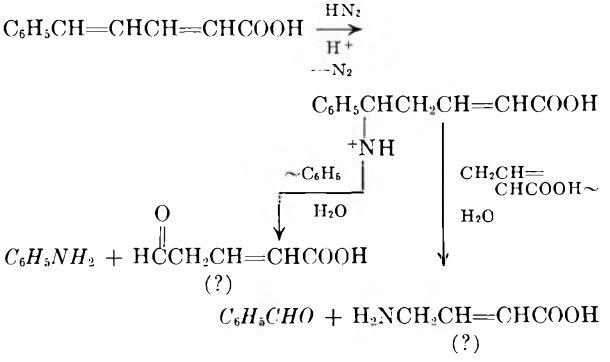
Anethole dibromide on treatment with hydrazoic acid yields *p*-anisidine and α-bromopropionaldehyde, presumably by displacement of the α-bromine by hydrazoic acid followed by migration of the *p*-methoxyphenyl group.[2]

A strong acid is required in the Schmidt reaction of α,β-unsaturated acids. Use of hydrochloric or phosphoric acids with cinnamic acid was unsuccessful. Cinnamic acid is reported not to react with hydrazoic acid in refluxing glacial acetic acid.[7b] Polyphosphoric acid did yield some reaction. The latter has been used with good results in the Schmidt reaction of ketones.[11]

Cinnamylidene acetic acid with hydrazoic acid gave aniline, benzaldehyde, nitrogen, and carbon dioxide. There may have been other products. In several instances, the odor of phenylacetaldehyde could be detected. The low yields may be due to the poor solubility of the acid in chloroform.



These products may be explained by a mechanism involving addition of hydrazoic acid to an olefinic bond followed by migration of alkyl or aryl groups.



EXPERIMENTAL

3-[p-Methoxyphenyl]-2-phenyl acrylic acid. This was prepared by the method of Buckles, Bellis, and Coder from phenylacetic acid, anisaldehyde, and acetic anhydride.[12]

Reaction of 3-[p-methoxyphenyl]-2-phenyl acrylic acid with hydrazoic acid. The acrylic acid (12.5 g., 0.05 mole) was suspended in 24 ml. of chloroform in a 250-ml., three necked flask equipped with a dropping funnel, a mechanical stirrer and a gas outlet tube. The gases from the reaction were passed through three washing bottles (one empty and two containing concentrated barium hydroxide solution) into an inverted water-filled graduated cylinder. The barium hydroxide absorbed the carbon dioxide and the progress of the reaction was followed qualitatively by observing the displacement of the water level in the graduated cylinder by nitrogen.

Concentrated sulfuric acid (10 ml.) and chloroform (20 ml.) were added with vigorous stirring. During 1 hr., 41 ml. (0.06 mole) of 1.58*N* hydrazoic acid in chloroform (prepared from sodium azide and sulfuric acid[2]) were added slowly while the temperature was kept at 52–55°.

The acid reaction mixture was poured into 400 ml. of ice water and steam distilled. The distillation was continued until the odor of phenylacetaldehyde was no longer noticeable and a Schiff test[13] for aldehydes was negative. About 2 l. of distillate were collected.

This distillate was extracted with five or six portions of ether. The ether solution was washed with a saturated solution of sodium bisulfite, prepared by dissolving 400 g. of sodium bisulfite in 600 ml. of water, adding 180 ml. ethanol and filtering. The bisulfite solution (containing the aldehyde as the bisulfite addition compound) was treated with sodium carbonate and extracted with ether. The ether extract was dried over magnesium sulfate, the ether removed and the phenylacetaldehyde converted to a methone derivative,[14] m.p. 163–165° (lit.[15] m.p. 164–165°). It was also identified

(3) L. P. Kuhn and J. Di Domenico, *J. Am. Chem. Soc.*, **72**, 5777 (1950); D. R. Nielsen and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 4042 (1954).

(4) W. E. McEwen, M. Gilliland, and B. I. Sparr, *J. Am. Chem. Soc.*, **72**, 3212 (1950).

(5) W. E. McEwen and N. B. Mehta, *J. Am. Chem. Soc.*, **74**, 526 (1952).

(6) C. Schuerch, Jr., and E. H. Huntress, *J. Am. Chem. Soc.*, **71**, 2238 (1949).

(7) (a) R. Westland and W. E. McEwen, *J. Am. Chem. Soc.*, **74**, 6141 (1952); (b) J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 5248 (1951); (c) Y. A. Sinnema and J. F. Arens, *Rec. trav. chim.*, **74**, 901 (1955).

(8) S. N. Ege and K. W. Sherk, *J. Am. Chem. Soc.*, **75**, 354 (1953); C. H. Gudmundsen and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 329 (1957); J. H. Boyer, F. C. Canter, J. Hamer and R. K. Putney, *J. Am. Chem. Soc.*, **78**, 325 (1956).

(9) S. C. Bunce and J. B. Cloke, *J. Am. Chem. Soc.*, **76**, 2244 (1954).

(10) P. A. S. Smith and J. R. Horwitz, *J. Am. Chem. Soc.*, **72**, 3718 (1950); L. Briggs, G. de Ath, and S. Ellis, *J. Chem. Soc.*, **61** (1942).

(11) R. T. Conley, *J. Org. Chem.*, **23**, 1330 (1958).

(12) R. E. Buckles, M. P. Bellis, and W. D. Coder, Jr., *J. Am. Chem. Soc.*, **73**, 4972 (1951).

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 114.

(14) Ref. 13, p. 220.

(15) K. Lin and R. Robinson, *J. Chem. Soc.*, 2005 (1938).

TABLE I

APPROXIMATE YIELDS IN THE REACTION OF 3-[*p*-METHOXYPHENYL]-2-PHENYL ACRYLIC ACID WITH HYDRAZOIC ACID

Acid Reacted, G.	*p*-Anisidine.HCl, G.	Per Cent	Methone Deriv. $C_6H_5CH_2CHO$, G.	Per Cent	2,4 DNP of Ketone, G.	Per Cent
4.1	0.76	29	1.86	30	0.29	4.5
3.7	.83	36	2.08	37	.38	6.5
3.9	.94	38	2.20	37	.40	6.5

as its 2,4-dinitrophenylhydrazone, m.p. 121–123° (lit.[16] m.p. 121°).

The residue from the steam distillation (nonvolatile material) was extracted with ether. The unreacted acrylic acid which was not extracted with the ether was recrystallized from ethanol. The ether extract was washed with sodium bicarbonate to remove unreacted starting material. The bicarbonate extract was neutralized and the 3-[*p*-methoxyphenyl]-2-phenyl acrylic acid recovered by this process was combined with that recovered earlier.

The ether extract from the steam distillate and from the residue were then combined and dried over anhydrous magnesium sulfate. The ether was removed and the *p*-methoxybenzyl phenyl ketone, m.p. 94–96° (lit.[17] m.p. 94.5–5°) was converted to its 2,4-dinitrophenylhydrazone, m.p. 179–182°. An oxime was prepared in several runs, m.p. 132–133° (lit.[18] m.p. 133°).

After the above ether extraction, the acidic residue from the steam distillation was made basic with 10% sodium hydroxide. The solution then was extracted with ether, the ether extract dried over anhydrous magnesium sulfate, and the ether removed to yield *p*-anisidine. It was identified as its benzenesulfonamide, m.p. 93–95° (lit.[19] m.p. 95°), *p*-toluenesulfonamide, m.p. 108–110° (lit.[19] m.p. 114°) and its acetamide, m.p. 124–126° (lit.[19] m.p. 127°).

In order to get an estimate of the yields, the phenylacetaldehyde in several runs was converted quantitatively to its methone derivative, the *p*-anisidine to its hydrochloride and the *p*-methoxybenzyl phenyl ketone to its 2,4-dinitrophenylhydrazone. The yield data are summarized in Table I. Yields are based on the amount of the acrylic acid reacted as calculated from the amount recovered. In all cases 12.5 g. (0.05 mole) of acid was used initially. The barium carbonate produced agreed well with the amount of acid consumed (over 90%).

Cinnamylidene malonic acid. This was prepared from cinnamaldehyde and malonic acid with pyridine as catalyst.[20]

Cinnamylidene acetic acid. This was prepared by decarboxylation of cinnamylidene malonic acid.[21]

Reaction of cinnamylidene acetic acid with hydrazoic acid. Cinnamylidene acetic acid (17.4 g., 0.1 mole) was dissolved in 50 ml. of chloroform in a 250-ml., three necked flask. The apparatus was the same as used in the previous reaction. Concentrated sulfuric acid (10 ml.) was added, followed by 70 ml. of 1.43*N* hydrazoic acid (0.1 mole) in chloroform. The temperature was maintained at 51–52°. After about an hour, the brown reaction mixture was poured into 500 ml. of ice water. The odor of benzaldehyde was observed.

Neutral and acidic substances were extracted with ether, and the acidic substances separated from neutral ones by extraction of the ether with sodium bicarbonate solution. Cinnamylidene acetic acid, 9.2 g., 53%, was recovered. Benzaldehyde was converted to its methone derivative,[14] (2.8 g., 13%), m.p. 192–193° (lit.[22] m.p. 193°). It was further identified as its semicarbazone, m.p. 218–220° (lit.[22] m.p. 217°).

Basic substances were obtained from the acid reaction mixture by neutralization and extraction with ether. The ether extract was dried and dry hydrogen chloride was passed into it to give a precipitate of an amine hydrochloride. This was treated with 5% sodium hydroxide, extracted with ether and the hydrochloride again made. The amine was identified as aniline by its hydrochloride (made quantitatively), 0.41 g., 6.4%, m.p. 193–196° (lit.[23] m.p. 198°), its benzenesulfonamide, m.p. 109–112° (lit.[24] m.p. 112°) and its acetyl derivative, m.p. 114° (lit.[23] m.p. 114°).

The barium carbonate (0.47 g.) recovered amounted to only 5% reaction based on acid consumed.

Reaction of cinnamic acid with hydrazoic acid. Hydrazoic acid (150 ml. of 2.125*N* solution in chloroform, 0.32 mole) was added dropwise to a stirred solution of cinnamic acid (49 g., 0.33 mole), concentrated sulfuric acid (98 ml.) and chloroform (150 ml.) in a three necked, 1-liter flask equipped with a mechanical stirrer, thermometer, gas outlet tube, and addition funnel. The temperature was between 45–50°.

After the addition of hydrazoic acid was completed and gas evolution ceased, the mixture was cooled, diluted with water, and steam distilled. A tar was produced on dilution. The distillate yielded phenylacetaldehyde, identified as its 2,4-dinitrophenylhydrazone, m.p. 120° (lit.[16] m.p. 121°).

The residue from the steam distillation was made alkaline and steam-distilled again. The distillate was led into hydrochloric acid solution which subsequently was evaporated to dryness. The residue was treated with sodium hydroxide to liberate aniline which was identified as its phenylthiourea, m.p. 152–153° (lit.[19] m.p. 154°). No evidence could be obtained in this or any other run for the presence of acetaldehyde or any other organic products (except the tar). Considerable amounts of cinnamic acid were usually recovered.

When polyphosphoric acid was substituted for sulfuric acid, reaction occurred but no new products were found. Hydrochloric acid or phosphoric acid could not replace sulfuric acid.

Acetaldehyde with concentrated sulfuric acid gave a dark brown viscous liquid. When acetaldehyde (0.2 mole) was added to the reaction mixture of cinnamic acid, hydrazoic acid, sulfuric acid, and chloroform during the reaction, only trace amounts of the aldehyde or none at all could be identified by the Simon's test.[25]

Acknowledgments. We are indebted to the University of Pennsylvania for a faculty summer scholarship (D. C. D.) and a summer research scholarship (A. S.).

PHILADELPHIA, PA.

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(17) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **76**, 3719 (1954).

(18) W. Neish, *Rec. trav. chim.*, **68**, 337 (1949); G. Drefahl and M. Hartmann, *Ann.*, **589**, 82 (1954).

(19) Ref. 13, p. 292.

(20) K. C. Pandya, *J. Ind. Chem. Soc.*, **24**, 443 (1947).

(21) G. P. Reynolds, *Am. Chem. J.*, **46**, 200 (1911).

(22) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, John Wiley & Sons, Inc., New York, 1941, p. 60.

(23) J. Heilbron, Editor, *Dictionary of Organic Compounds*, Vol. 1, Oxford University Press, New York, 1953, p. 174.

(24) Ref. 13, p. 288.

(25) Ref. 22, p. 43.

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis and Spectra of a Matched Series of 1,5-Disubstituted Tetrazoles

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Received December 5, 1958

The 1-methyl-5-(*o*-chlorophenyl)-, -5-(*m*-chlorophenyl)-, and -5-(*p*-chlorophenyl)tetrazoles as well as 1-(*o*-chlorophenyl)-, 1-(*m*-chlorophenyl)-, and 1-(*p*-chlorophenyl)-5-methyltetrazoles have been synthesized from the corresponding benzamides and acetanilides, respectively. Ultraviolet spectra of the tetrazoles are compared with those of the parent amides. Evidence is presented to support the first order interaction of the tetrazole ring with an aromatic substituent in the 5- position and the second order interaction of the tetrazole ring with an aromatic substituent in the 1-position. Infrared bands at 9.12–9.20μ and 10.05–10.25μ are assigned to the tetrazole ring system.

There have been several reports of the ultraviolet absorption spectra of tetrazoles which have a bare or substituted benzene ring attached to the 1-nitrogen or 5-carbon of the tetrazole ring. Garbrecht and Herbst[4] reported that 5-phenyltetrazole displays a λ_{max} 2400 Å with a log ϵ_{max} 4.16 and that 1-phenyl-5-methyltetrazole has a λ_{max} 2200Å with a log ϵ_{max} 3.85.[5,6] They state that a phenyl group in the 5 position gives rise to an absorption in the range of 2320–2400 Å, and that a phenyl in the 1-position appears to be without effect on the basic absorption characteristics of the tetrazole ring. Murphy and Picard[7] reported the spectra of 1-(3-nitrophenyl)-5-aminotetrazole, λ_{max} 2250 Å, log ϵ_{max} 4.07, and 1-(3-methylphenyl)-5-aminotetrazole, λ_{max} 2280 Å, log ϵ_{max} 4.15. The initial report of ultraviolet spectra characteristics of tetrazoles was by Elpern and Nachod[8]; they concluded that the tetrazole ring had little or no absorption itself in the usual ultraviolet region. They compared 1-cyclohexyltetrazole, no absorption above 2050 Å, with 1-phenyltetrazole, absorption from 2200 to 2500 Å. They also report the absorption of 1-methyl-5-phenyltetrazole, λ_{max} 2320 Å and log ϵ_{max} 4.02. This is in contrast to a report by Benson[9] that 1-(3′,4′-dimethylphenyl)-5-methyltetrazole showed a λ_{max} 2310 Å with a log ϵ_{max} 3.85. On the basis of these reports it appeared possible to prove the interaction or lack of interaction of the tetrazole ring with an aromatic substituent either at the 1- or 5- position of the tetrazole ring by the choice of proper systems.

This paper reports the synthesis of two series of 1,5-disubstituted tetrazoles wherein the interaction of an *ortho*, *meta*, and *para* chlorophenyl with the tetrazole ring could be shown when the aromatic substituent was first in the 1- position on the tetrazole ring, and second, when the aromatic substituent was in the 5- position, the carbon, of the tetrazole ring. The balancing substituent, usually without effect on the ultraviolet spectra, was chosen as the methyl group. The known *o*-chloro-, *m*-chloro, and *p*-chloroanilines were converted to the corresponding acetyl derivatives; the known *o*-chloro-, *m*-chloro-, and *p*-chlorobenzoic acids were converted to their corresponding *N*-methyl amides by way of the acid chlorides (Table I). Both sets of amides were studied in the ultraviolet and infrared regions. The amides were converted to the corresponding 1,5-disubstituted tetrazoles by way of the imino chlorides (not isolated) and subsequent *in situ* treatment with a benzene solution of hydrazoic acid.[10–12] The tetrazoles were carefully purified both by recrystallization and removal of the contaminating amides by hydrolysis of the latter in boiling 10% sulfuric acid (Table II). The pure

TABLE I

N-SUBSTITUTED AMIDES

R_1CONHR_2

Substituent			M.P	
R_1	R_2	Yield, %	Found	Reported
o-ClC_6H_4	CH_3	72	119–120	121.5[a]
m-ClC_6H_4	CH_3	72	71–73	75.0[a]
p-ClC_6H_4	CH_3	65	158–159	161[a]
CH_3	*o*-ClC_6H_4	64	87–88	86.7[b]
CH_3	*m*-ClC_6H_4	41	77–78	76.6[b]
CH_3	*p*-ClC_6H_4	79	178–179	178.4[b]

[a] P. J. Montagne, *Rec. trav. chim.*, **19**, 46 (1900). [b] N. V. Sidgwick and H. E. Rubie, *J. Chem. Soc.*, **119**, 1013 (1921).

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(3) Submitted in partial fulfillment of the requirements for the Bachelor of Science degree in Chemistry to the Faculty of Purdue University, June, 1956.

(4) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1275 (1953).

(5) Ultraviolet wave lengths are reported in Angstroms (Å) because the differences in λ_{max} between compounds and between series are more clearly shown by this representation. The significance of the last figure is admittedly doubtful.

(6) G. W. Wheland "Resonance in Organic Chemistry," J. Wiley & Sons, Inc., New York, 1955, p. 245.

(7) D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1908 (1954).

(8) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

(9) F. Benson, L. W. Hartzel, and W. L. Savill, *J. Am. Chem. Soc.*, **73**, 4457 (1951).

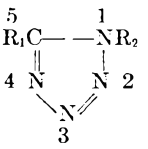
(10) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

(11) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(12) R. M. Herbst, C. W. Roberts, H. T. F. Givens and E. K. Harvill, *J. Org. Chem.*, **17**, 262 (1952).

TABLE II

1,5-DISUBSTITUTED TETRAZOLES



Substituents		Yield,		Percentage Composition					
				Carbon		Hydrogen		Nitrogen	
R_1	R_2	%	M.P.	Calcd.	Found	Calcd.	Found	Calcd.	Found
o-ClC_6H_4	CH_3	27	69–70	49.36	49.71	3.63	3.57	28.79	28.51
m-ClC_6H_4	CH_3	79	86–88	49.36	49.29	3.63	3.65	28.79	28.98
p-ClC_6H_4	CH_3	31	119–120	49.36	49.70	3.63	3.84	28.79	28.60
CH_3	*o*-ClC_6H_4	55	80.5–82	49.36	49.55	3.63	3.95	28.79	28.76
CH_3	*m*-ClC_6H_4	73	98.5–99	49.36	49.61	3.63	3.90	28.79	28.65
CH_3	*p*-ClC_6H_4	72	86–88	49.36	49.61	3.63	3.75	28.79	28.86

TABLE III

ULTRAVIOLET ABSORPTION *B* BANDS OF *N*-SUBSTITUTED AMIDES AND DERIVED 1,5-DISUBSTITUTED TETRAZOLES

Substituents		Amides[a]		Tetrazoles[a]	
C or 5	N or 1	λ_{max} Å	log ϵ_{max}	λ_{max} Å	log ϵ_{max}
o-ClC_6H_4	CH_3	2300	3.95	2250	3.96
m-ClC_6H_4	CH_3	2320	3.99	2350	4.03
p-ClC_6H_4	CH_3	2360	4.11	2410	4.20
CH_3	*o*-ClC_6H_4	2400[b]	4.02	2220	4.01
CH_3	*m*-ClC_6H_4	2450[c]	4.19	2260	4.11
CH_3	*p*-ClC_6H_4	2490[d]	4.25	2290	4.07

[a] In 95% ethanol. [b] Reference 18 reports λ_{max} 2400 Å, log ϵ_{max} 4.02 for o-chloroacetanilide. [c] Reference 18 reports λ_{max} 2450 D, log ϵ_{max} 4.18 for *m*-chloroacetanilide. [d] Reference 18 reports λ_{max} 2490 Å, log ϵ_{max} 4.25 for *p*-chloroacetanilide.

tetrazoles from each series were studied in the ultraviolet and infrared regions (Tables III and IV).

Ultraviolet spectra. For the purpose of discussion, the ultraviolet spectra of the amides and corresponding tetrazoles are separated into the compounds belonging to each class of substituted tetrazoles. Thus, the results for the chloroacetanilides and their 1-chlorophenyl-5-methyltetrazoles will be considered apart from the *N*-methylchlorobenzamides and the 1-methyl-5-chlorophenyltetrazoles.

1-Chlorophenyl-5-methyltetrazoles. Perhaps the most informative area of the ultraviolet spectrum for consideration of the interaction of an aromatic substituent with either an unshared pair of electrons or an unsaturated system is that classified by Moser and Konlenberg[13] as the B band of benzene and substituted benzenes. This is also called the "first primary band" and is usually centered about the 2300 Å. region.[14–16] The parent chloroanilines show spectra peaks in the B band region at 2380 Å (log ϵ_{max} 3.98) for the *o*-chloroaniline, 2400 Å (log ϵ_{max} 3.87) for the *m*-chloroaniline, and 2440 Å (log ϵ_{max} 3.95) for the *p*-chloroaniline.[17] The derived acetanilides show peaks in the B band region at 2400 Å (log ϵ_{max} 4.02) for the *o*-chloroacetanilide, 2450 Å (log ϵ_{max} 4.19) for the *m*-chloroacetanilide, and 2490 Å (log ϵ_{max} 4.25) for the *p*-chloroacetanilide.[18] A comparison of these data indicates that the acetylation of the amino group introduces an electron withdrawing moiety, decreasing the availability of the unshared electron pair on the nitrogen for interaction with the pi electrons of the benzene ring during a N→V transition,[19] but increasing the ease of the transition to the first excited state with the resonance form derivable from the spreading out of a negative charge on the acetamino moiety. This is evidenced by the slight, but real, bathochromic and hyperchromic shifts. When the anilides are converted to the corresponding 1-chlorophenyl-5-methyltetrazoles (see Table III) large hypsochromic effects with only moderate hypochromic effects are observed. This is to be compared with the fundamental absorption of the parent aromatic structures; if chlorobenzene, λ_{max} 2095 Å (log ϵ_{max} 3.87)[16] is compared with *o*-chlorodimethylaniline, λ_{max} 2550 Å (log ϵ_{max} 3.88)[20] it can be seen that the interaction of the tetrazole ring through the 1-nitrogen with the aromatic system is less than might be expected. It may also be noted, however, that there is not an absence of interaction. That there is some interaction either by the tetrazole ring itself or by the unshared pair of electrons on the 1-nitrogen is evidenced by the higher wave

(13) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).

(14) L. Daub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(15) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **33**, 1145 (1955).

(16) W. F. Forbes and A. S. Ralph, *Can. J. Chem.*, **34**, 1447 (1956).

(17) P. Grammaticakis, *Bull. soc. chim. France*, 534 (1951).

(18) H. Ungnade, *J. Am. Chem. Soc.*, **76**, 5133 (1954).

(19) Ref. 6, pp. 278–282.

(20) H. B. Klevens and J. R. Platt, *J. Am. Chem. Soc.*, **71**, 1714 (1949).

length of B band absorption in these tetrazoles or substituted chlorobenzenes than is found in dichlorobenzene itself.[21] It should also be noted that the tetrazole ring is effectively hypsochromic when compared to the dimethylamino group, it being postulated that the long unshared pair on nitrogen, in both series, should be nearly equivalently available for resonance interaction with the aromatic system. The apparent unavailability of these electrons for resonance interaction does not, however, appear to have the same effect on the intensity of the B band absorption at these lower wave lengths.

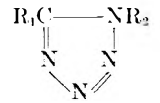
1-Methyl-5-chlorophenyltetrazoles. In the case of the three 1-methyl-5-chlorophenyltetrazoles there appears to be a greater interaction of either the tetrazole ring itself or the pi electrons of the –C=N– portion of the tetrazole ring with the aromatic substituent in the 5-position. Chlorobenzene with a λ_{max} 2095 Å (log ϵ_{max} 3.87) has its B band shifted to higher wave lengths by a number of *para*-substituents. Daub and Vandenbelt[14] report *p*-chlorobenzonitrile (λ_{max} 2375 Å; log ϵ_{max} 4.28) and *p*-chlorobenzoic acid (λ_{max} 2410 Å; log ϵ_{max} 4.21); both of these compounds have groups which possess electronic structures capable of entering into resonance interaction with the benzene ring, and hence, they produce bathochromic as well as hyperchromic effects. The interaction of the carbonyl bond pi electrons in the excited state obtains even when the *N*-methyl amide is formed (λ_{max} 2360 Å log ϵ_{max} 4.11) from the acid, although there is a slight hypsochromic effect.[22] On going from the *N*-methyl-*p*-chlorobenzamide to the corresponding 1-methyl-5-*p*-chlorophenyltetrazole there is a definite bathochromic effect of some 50 Å and a hyperchromic effect of some 3.47 log units. This contrasts with the hypsochromic effect of some 200 Å and a hypochromic shift of some 3.79 log units when the spectrum of the *p*-chloroacetanilide is compared with that of the corresponding 1-*p*-chlorophenyl-5-methyltetrazole.

The evidence presented appears to indicate that the tetrazole ring may interact with an aromatic moiety when the tetrazole ring is substituted by the aromatic moiety in the 5-position. The interaction when the aromatic moiety is in the 1-position appears to be less than the former case and in the compounds studied a second order effect. These conclusions support the results described by Garbrecht and Herbst.[4]

Infrared spectra. Infrared spectra were obtained on both series of amides and the derived tetrazoles. Lieber and co-workers report an extensive series of spectra of tetrazoles.[23] Tetrazole itself was assigned an absorption associated with the ring modes at 9.44 μ; 5-bromotetrazole, 9.36μ; 5-hydrazinotetrazole, 9.43μ and 10.09μ; and 5-aminotetrazole, 9.40μ and 10.04μ. Comparison of the spectra of the amides and tetrazoles of this report are in Table IV. The bands which are absent in the amides but which show up in the tetrazoles are indicated.

TABLE IV

INFRARED ABSORPTION PEAKS ASSIGNED TO THE 1,5-DISUBSTITUTED TETRAZOLES. PEAKS NOT PRESENT IN PARENT AMIDES



Substituents		Absorption Maxima In Microns[a] Nujol Mull			
R_1	R_2				
o-ClC_6H_4	CH_3	*8.35*	9.19	10.27	...
m-ClC_6H_4	CH_3	*8.35*	9.14	10.13	...
p-ClC_6H_4	CH_3	*8.33*	9.15	10.25	...
CH_3	*o*-ClC_6H_4	..	9.17	10.08	*13.97*
CH_3	*m*-ClC_6H_4	..	9.13	10.15	*13.98*
CH_3	*p*-ClC_6H_4	..	9.14	10.17	*14.05*

[a] The bands in *italics* are those which appear unique to the tetrazoles but which are not unassignable to other structures which were masked in the amides.

EXPERIMENTAL[24]

Acetanilides. The *o*-chloro-, *m*-chloro-, and *p*-chloroacetanilides were prepared in a standard fashion from the chloroanilines and acetic anhydride.[25]

N-Methylbenzamides. The *N*-methyl-*o*-chloro-, *N*-methyl-*m*-chloro-, and *N*-methyl-*p*-chlorobenzamides were prepared from the corresponding acid chlorides, distilled under reduced pressure,[25] and methylamine The known acetanilides and benzamides are in Table I.

1,5-Disubstituted tetrazoles. Both series of tetrazoles were made from the corresponding N-substituted amides by the procedure originally described by von Braun and Rudolph[10] and further investigated by Herbst.[11,12] A typical procedure, applicable to either type of amide, is presented for the sake of clarity.

Preparation of 1-methyl-5-(p-chlorophenyl)tetrazole. *N*-Methyl-*p*-chlorobenzamide (35.6 g.; 0.21 mole) was covered with 650 ml. of anhydrous benzene in a 3 necked, round bottomed flask equipped with a stirrer, dry addition port, and condenser with a drying tube and connected to an open T tube to a water aspirator. Phosphorus pentachloride (44.1 g.; 0.212 mole) was added portion-wise with rapid stirring through the dry port. The resulting mixture was stirred for

(21) G. N. Lewis and M. Kasha, *J. Am. Chem. Soc.*, **67**, 992 (1945).

(22) It should be noted that H. Ley and H. Specker, *Ber.*, **7b**, 192 (1939) report other derivatives of benzoic acid which also appear to have a slight hypsochromic effect: benzoic acid (λ_{max} 2280 Å, log ϵ_{max} 4.0),[13] benzamide (λ_{max} 2250 Å, log ϵ_{max} 3.78), *N*,*N*-dimethylbenzamide (λ_{max} 2300 Å, log ϵ_{max} 3.75) (shoulder), and ethyl benzoate (λ_{max} 2300 Å, log ϵ_{max} 4.20).

(23) E. Lieber, D. R., Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(24) Melting points (capillary) corrected. Analysis by Dr. C. S. Yeh and Mrs. S. L. Margerum of this Department. Ultraviolet spectra were obtained with a Cary recording spectrophotometer by Mr. Robert Curry. Infrared spectra by Dr. J. Amy.

(25) P. F. Frankland, S. R. Carter and E. B. Adams, *J. Chem. Soc.*, **101**, 2470 (1915).

1 hr. at room temperature and then for 15 min. at 40°. The mixture was nearly clear at this time. A slight vacuum was applied to remove hydrogen chloride and the resulting solution of the imino chloride was cooled to 15°. A solution of hydrazoic acid (330 ml.; 5.5% or 0.424 mole) was added dropwise from a funnel replacing the dry port. A slight vacuum was maintained on the system to prevent escape of hydrazoic acid to the hood and room. The mixture was stirred at 25° for 2 hr. and under reflux (no vacuum) for 3 hr. The benzene was removed by distillation (under reduced pressure) and the residue treated with 100 ml. of water and sufficient sodium hydroxide to make alkaline (*p*H 8.5). The resulting solid was filtered by suction and washed with water. There was obtained 27.9 g. of crude product, m.p. 113.6–118.6°; on three recrystallizations from benzene the melting point was still not sharp. It was suspected that there was unreacted amide present (in these compounds mixed melting points rarely show depression), and the total crude material was boiled under reflux in 400 ml. of 10% sulfuric acid. This gave a product free of amide, m.p. 118.8–120.3°, from benzene.

In the preparations of the other new tetrazoles similar purifications were followed. The data for these compounds are in Table II.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, ST. VINCENT COLLEGE]

Sterically Hindered Reactions of Grignard Reagents with Schiff Bases

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N-Benzylidene-*tert*-butylamine added methyllithium and allylmagnesium bromide, but not methylmagnesium iodide. Lithium aluminum hydride smoothly reduced *N*-benzylidene-*tert*-butylamine to *N*-*tert*-butylbenzylamine. With allylmagnesium bromide, *N*-benzylidene-*n*-octadecylamine formed *N*-*n*-octadecyl(α-allylbenzyl)amine. *N*-Benzylidenemethylamine reacted with *tert*-butylmagnesium chloride to give *N*-methyl(α-*tert*-butylbenzyl)amine and with *n*-octadecylmagnesium iodide to give *N*-methyl(α-octadecylbenzyl)amine.

Campbell *et al.*[1] treated a number of *N*-benzylidenealkylamines with various alkylmagnesium halides to synthesize *N*-alkyl(α-alkylbenzyl)amines:

$$C_6H_5—CH{:}N—R' + RMgX \longrightarrow C_6H_5—CH(R)—NHR'$$

They found that, when equimolar amounts of Grignard reagent and aldimines were used, satisfactory yields (60–75%) were obtained only with the most reactive Grignard reagents and the simplest Schiff bases. Thus with *N*-benzylidenemethylamine ethylmagnesium bromide gave a 75% yield of *N*-methyl(α-ethylbenzyl)amine, but with *N*-benzylideneethylamine only a 39% yield of *N*-ethyl(α-ethylbenzyl)amine was obtained.

The present work was undertaken to obtain some knowledge of: (1) the effect of bulky alkyl groups in the Schiff base on the reactivity of the C:N; and (2) the steric requirements of the alkyl Grignard reagent. *N*-Benzylidene-*tert*-butylamine was selected as a bulky *N*-alkyl Schiff base, and *tert*-butylmagnesium chloride as a Grignard of high steric requirement.

N-Benzylidene-*tert*-butylamine was prepared by Hurwitz[2] in a 63% yield. However, he recorded no physical constants. Methylmagnesium iodide would not add to this Schiff base even under forcing conditions. This indicates that the steric requirements of the *N*-*tert*-butyl group are appreciable. On the other hand methyllithium did add to give *tert*-butyl(α-methylbenzyl)amine. Organolithium compounds are known to be much more reactive than the corresponding Grignard reagents.[3]

The failure of methylmagnesium iodide to react with *N*-benzylidene-*tert*-butylamine prompted an attempt to add allylmagnesium bromide. Gilman and Eisch[4] found that this latter Grignard reagent added in a 1,2-manner to aromatic ketimines having high steric requirements. In line with Gilman's observation we found that allylmagnesium bromide gave good yields of *N*-*tert*-butyl(α-allylbenzyl)-amine. The reactivity of this Grignard reagent as compared to that of methylmagnesium iodide seems to confirm Gilman's view that the mechanism of this 1,2-addition to the azomethine linkage proceeds by a nucleophilic attack of the allyl anion on the positively polarized carbon atom adjacent to the nitrogen in the Schiff base. The reactivity of allylmagnesium bromide was also shown by its addition to the high molecular weight *N*-benzylidene-*n*-octadecylamine to form *N*-octadecyl(α-allylbenzyl)amine.

N-Benzylidenemethylamine was used to test the reactivity of *tert*-butylmagnesium chloride. During the progress of this work Thies and Schoenenberger[5] carried out the same reaction but were unable to isolate any product from addition. They obtained only starting material and the dimer of the Schiff base, *N*,*N*'-dimethyl-1,2-diphenylethylenediamine. In this work the 1,2-addition product,

(1) K. N. Campbell, C. H. Helbing, M. P. Florkowski, and B. K. Campbell, *J. Am. Chem. Soc.*, **70**, 3868 (1948).

(2) M. D. Hurwitz, U. S. Patent **2,582,128**, (Jan. 8, 1952); *Chem. Abstr.*, **46**, 8146 (1952).

(3) H. Gilman and R. H. Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

(4) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **79**, 2150 (1957).

(5) H. Thies and H. Schoenenberger, *Arch. Pharm.*, **289**, 408 (1956).

TABLE I

N-ALKYL(*α*-ALKYLBENZYL)AMINES, (C_6H_5—CH(R)—NHR')

R—	R'—	B. P., °C./mm. Hg	Yield, %	n_D^{25}	d_4^{25}	% N Calcd.	% N Found	Amine Hydrochloride M. P., °C.	Amine Hydrochloride % N Calcd.	Amine Hydrochloride % N Found
CH_3	*t*-C_4H_9	93/14	26	1.4896	0.884	7.91	7.96	240	6.55	6.59
H	*t*-C_4H_9	109–110/25	63	1.4942	0.899	8.58	8.57	245–247[a]	7.00	7.00
C_3H_5	*t*-C_4H_9	87–88/3	45	1.4954	0.888	6.89	6.94	186–187	5.85	5.87
C_3H_5	*n*-$C_{18}H_{37}$	27–29[b]	48			3.51	3.53[c]	124–126.5	3.22	3.20
t-C_4H_9	CH_3	92–92.5/10	22	1.5014	0.905	7.90	8.01	314–315	6.56	6.51
n-$C_{18}H_{37}$	CH_3	34.5–35[b]	11			3.75	3.78	118.5–119	3.42	3.40

[a] Recrystallized from 1–3 *n*-butyl alcohol–ethyl acetate. A. Einhorn and H. Pfeiffer [*Ann.*, **310**, 225 (1900)] report a melting point of 228°. [b] Melting point. [c] Material analyzed melted at 22–26°.

N-methyl(*α*-*tert*-butylbenzyl)amine was isolated in a 22% yield.

The facile tendency of *N*-benzylidenemethylamine to undergo addition was also demonstrated by the additon of *n*-octadecylmagnesium iodide to give *N*-methyl(*α*-*n*-octadecylbenzyl)amine in fair to good yields.

Gilman, Kirby, and Kinney[6] reported a case of 1,4-addition of phenylmagnesium bromide to *N*-diphenylmethyleneaniline under conditions involving high temperature and a long period of heating. To show that substitution did not occur in the ortho position of the benzene ring of our Schiff bases, we oxidized the addition products from: (1) *tert*-butylmagnesium chloride and *N*-benzylidenemethylamine; (2) methyllithium and *N*-benzylidene-*tert*-butylamine; and (3) allylmagnesium bromide and *N*-benzylidene-*tert*-butylamine. In all cases benzoic acid was obtained showing that there was only one substituent on the benzene ring.

In connection with this work a new Schiff base, *N*-benzylidene-*n*-octadecylamine, and five new secondary amines (Table I) have been characterized.

EXPERIMENTAL[7]

N-Benzylidene-tert-butylamine. To 30.0 g. of redistilled *tert*-butylamine (Eastman Grade) was added 44.5 g. of freshly distilled benzaldehyde at 2–3°. Stirring was continued for 30 min., and the reaction was allowed to stand 2 days over a few grams of sodium hydroxide. The aqueous layer which formed was removed and extracted with ether. The ether extract was added to the water-insoluble material and dried over potassium hydroxide. After removal of the ether, the product was distilled to give 60.0 g. (90%): b.p. 92°/8 mm., n_D^{25} 1.5179, d_4^{25} 0.904.

The procedure described by Freeman[8] was used to determine quantitatively the Schiff base as benzaldehyde 2,4-dinitrophenylhydrazone. Milliequivalents used: 1.074, 0.941. Found: 1.060, 0.940.

Methylmagnesium iodide and benzylidene-tert-butylamine. To the Grignard reagent prepared from 24.0 g. of magnesium and 125 g. of methyl iodide was added dropwise 43.0 g. of benzylidene-*tert*-butylamine (b.p. 110–112°/29 mm.) dissolved in an equal volume of ether, over a period of 20 min. The mixture was refluxed for 2 hr. It was hydrolyzed with ice. On acidification with concentrated hydrochloric acid a yellow solid formed, which was filtered off and added to a solution of 10 g. of concentrated hydrochloric acid in 100 ml. of water. The two liquid layers which formed overnight were separated. The organic layer yielded 9.7 g. of benzaldehyde: b.p. 60°/10 mm., $n_D^{17.6}$ 1.5461; oxidation product, m.p. 122–123°. The water layer was evaporated. It yielded a solid which after washing with ether weighed 18.6 g. Part of the solid was redissolved in water, filtered, and the filtrate made basic with sodium hydroxide and extracted with ether. On treatment with hydrogen chloride gas, the dried ether solution precipitated a white solid. The solid was filtered and treated with concentrated sodium hydroxide in contact with ligroin. Phenyl isothiocyanate was added to the dried ligroin solution. The precipitate which formed melted at 122–123°. Mixture m.p. with 1-phenyl-3-*tert*-butylthiourea prepared in ligroin from *tert*-butylamine and phenyl isothiocyanate, 122–124°.

The filtrate from the original Grignard mixture, consisting of an ether and a water phase, was next worked up. The ether was separated, dried over anhydrous magnesium sulfate, and then distilled yielding 6 g. of benzaldehyde, b.p. 83–85°/30 mm. It was identified as its air oxidation product, benzoic acid, m.p. 118–119°, and its 2,4-dinitrophenylhydrazone, m.p. 239–240°.

The water phase from the Grignard was made strongly basic with ammonium hydroxide and some ammonium chloride added to dissolve magnesium hydroxide. Extraction with ether and subsequent distillation gave 2.1 g. of unreacted *N*-benzylidene-*tert*-butylamine, determined as benzaldehyde-2,4-dinitrophenylhydrazone.[8] Milliequivalents used: 0.980. Found: 1.00

In another run when the Grignard reaction was forced in dry toluene at 100° for 2 hr. the same yellow solid was obtained. No addition product was isolated.

Lithium aluminum hydride and N-benzylidene-tert-butylamine. The reaction was carried out according to the procedure of Nystrom and Brown.[9] Lithium aluminum hydride (9.5 g., 0.25 mole) was dissolved in 400 ml. of ether. Forty grams (0.25 mole) of *N*-benzylidene-*tert*-butylamine was added dropwise in 35 min. The mixture was refluxed 4.5 hr. and then allowed to stand for 2 hr. It was hydrolyzed in the usual manner. The ether layer was separated and dried over anhydrous magnesium sulfate. After removal of the ether, the product distilled to give 32.5 g. (80%): b.p. 109–109.5°/23 mm., n_D^{25} 1.4956. This contained about 5% unreacted Schiff base which was removed by refluxing 0.5 hr. with dilute hydrochloric acid, washing with ether, making basic with sodium hydroxide, and extracting the amine with

(6) H. Gilman, J. E. Kirby, and C. R. Kinney, *J. Am. Chem. Soc.*, **51**, 2252 (1929).

(7) The boiling points and melting points reported in this work are uncorrected. Those reported in Table I were taken with 76 mm. immersion thermometers.

(8) S. K. Freeman, *Anal. Chem.*, **25**, 1750 (1953).

(9) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

ether. After drying, distillation gave 25.6 g. of pure amine, n_D^{25} 1.4942.

Methyllithium and N-benzylidene-tert-butylamine. An ether solution of 0.43 mole of methyllithium prepared by the procedure of Tegner[10] was added dropwise under nitrogen with stirring to 28.4 g. (0.177 mole) of freshly distilled benzylidene-*tert*-butylamine dissolved in 75 ml. of ether. The reaction mixture was refluxed for 10.5 hr., and then poured into 250 g. of ice. The organic layer was extracted with ether, dried over anhydrous magnesium sulfate, and distilled to give: 23 g., b.p. 88–90°/11 mm., n_D^{25} 1.4950. After removing unreacted Schiff base by acid hydrolysis, as described in the reduction with lithium aluminum hydride, distillation gave 8.0 g., n_D^{25} 1.4896.

The hydrochloride was prepared by passing dry hydrogen chloride into an ether solution of the amine. It was recrystallized from an equal mixture of ligroin (b.p. 90–100°) and butyl alcohol, m.p. 240°. Oxidation of the amine with sodium dichromate and sulfuric acid gave a poor yield of benzoic acid, m.p. and mixture m.p. 123–124°.

Allylmagnesium bromide and N-benzylidene-tert-butylamine. Fifty-three grams (0.330 mole) of *N*-benzylidene-*tert*-butylamine dissolved in an equal volume of ether was added dropwise to 0.385 mole of allylmagnesium bromide prepared as described by Mikulasova, Hrivik, and Simek.[11] The reaction mixture was refluxed for 2 hr. and then allowed to stand sealed for 19 hr. It was hydrolyzed with ice and then acidified with hydrochloric acid. A white solid formed which was filtered off 2 days later and dried. After washing with ether, 52.5 g. was obtained, m.p. 182–183°. Recrystallization from equal volumes of ligroin (90–120) and butyl alcohol gave 44.0 g. (56%): m.p. 186–187°. Further recrystallization did not change the melting point.

To obtain the free amine 44 g. of the *N-tert*-butyl(α-allylbenzyl)amine was added to 200 ml. of a 6% solution of sodium hydroxide and allowed to stand overnight. The organic layer was taken up with ether, dried over anhydrous magnesium sulfate, and distilled, yielding 30 g. of a colorless liquid: b.p. 87–88°/3 mm. The product gave no precipitate when tested with a 2*N* hydrochloric acid solution of 2,4-dinitrophenylhydrazine.

One gram of the distillate was oxidized with alkaline permanganate[12] and yielded 0.11 g. benzoic acid, m.p. 121.5–122.5°.

N-Benzylidene-n-octadecylamine. To a filtered solution of 23.4 g. of *n*-octadecylamine[13] in 200 ml. of methanol was added slowly, at 60°, 20.0 g. of benzaldehyde which had been previously washed with sodium carbonate solution. The mixture was permitted to cool slowly to room temperature and then kept at 5° for 4 hr. The solid which separated was filtered and washed with a little cold methanol, yield 27.5 g., m.p. 35.5–37°. Recrystallization from 500 ml. of methanol gave 23.5 g. of *N*-benzylidene-*n*-octadecylamine, m.p. 36–37°.

Anal. Calcd. for $C_{25}H_{43}N$: N, 3.91%. Found: N, 3.95%.

Allylmagnesium bromide and N-benzylidene-n-octadecylamine. Allylmagnesium bromide was prepared as indicated for the preparation of *N-tert*-butyl(α-allylbenzyl)amine, 36.3 g. of allyl bromide being used. To this was added, in 45 min., 21 g. of *N*-benzylidene-*n*-octadecylamine dissolved in 100 ml. of ether. The reaction mixture was refluxed 2 hr. and then allowed to stand overnight. The solid obtained by acid hydrolysis was filtered, dried, washed thoroughly with ether, and after two recrystallizations from a mixture of equal volumes of ligroin (90–120) and butyl alcohol weighed 19 g. (74%): m.p. 117–120°.

Conversion, in the usual manner, of the hydrochloride to the free amine gave a reddish liquid, which was crystallized by dissolving in methanol, and prolonged cooling. The filtered crystals, after drying in a vacuum desiccator, melted at 22–26°. Another recrystallization raised the melting point to 27–29°, yield 11.4 g. Dry hydrogen chloride was passed into an ether solution of the recrystallized amine to reconvert it to *N*-*n*-octadecyl(α-allylbenyl)amine hydrochloride, m.p. 124–126.5° after one recrystallization.

tert-Butylmagnesium chloride and N-benzylidenemethylamine. tert-Butylmagnesium chloride was prepared by a standard procedure.[14] Two moles (185 g.) of *tert*-butyl chloride was used. Addition of the initial batch of halide should be made cautiously. To the *tert*-butylmagnesium chloride, 60.0 g. (0.50 mole) of *N*-benzylidenemethylamine (b.p. 64–64.5°/8 mm.) was added in 0.5 hr. About 650 ml. of dry toluene was then added, and the ether was distilled off until the temperature of the reaction mixture reached 95°. It was maintained at this temperature and stirred for 1 hr. It was then cooled, sealed, and allowed to stand overnight. It was hydrolyzed with ice, made acidic with hydrochloric acid, and allowed to stand for 2 days to hydrolyze unreacted Schiff base. The ether-toluene layer was then separated, and the acid layer made basic with concentrated ammonium hydroxide. Solid ammonium chloride was added until most of the solid dissolved and the amine was extracted with ether. The ether layer was dried over solid potassium hydroxide and then distilled, yielding 24 g. of a colorless liquid, b.p. 53–70°/1 mm. The distillate residue solidified overnight. After washing with ether it melted at 132–134°. At the melting point it sublimed. The sublimate melted at 133°. This was probably *N*,*N*′-dimethyl-1,2-diphenylethylenediamine. Thies and Schoenenberger[5] recorded a melting point of 135° for this compound.

The distillate (b.p. 53–70°/1 mm.) was dissolved in ether and treated with dry hydrogen chloride to give 27.5 g. of a white solid, which after recrystallization from a solution of equal volumes of ligroin (90–120) and butyl alcohol melted at 314–315°. The nitrogen content (Table I) corresponded to that of *N*-methyl(α-*tert*-butylbenzyl)amine hydrochloride. Conversion, in the usual way, to the free amine gave 19.4 g. of *N*-methyl(α-*tert*-butylbenzyl)amine. Alkaline permanganate oxidation[12] of the amine gave, after 5 hr. refluxing with vigorous stirring, 0.2 g. of benzoic acid, which after recrystallization from water had a m.p. and mixture m.p. of 122–123°. No phthalic acid was produced in the oxidation.

When the Grignard reaction was not forced a slightly lower yield (14%) of the pure amine was obtained.

n-Octadecylmagnesium iodide and N-benzylidenemethylamine. This reaction was conducted several times. The results are considered anomalous because of unexplainable variations in the yields. The following run is described as typical.

n-Octadecyl iodide was prepared by a published procedure.[15] In a 1-l. three-neck flask equipped in the usual manner for Grignard preparations were placed 20 g. (0.83 g.-atom) of magnesium turnings and 120 g. of ethyl ether. A few crystals of iodine and about 0.5 ml. of methyl iodide were used to start the reaction. Sixty grams (0.158 mole) of *n*-octadecyl iodide dissolved in 200 g. of ether was added over a period of 4 hr. The reaction mixture was stirred for an additional 0.5 hr., and then 15 g. (0.126 mole) of *N*-benzylidenemethylamine dissolved in an equal volume of ether was added in 0.5 hr. while the reaction mixture was maintained at 32°. The product was then refluxed for 2 hr., after which the reaction flask was tightly corked and allowed to stand overnight. Hydrolysis and acidification with hydrochloric acid yielded a solid which was filtered from the ether-water

(10) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(11) D. Mikulasova, A. Hrivik, and I. Simek, *Chem. zvesti*, **10**, 622 (1956); *Chem. Abstr.*, **51**, 8002 (1957).

(12) B. L. Emling, J. E. Beatty, and J. R. Stevens, *J. Am. Chem. Soc.*, **71**, 703 (1949).

(13) Armeen 18D, supplied through the courtesy of Armour and Co.

(14) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York (1954), pp. 26, 27.

(15) C. A. Kind and W. Bergman, *J. Org. Chem.*, **7**, 424 (1942).

mixture. The ether was separated and preserved. The solid was washed thoroughly with dilute hydrochloric acid and then with water. It was dried and then shaken with ether for 40 min. The ether was added to that from the hydrolysis mixture. The solid was next washed twice with ligroin (60–90) and after drying weighed 14.6 g., m.p. 101–104°. Two recrystallizations from ethanol gave 7.5 g. (14.6%) of *N*-methyl(α-*n*-octadecylbenzyl)amine hydrochloride, m.p. 115–117.5°. Yields from several additional runs varied greatly, the two largest being 55% (m.p. 118–118.5°) and 48% (m.p. 118.5–119°).

In the run described the ether phase on evaporation gave 17.6 g. of octadecane, which on recrystallization from ethanol melted at 25–26°. The ligroin on partial evaporation and cooling gave 4.7 g. of hexatriacontane, m.p. 73–76°.

N-Methyl(α-*n*-octadecylbenzyl)amine hydrochloride (10 g.) was converted to the free amine by refluxing with an excess of 15% sodium hydroxide, extraction of the cold mixture with ether, and subsequent evaporation of the ether; yield 7.3 g. This was dissolved in methanol, filtered, and the methanol removed under vacuum to give 6.8 g.: m.p. 34.5–35°.

LATROBE, PA.

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

Alkylation of Acylhydrazines. The Synthesis of Trimethylamine-benzimide

R. L. HINMAN[1] AND MINERVA C. FLORES[2]

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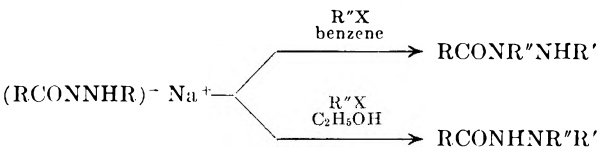
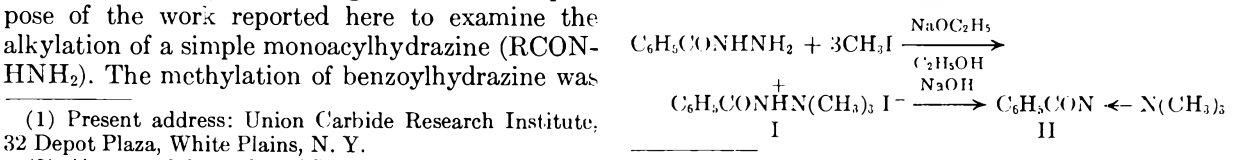
Trimethylamine-benzimide has been prepared from benzoylhydrazine and from 1-benzoyl-2,2-dimethylhydrazine by reaction with methyl iodide in the presence of sodium ethoxide. Under similar conditions 1-isonicotinyl-2,2-dimethylhydrazine was converted to trimethylamine-isonicotinimide, rather than 1-isonicotinyl-1,2,2-trimethylhydrazine, as previously reported. The reaction of benzoylhydrazine with *n*-propyl bromide, however, yielded only 1-benzoyl-2,2-di-*n*-propylhydrazine. Treatment of benzoylhydrazine with sodium in benzene, followed by methyl iodide, produced a small quantity of 1-benzoyl-1-methylhydrazine. A similar procedure converted 1-benzoyl-2,2-dimethylhydrazine to trimethylamine-benzimide.

Previous investigations of the alkylation of acylhydrazines have revealed that alkylation of the salt of a monoacylhydrazine in a nonpolar solvent such as ether or benzene takes place on the acylated nitrogen.[3] When alkylation is carried out in ethanol, the alkyl groups are introduced on the unacylated nitrogen.[3a,c,4] Treatment of the



acylhydrazine itself with alkylating agents in neutral solvents effects alkylation of the unacylated nitrogen[5], in accord with the electron-withdrawing properties of the acyl group. Although this pattern of behavior appears to be fairly general, the acylhydrazines studied have generally borne a substituent on the unacylated nitrogen. It was the purpose of the work reported here to examine the alkylation of a simple monoacylhydrazine ($RCONHNH_2$). The methylation of benzoylhydrazine was selected since the likely products are all known, easily accessible compounds.

From the reaction of an ethanolic solution of benzoylhydrazine, sodium ethoxide, and methyl iodide (mole ratio 1:2:2, respectively) an acidic product (I), containing ionic iodine, was isolated. Compound I was converted to the free base (II) by dissolving it in sodium hydroxide and extracting with chloroform. Analysis of the basic material and its hydriodide showed that three methyl groups had been introduced. Although the composition of 1-benzoyl-1,2,2-trimethylhydrazine agrees with the analytical data, from the high melting point[6] of II (167–169°) and the marked acidity of its hydriodide (decomposes bicarbonate) we inferred that the product of the reaction of benzoylhydrazine and methyl iodide in the presence of two moles of sodium ethoxide is the hydriodide of trimethylamine-benzimide (I), which is converted by base to trimethylamine-benzimide (II)[7]. Verifi-



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(2) Abstracted from the M.S. thesis submitted by Minerva C. Flores to the Graduate College of the State University of Iowa, August 1957.

(3) (a) P. C. Freer and P. L. Sherman, *J. Am. Chem. Soc.*, **18**, 574 (1896); (b) C. D. Harries, *Ber.*, **27**, 697 (1894); (c) W. Stühmer and E. A. Elbrachter, *Arch. Pharm.*, **285**, 161 (1952).

(4) K. von Auwers and G. Wegener, *J. prakt. Chem.*, (2), **102**, 243 (1923).

(5) See for example: R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).

(6) A survey of the literature has revealed that substitution of an alkyl group for a hydrogen on the acylated nitrogen of an acylhydrazine is generally accompanied by a marked decrease in melting point. Thus, benzoylhydrazine melts at 112°, whereas 1-benzoyl-1-methylhydrazine is an oil. It would be expected that 1-benzoyl-1,2,2-trimethylhydrazine would melt below 106°, the m.p. of 1-benzoyl-2,2-dimethylhydrazine.

(7) For an explanation of the nomenclature of compounds of this type see H. H. Sisler, G. M. Omietanski, and B. Rudner, *Chem. Revs.*, **57**, 1021 (1957).

cation of this hypothesis was obtained by hydrogenolysis of the nitrogen-nitrogen bond by Raney nickel in ethanol. From both the hydriodide and the free base benzamide was obtained. In addition trimethylamine was obtained from the cleavage of II. The best conditions found to date for the prep-

$$C_6H_5CON \leftarrow N(CH_3)_3 \xrightarrow[C_2H_5OH]{Ni} C_6H_5CONH_2 + N(CH_3)_3$$
II

aration of II from benzoylhydrazine require a reaction time of 10 hr., and a molar ratio of benzoyl hydrazine, sodium ethoxide, and methyl iodide of 1:2:4, respectively. The relative quantity of sodium ethoxide is particularly critical. With a mole ratio of benzoylhydrazine, sodium ethoxide, and methyl iodide of 1:2:2, respectively, the yield of I was 36%. When the ratio was 1:1:2, respectively, the yield of I was only 8%. Since the alkylation of benzoylhydrazine undoubtedly occurs in a stepwise fashion, the sodium ethoxide must be consumed in removing a proton after each step of the alkylation (Equation 1). When only one mole of base is present per mole

$$\begin{array}{l} C_6H_5CONHNH_2 \longrightarrow C_6H_5CO\overset{+}{N}HNH_2CH_3\ I^- \\ \qquad\qquad\qquad\qquad\qquad\qquad \downarrow :B^- \\ I^-\ C_6H_5CO\overset{+}{N}HNH(CH_3)_2 \leftarrow C_6H_5CONHNHCH_3 + \\ \qquad\qquad\qquad\qquad\qquad\qquad BH + I^- \quad (1) \\ \qquad \downarrow :B^- \\ \qquad \text{etc.} \end{array}$$

of benzoylhydrazine, the principal reaction probably stops when 1-benzoyl-2,2-dimethylhydrazinium iodide is formed. Conversion of a small quantity of the last compound to 1-benzoyl-2,2-dimethylhydrazine by reaction of the hydriodide with sodium ethoxide before the latter is exhausted would account for the formation of the small amount of trimethylamine-benzimide which was isolated.

Benzoylhydrazine itself must also be capable of acting as the base in Equation 1, since 1-benzoyl-2,2-dimethylhydrazine was isolated in 8% yield from the alkylation of benzoylhydrazine in neutral solution. Thirty-two percent of the starting material was recovered. Since the reaction time was twenty-four hours, and a large excess of methyl iodide was used, it is unlikely that the recovered benzoylhydrazine simply did not undergo alkylation. More likely it was converted to its salt by proton-abstraction from alkylated molecules, and was thereby prevented from undergoing alkylation itself.

As would be expected, 1-benzoyl-2,2-dimethylhydrazine was converted by methyl iodide to 1-benzoyl-2,2,2-trimethylhydrazinium iodide by simply refluxing an alcoholic mixture of the two reagents. The use of 1 mole of sodium ethoxide per mole of 1-benzoyl-2,2-dimethylhydrazine and an excess of methyl iodide produced trimethylamine-benzimide directly.

Recently reported results of the alkylation of 1-isonicotinyl-2,2-dimethylhydrazine conflict with the results reported here for the reaction of 1-benzoyl-2,2-dimethylhydrazine. It has been claimed[8] that the reaction of methyl iodide with 1-isonicotinyl-2,2-dimethylhydrazine in the presence of sodium ethoxide yields 1-isonicotinyl-1,2,2-trimethylhydrazine. No proof of structure was given.

$$C_5H_5NCONHN(CH_3)_2 \xrightarrow[NaOC_2H_5]{CH_3I} C_5H_5NCON(CH_3)N(CH_3)_2$$

The fact that the melting point of the product (191.5–193.5°) is much higher than that of the starting material (120–121°)[9] raises considerable doubt about the position of the newly introduced methyl group.[6] The methylation of 1-isonicotinyl-2,2-dimethylhydrazine was therefore repeated according to the original directions, and the compound of m.p. 191.5–193.5° was obtained. Hydrogenolysis of this material with Raney nickel yielded isonicotinamide and trimethylamine, proving that the product of the methylation of 1-isonicotinyl-2,2-dimethylhydrazine is actually trimethylamine-isonicotinimide (IV).

$$C_5H_5NCONHN(CH_3)_2 \xrightarrow[NaOC_2H_5]{CH_3I} C_5H_5NCON \leftarrow N(CH_3)_3 \quad IV$$

Other compounds prepared by alkylation of 1-isonicotinyl - 2,2 - dimethylhydrazine with higher alkyl halides were assumed by the same authors to have the structures of 1-isonicotinyl-1,2,2-trialkylhydrazines. From the present work, however, it seems likely that some, if not all, of these compounds are of the amine-imide type. The water-solubility of the compound described as 1-isonicotinyl-1-benzyl-2,2-dimethylhydrazine is more in accord with an amine-imide structure. Until a conclusive proof of structure has been carried out, the structures of this series of compounds will remain in doubt.

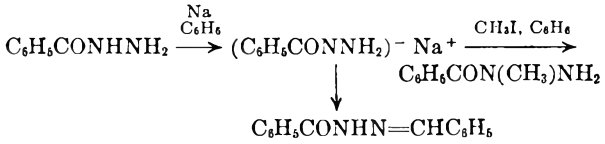
In exploring the scope of the conversion of benzoylhydrazines to amine-imides, the reaction of benzoylhydrazine and *n*-propyl bromide was investigated. Even with a mole ratio of 1:2:6 (acylhydrazine: base: alkyl halide) the only product isolated was 1-benzoyl-2,2-di-*n*-propylhydrazine.[10] No reaction occurred when 1-benzoyl-2,2-di-*n*-propylhydrazine was refluxed with ethanolic solutions of *n*-propyl bromide or methyl iodide. The formation of trialkylamine-benzimides or their hydrohalides under the conditions used in this study is therefore limited to the reactions of benzoylhydrazines bearing small alkyl groups in the dialkyl stage of alkylation.[11]

(8) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **21**, 356 (1956).

(9) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **20**, 60 (1955).

The trialkylamine-benzimides prepared in this investigation represent the first examples of amine-imides in which one nitrogen bears a simple acyl group. Previously reported examples have borne the tosyl group and various other substituents.[7]

We turned our attention next to the reaction of methyl iodide with the sodium salt of benzoylhydrazine in benzene. Using a mole ratio of benzoylhydrazine, sodium and methyl iodide of 1:1:1, a large part of the sodium salt of benzoylhydrazine was recovered unreacted. The products consisted of a small quantity of 1-benzoyl-1-methylhydrazine and a larger amount of a neutral solid, which proved to be 1-benzoyl-2-benzylidenehydrazine.[12]



From this result it was expected that 1-benzoyl-1,2,2-trimethylhydrazine would be formed from 1-benzoyl-2,2-dimethylhydrazine, when the latter was refluxed with sodium and then treated with methyl iodide. However, trimethylamine-benzimide was isolated in this case.

The results obtained in this study support the general observation that alkylation of an acylhydrazine in neutral solution takes place on the unacylated nitrogen. In the presence of sodium ethoxide in ethanol alkylation of an acylhydrazine also takes place on the unacylated nitrogen. When the salt of the acylhydrazine is formed in an inert solvent and alkylated therein, alkylation *may* take place on the nitrogen which bears the acyl group. Since salts are presumably formed under both of the last two sets of conditions,[10,13] the difference in the products may be due to incomplete conversion of the acylhydrazine to its salt in ethanolic sodium ethoxide with the result that it is actually the unreacted acylhydrazine which undergoes alkylation. Hydrolysis of salts of this type in ethanol has been reported.[13a,b]

EXPERIMENTAL[14]

Reaction of benzoylhydrazine and methyl iodide in the presence of sodium ethoxide. A solution of methyl iodide (56.8 g., 0.4 mole) in 25 ml. of absolute ethanol was added to a stirred solution of 4.6 g. (0.2 mole) of sodium and 13.6 g. (0.1 mole) of benzoylhydrazine in 140 ml. of absolute ethanol (previously dried with sodium and diethyl phthalate). Initially, the solution was a deep yellow, but after 10 hr. of refluxing the color was pale yellow, and the *p*H was 4–5. The stirred reaction mixture was then cooled until a white crystalline precipitate was deposited. The filtered solid weighed 15.0 g. (49%) and melted at 187–189° (dec.). Three crystallizations from absolute ethanol gave an analytical sample, m.p. 194–196° (dec.), which gave a yellow precipitate with aqueous silver nitrate, decomposed aqueous sodium bicarbonate, and had the composition of 1-benzoyl-2,2,2-trimethylhydrazinium iodide.

Anal. Calcd. for $C_{10}H_{15}N_2OI$: C, 39.21; H, 4.90; N, 9.01. Found: C, 39.13; H, 5.03; N, 9.08.

Trimethylamine-benzimide. The procedure above was repeated, but in working up the reaction mixture the solvent was distilled under reduced pressure. The residue from the distillation was made basic with 6*N* sodium hydroxide and extracted with chloroform. After the combined extracts had been dried over magnesium sulfate, the solvent was removed under reduced pressure and *n*-pentane was added to the residue. The white crystals which formed were collected on a filter. Recrystallization from a mixture of chloroform and *n*-pentane provided an analytical sample, m.p. 168–169°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.72. Found: C, 67.15; H, 7.85; N, 15.07.

Trimethylamine-benzimide was also obtained when a sample of 1-benzoyl-2,2,2-trimethylhydrazinium iodide was treated with 6*N* sodium hydroxide and the solution then extracted with chloroform. Evaporation of the chloroform left the product as a crystalline residue.

Hydrogenolysis of trimethylamine-benzimide. A mixture of 0.6 g. of trimethylamine-benzimide, 10 g. of Raney nickel, and 50 ml. of absolute ethanol was refluxed with vigorous stirring for 3 hr.[15] The liberated gas was entrained with nitrogen and passed through a solution of hydrochloric acid. The Raney nickel was collected on a filter and the alcoholic

(10) It has been reported [D. Liberman, F. Grumbach, and N. Rist, *Compt. rend.*, **237**, 338 (1953)] that the reaction of benzoylhydrazine and *n*-propyl bromide in the presence of sodium ethoxide yields a product with one alkyl group on oxygen and one on the terminal nitrogen ($C_6H_5C(OPr)=NNHPr$). However, the infrared spectrum of the product shows the two characteristic bands of a secondary amide in the carbonyl region, where it is almost identical with the spectrum of 1-benzoyl-2,2-dimethylhydrazine. It seems certain that both propyl groups are attached to the terminal nitrogen. Similar structures bearing alkyl groups on oxygen and nitrogen, proposed for the products of alkylations of isonicotinylhydrazine, have been refuted by Fox and Gibas [*J. Org. Chem.*, **21**, 349 (1956)], who also showed that both alkyl groups are attached to the terminal nitrogen.

(11) Our experiments also suggest that if two alkyl groups are small, a larger, third one can be introduced. Thus, 1-benzoyl-2,2-dimethylhydrazine reacted with *n*-propyl bromide, yielding a product which had the characteristics of an amine-imide hydrobromide, *i.e.* it contained ionic bromine, was sufficiently acidic to decompose bicarbonate, and was converted to a bromine-free compound on treatment with base. Neither the hydrobromide nor the supposed free base could be purified sufficiently for analysis, however, and the study was terminated without a satisfactory structure proof.

(12) 1-Benzoyl-2-benzylidenehydrazine may have been formed in a manner similar to the well known MacFayden-Stevens synthesis of aldehydes from 1-acyl-2-sulfonylhydrazines; *i.e.* during the reaction with sodium, part of the benzoylhydrazine was converted to benzaldehyde or an equivalent fragment, which then reacted with more benzoylhydrazine to give the hydrazone. The last substance has been isolated on other occasions from reactions of benzoylhydrazine under alkaline conditions: see for example, Th. Curtius, *Ber.*, **33**, 2560 (1900); Th. Curtius and R. Mels-bach, *J. prakt. Chem.*, [2], **81**, 505 (1901). In this laboratory 1-benzoyl-2-benzylidenehydrazine was obtained in low yield from the attempted reduction of benzoylhydrazine with lithium aluminum hydride.

(13) (a) Th. Curtius and G. Struve, *J. prakt. Chem.* [2], **50**, 295 (1894); (b) Th. Curtius and O. Trachmann, *J. prakt. Chem.*, [4], **51**, 165 (1895).

(14) Melting points are uncorrected.

(15) R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).

filtrate evaporated to dryness. After recrystallization from water the residue melted at 126–127°, and did not depress the m.p. of an authentic sample of benzamide. The yield was 0.21 g. (51%). The hydrochloric acid solution was also evaporated to dryness. The residue was recrystallized from a mixture of absolute ethanol and ether, and then melted at 276–278° (dec.). It did not depress the m.p. of an authentic sample of trimethylamine hydrochloride.

Hydrogenolysis of 1-benzoyl-2,2,2-trimethylhydrazinium iodide. The procedure used for the hydrogenolysis of trimethylamine-benzimide was employed and an 88% yield of benzamide was obtained.

Reaction of benzoylhydrazine, sodium, and methyl iodide in benzene. A mixture of 13.6 g. (0.1 mole) of benzoylhydrazine, 2.3 g. (0.1 mole) of sodium, and 150 ml. of dry benzene was refluxed with vigorous stirring until the sodium had disappeared (about 48 hr.). A creamy, water-soluble precipitate formed. After the mixture had been cooled, 14.2 g. (0.1 mole) of methyl iodide in 30 ml. of benzene was added and stirring was continued for 15 min. more. The mixture was filtered and the filtrate was evaporated to dryness, giving approximately 0.5 g. of an oil (A) which was shown to be 1-benzoyl-1-methylhydrazine (see below). The filtered solid (B), which melted above 300°, was partially soluble in water, giving a basic solution. Neutralization of this solution with hydrochloric acid produced a creamy, water-insoluble precipitate (C), which melted at 204–206°. Compound C was also obtained by recrystallization of B from an acetic acid–water mixture. The melting point of an authentic sample of the benzoylhydrazone of benzaldehyde (m.p. 206°[16]) when mixed with compound C showed no depression. The solid (B), isolated by filtration of the original reaction mixture, was therefore the sodium salt of 1-benzoyl-2-benzylidenehydrazine. The over-all yield of the hydrazone (C) was 4.5 g. (40%).

p-Nitrobenzaldehyde (0.2 g.), was added to approximately 0.2 g. of the oil (A) obtained in the previous experiment in 7 ml. of glacial acetic acid. The homogeneous mixture was heated to boiling and after cooling, crystallization was induced by addition of water. The crystals, which were collected on a filter, melted at 172–174°. A mixed melting point with an authentic sample of the 1-benzoyl-1-methylhydrazone of *p*-nitrobenzaldehyde (reported m.p. 172–173°[17]) showed no depression.

The reaction of benzoylhydrazine and methyl iodide in neutral solution. A solution of benzoylhydrazine (6.8 g., 0.05 mole) in 10 ml. of absolute ethanol and 71 g. (0.5 mole) of methyl iodide was refluxed for 24 hr. At the end of this period, the acidic solution (*p*H 1–2) was concentrated under reduced pressure. The residue was a dark oil which partially crystallized on standing. The crystals were collected by filtration, and the filtrate (A) was set aside. The crystals, m.p. 185–187°, were water-soluble and the water solution gave a positive test for iodide with silver nitrate. This compound, which was apparently 1-benzoyl-2,2-dimethylhydrazinium iodide, was treated with 6*N* sodium hydroxide and the solution was extracted with chloroform; upon evaporation of the solvent a white crystalline product was obtained, m.p. 99–103°, which did not depress the melting point of an authentic sample of 1-benzoyl-2,2-dimethylhydrazine. The yield was 0.65 g. (8%). The hydrochloride of the product was prepared and it did not depress the melting point of an authentic sample of 1-benzoyl-2,2-dimethylhydrazinium chloride (see below). From the residual dark oil (filtrate A) benzoylhydrazine (2.2 g., 32%) was recovered by neutralization with 6*N* sodium hydroxide and extraction with chloroform.

When the above procedure was repeated without the addition of absolute ethanol, the yield of 1-benzoyl-2,2-dimethylhydrazine was 0.6 g. (7%).

1-Benzoyl-2,2-dimethylhydrazinium chloride. Hydrogen chloride was bubbled through a solution of 0.5 g. of 1-benzoyl-2,2-dimethylhydrazine in 23 ml. of chloroform for 30 min. After evaporation of the solvent on a steam bath, the solid residue was recrystallized from a mixture of chloroform and *n*-hexane to provide an analytical sample, m.p. 187–188° (dec.).

Anal. Calcd. for $C_9H_{13}N_2OCl$: C, 53.80; H, 6.48; N, 13.96. Found: C, 53.36; H, 6.36; N, 14.53.

Reaction of 1-benzoyl-2,2-dimethylhydrazine and methyl iodide in the presence of sodium ethoxide. Methyl iodide (9 g., 0.063 mole) in 10 ml. of absolute ethanol was added to a solution of 0.6 g. (0.025 mole) of sodium in 60 ml. of absolute ethanol and 4.1 g. (0.025 mole) of 1-benzoyl-2,2-dimethylhydrazine.[5] The mixture was refluxed for 10 hr., at the end of which the *p*H of the solution was 4–5. The solvent was distilled under reduced pressure and the residue was treated as in the procedure described above for the isolation of trimethylamine-benzimide. The yield was 2.1 g. (48%) of trimethylamine-benzimide, m.p. 167–169°.

Reaction of 1-benzoyl-2,2-dimethylhydrazine, sodium, and methyl iodide, in benzene. (A) In a 1:1:1 mole proportion. A mixture of 4.1 g. (0.025 mole) of 1-benzoyl-2,2-dimethylhydrazine, 0.6 g. (0.025 mole) of sodium, and 50 ml. of dry benzene, was refluxed for 6 hr. During this period a precipitate separated. After the solution had been cooled, 3.5 g. (0.025 mole) of methyl iodide in 10 ml. of benzene was added and the reaction mixture was refluxed for 1 hr. more. The solvent was distilled under reduced pressure and the residue was dissolved in chloroform and washed with water. The chloroform solution was dried over magnesium sulfate and the solution evaporated to dryness. The residual oil crystallized on standing giving a few crystals of trimethylamine-benzimide, m.p. 162–164° (167–169° after recrystallization from a mixture of chloroform and *n*-hexane).

(B) With a 1:1:2 mole proportion and 10-hr. reflux period. The reaction was carried out using procedure A but 7.1 g. (0.05 mole) of methyl iodide was used and the reaction was refluxed for 10 hr. instead of 1 hr. after the addition of this reagent. The yield was 2.1 g. (48%) of trimethylamine-benzimide, m.p. 167–169°.

Trimethylamine-isonicotinimide. Methyl iodide (3.6 g,. 0.025 mole) was added to a solution of 0.6 g. (0.025 mole) of sodium and 4.1 g. (0.025 mole) of 1-isonicotinyl-2,2-dimethylhydrazine[9] in 50 ml. of absolute ethanol. The mixture was refluxed for 5 hr. (*p*H 7–8), at the end of which the ethanol was removed and the residue was treated with an excess of ammonium hydroxide which was also removed under reduced pressure. The residue was extracted with chloroform and the chloroform solution was dried over magnesium sulfate and then distilled partially under reduced pressure: crystallization was induced by addition of isopentane. The white crystals melted at 191–192° (reported[8] m.p. 191.5–193.5°) and weighed 1.8 g. (40%).

Hydrogenolysis of trimethylamine-isonicotinimide. A mixture of 1 g. of the product of the previous reaction, 15 g. of Raney nickel, and 60 ml. of 95% ethanol was refluxed with vigorous stirring for 3 hr. The liberated gas was entrained with nitrogen and passed through a solution of hydrochloric acid. The Raney nickel was collected on a filter and the filtrate evaporated to dryness; the residue was recrystallized from a mixture of chloroform and *n*-pentane, yielding white crystals which melted at 155–156° (reported[18] m.p. of isonicotinamide 155.5–156°).

The hydrochloric acid solution was evaporated to dryness and the residue, after recrystallization from a mixture of absolute ethanol and ether, melted at 272–274° (dec.). The melting point of a mixture with an authentic sample of trimethylamine hydrochloride showed no depression.

(16) A. Michaelis and E. Hadanck, *Ber.*, 41, 3288 (1908).

(17) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, 80, 1895 (1958).

(18) I. Heilbron and H. H. Bunbury, *Dictionary of Organic Compounds*, Vol. 3, Eyre and Spottisworde, London 1953, p. 97.

1-Benzoyl-2,2-di-n-propyl-hydrazine. Prepared by the method of Liberman, Grumbach, and Rist[10] (mole ratio of benzoylhydrazine: sodium ethoxide: *n*-propyl bromide = 1:2:2, reaction time, 10 hr.), the yield was 30%. When the mole ratio was increased to 1:2:6, and the reaction time to 18 hr., the yield was 70%. M.p. and reported[10] m.p. 100–101°. The infrared spectrum of a sample in a potassium bromide pellet showed two strong bands at 1535 cm.$^{-1}$ and 1653 cm.$^{-1}$, characteristic of a secondary amide.[19] A strong band characteristic of bonded N—H appeared at 3210 cm.$^{-1}$ 1-Benzoyl-2,2-dimethylhydrazine has similar bands at 1555, 1653, and 3250 cm.$^{-1}$

1-Benzoyl-2,2-di-*n*-propylhydrazine was recovered unchanged from 20 hr. of refluxing with a large excess of either *n*-propyl bromide or methyl iodide in ethanolic solution.

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(19) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley, New York, 1954, p. 175. See also; R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KENTUCKY]

Ultraviolet Spectra of *N*-Sulfinyl Amines. Influence of Structure and Solvent[1]

WALTER T. SMITH, JR., DONALD TRIMNELL, AND LOWELL D. GRINNINGER

Received November 7, 1958

The ultraviolet spectra of some *N*-sulfinylanilines have been determined in ether and in several alcohols. The effect of substituents on the spectra and on the reaction of *N*-sulfinylanilines with alcohol is discussed.

The ultraviolet absorption spectra of some aliphatic and aromatic *N*-sulfinyl amines in hexane and cyclohexane have been reported by Mangini and Leandri.[2]

The work reported here is concerned with the spectra of some of these compounds in ether and in alcohols. In the cases where we have measured the spectra of compounds reported by Mangini and Leandri we find that there is little difference, if any, between the spectra in ether and in cyclohexane. Our work in ether has been primarily concerned with studying steric effects of ring substituents in *N*-sulfinylaniline. Such work, together with the spectra in alcohol, is of value in interpreting the structure of the NSO group.

The aliphatic *N*-sulfinyl amines characteristically absorb at about 230–240 mμ. The aromatic derivatives have a first primary band[3] at about 314–330 mμ, and in addition have a second primary band at about 230–240 mμ. The exact position of the first primary band is influenced to a small extent by the nature and position of a single substituent on the aromatic ring.

We interpret the second primary band (at 230–240 mμ) as being due to the ordinary isolated NSO grouping. The first primary band (at 314–330 mμ) is apparently due to the overall conjugated system consisting of the NSO group and the aromatic ring.

To obtain evidence that the band at 313–330 mμ is due to the conjugation of the NSO group with the aromatic ring we have prepared 2,4-dimethyl-*N*-sulfinylaniline and 2,6-dimethyl-*N*-sulfinylaniline and have compared the spectra of these two compounds.

In order for the NSO group to be conjugated with the aromatic ring the sulfur and nitrogen must be coplanar with the ring. Molecular models show that there will be considerable interference between the NSO group of *N*-sulfinylaniline and methyl groups in the *ortho* position. A comparison of the spectra of 2,4-dimethyl-*N*-sulfinylaniline shows that the interference caused by two *ortho* methyls has a pronounced effect on the spectra. 2,4-dimethyl-*N*-sulfinylaniline has a log ϵ of 4.05 at 337 mμ. In the 2,6-isomer the first primary band at 337 mμ has shifted to shorter wave lengths and has decreased in intensity to such an extent (log ϵ 3.27) that it is apparent only as a shoulder at 285 mμ of the second primary band. This result is in agreement with the idea outlined above that the first primary band is due to the over-all system consisting of the aromatic ring and the NSO group.

A secondary band which is either absent or is fused with the first primary band in 2,4-dimethyl-*N*-sulfinylaniline is accentuated by the two *ortho* methyl groups and appears at 367 mμ, log ϵ 3.24.

The shift of the first primary band to longer wave lengths in 2-methyl-, 4-methyl-, and 2,4-dimethyl-*N*-sulfinylanilines appears to be related to the methyl substituents. Thus unsubstituted *N*-sulfinylaniline has a maximum at 314 mμ. The introduction of a methyl group in the 4-position shifts the maximum 14 mμ to 328 mμ. A 2-methyl substituent shifts the maximum 8 mμ to 322 mμ. In 2,4-dimethyl-*N*-sulfinylaniline the shift is 23 mμ. This is approximately equal to the

(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 49(638)-49. Reproduction in whole or in part is permitted for any purpose of the United States government.

(2) A. Mangini and G. Leandri, *Spectrochim. Acta*, **8**, 283 (1956). Also paper presented at XVIth International Congress of Pure and Applied Chemistry, Paris, July 1957.

(3) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2715 (1947).

sum of the shifts due to a 2-methyl and 4-methyl group.

A slight steric effect of a single *ortho* methyl group is seen in the decrease of log ϵ from 4.00 in *N*-sulfinylaniline to 3.98 in 2-methyl-*N*-sulfinylaniline. Even this slight decrease is significant here, since a methyl group in the *para* position causes an increase in log ϵ to 4.10.

The results with 4-bromo-*N*-sulfinylaniline and 2,4,6-tribromo-*N*-sulfinylaniline confirm the conclusions drawn from the methyl derivatives. The maximum at 325 mμ (log ϵ 4.07) for 4-bomo-*N*-sulfinylaniline is reduced to a shoulder at 318 mμ having a log ϵ of only 2.53 in the case of 2,4,6-tribromo-*N*-sulfinylaniline.

The literature contains conflicting reports as to the stability of *N*-sulfinyl amines in alcohol solvents. Michaelis[4] reported that *N*-sulfinylaniline could be distilled without decomposition from an absolute ethyl alcohol solution. Carré and Libermann[5] also reported that the *N*-sulfinyl amines which they investigated were soluble in absolute alcohol without decomposition. Carré and Libermann did report, however, that when *N*-sulfinylaniline was refluxed with *n*-butyl alcohol, the alcohol was dehydrated to unsaturated compounds which polymerized. Under vigorous conditions *N*-sulfinylaniline reportedly reacts with ethyl alcohol to give hydrogen sulfide. In view of these confusing reports, we have extended our study to include the ultraviolet absorption spectra of *N*-sulfinyl amines in alcohol solvents.

The spectra of both *N*-sulfinylaniline and *p*-nitro-*N*-sulfinylaniline have been determined in several alcohols. Since aniline shows a maximum at 285 mμ, compared to 314 for *N*-sulfinylaniline and *p*-nitroaniline has a maximum at 228, compared to 314 for *p*-nitro-*N*-sulfinylaniline it is possible to observe any disappearance of the NSO group by observing the wave length of maximal absorption. This wave length and the corresponding log ϵ value were taken as the criteria in determining whether any reaction had taken place. The extent of any reaction can also be estimated from the absorption data.

The spectrum of *N*-sulfinylaniline in absolute methyl alcohol is nearly identical with that of aniline in methyl alcohol, thus indicating rapid and complete reaction of *N*-sulfinylaniline with methyl alcohol. The spectrum in 2-chloroethanol indicates complete reaction in that solvent also. The spectrum of *N*-sulfinylaniline in ethanol shows no reaction in fresh solutions, but solutions on keeping for six days show a slow and eventually complete reaction.

N-Sulfinylaniline shows no reaction with allyl alcohol, ethylene glycol, isopropyl alcohol, *tert*-butyl alcohol, benzyl alcohol, and triethyl carbinol.

The spectrum of *p*-nitro-*N*-sulfinylaniline in each of the several solvents studied is similar to the spectrum of *p*-nitroaniline. The solvents used include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, and *tert*-butyl alcohols and ethylene glycol. It is thus apparent that *p*-nitro-*N*-sulfinylaniline reacts with all of these alcohols.

The addition of alcohol to the NSO group might occur in the following way:

$$\mathrm{ArNSO + ROH \longrightarrow ArNHS(=O)OR}$$

Such a reaction would destroy the conjugated system present in aromatic *N*-sulfinylamines and explain the observed change in the ultraviolet spectrum. An experiment with *N*-sulfinylaniline and methyl alcohol shows that the reaction goes further than shown above.

$$\mathrm{ArNHSO_2R + ROH \longrightarrow ArNH_2 + (RO)_2SO}$$

A 24% yield of dimethyl sulfite was obtained from methyl alcohol and *N*-sulfinylaniline in ethyl ether. The conditions used were almost certainly not optimum conditions. A much higher yield of dimethyl sulfite can be expected from this reaction when carried out under better conditions.

It will be recalled that the spectrum of *N*-sulfinylaniline in methyl alcohol indicated that one of the products was aniline. We have found that dimethyl sulfite exhibits a negligible absorption in the spectral region studied and would not show up as a product in the spectral study.

Earlier workers[6,7] have attempted to interpret the structure of the *N*-sulfinyl amino group on the basis of dipole moment studies. The structure Ar—N=S=O was found to fit the dipole moment measurements, but was ruled out because of the failure of *N*-sulfinyl amines to show any chemical

ULTRAVIOLET ABSORPTION OF AROMATIC *N*-SULFINYL AMINES[a]

	λ_1	log ϵ_1	λ_2	log ϵ_2	λ_3	log ϵ_3
N-Sulfinylaniline	231	3.78	314	4.00		
2-Methyl-*N*-sulfinylaniline	235	3.83	322	3.98		
4-Methyl-*N*-sulfinylaniline	238	3.75	328	4.11		
2,4-Dimethyl-*N*-sulfinylaniline	241	3.80	337	4.05		
2,6-Dimethyl-*N*-sulfinylaniline	235	3.78	285[b]	3.27	367	3.24
4-Bromo-*N*-sulfinylaniline	239	3.83	325	4.07		
2,4,5-Tribromo-*N*-sulfinylaniline	250[b]	3.45	318[b]	2.53	366	2.57
4-Nitro-*N*-sulfinylaniline	220[b]	4.00	314	4.12		

[a] Solvent is dry ethyl ether. [b] Shoulder.

(4) A. Michaelis, *Ber.*, **24**, 745 (1891).

(5) P. Carré and D. Libermann, *Compt. rend.*, **194**, 2218 (1932).

(6) E. Bergmann and M. Tschudnowsky, *Z. Physikal. Chem.*, **17B**, 100 (1932).

(7) K. A. Jensen and N. H. Bang, *Ann.*, **548**, 95 (1941).

behavior similar to that of isocyanates. The reaction with alcohols which we have shown to take place is similar, at least in the first step, to the reaction of isocyanates with alcohols. The structure Ar—N=S=O must therefore be reconsidered as a possible structure for the N-sulfinyl amine group.

EXPERIMENTAL

The ultraviolet spectra were determined using either a Beckman DU spectrophotometer or a Beckman DK recording spectrophotometer. Solutions of the *N*-sulfinyl amines containing about 5×10^{-3} grams/liter were measured in 1 or 2 cm. silica absorption cells.

The following aliphatic *N*-sulfinyl amines have a single maximum as indicated: *n*-propyl- 234 mμ, log ε 3.68; *n*-butyl- 234 mμ, log ε 3.72; *n*-heptyl- 235 mμ, log ε 3.67; cyclohexyl- 235 mμ, log ε 3.85.

Isolation of dimethyl sulfite from N-sulfinylaniline and methyl alcohol. A mixture of 13.9 g. (0.10 mole) of *N*-sulfinylaniline, 9.6 g. (0.30 mole) of methyl alcohol, and 20 ml. of dry ether was allowed to stand at room temperature for 3 days. Distillation of the mixture gave 2.4 g. (24%) of dimethyl sulfite boiling at 122–123°.

Preparation of N-sulfinyl amines. These compounds were prepared in good yield following a procedure similar to that described by Michaelis.[4]

LEXINGTON, KY.

[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

Nitration of α-Oximino Esters and Acids[1]

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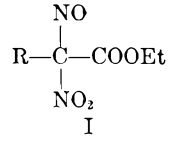
α-Oximino esters RC(=NOH)COOEt react with an equimolar mixture of 100% nitric acid and ammonium nitrate or with nitrogen dioxide in ether to give good yields of α-nitro-α-nitroso esters. The latter can be reconverted to α-oximino esters or oxidized to α,α-dinitro esters. The action of 100% nitric acid and ammonium nitrate upon other oximino esters, oximino acids, and related compounds has been investigated.

Oximino compounds have been utilized in various ways for the preparation of nitro compounds. A direct conversion of isonitroso to nitro groups can be accomplished by the oxidation of oximino compounds with sodium dichromate and sulfuric acid,[2] potassium permanganate,[3] hydrogen peroxide,[4] or peroxytrifluoroacetic acid.[5] The method of Iffland is less direct and involves bromination, oxidation, and debromination of oximes.[6]

Ketoximes react with nitrogen dioxide to yield pseudonitroles[7-11] which can be oxidized to *gem*-dinitro compounds with chromium trioxide in acetic acid,[7a] with nitric acid,[8] boiling ethanol,[10] or photochemically in benzene or ether.[8] In some cases the pseudonitroles are formed from ketoximes also by the action of fuming nitric acid,[10] and in a few instances the reaction with nitrogen dioxide[12,13] or nitric acid[13] will produce *gem*-dinitro compounds from ketoximes in one step.

In the present investigation α-oximino esters RC(=NOH)COOEt (R=alkyl) have been nitrated under various conditions. A mixture of 90% nitric acid and 15% fuming sulfuric acid at 5–15° gives products characterized by strong nitrate bands in the infrared (at 6.06, 7.86 ,and 11.74μ). Nitration with 100% nitric acid at 0–10° produces only small yields of mixtures containing nitrate esters which cannot be separated by molecular distillation. When the oximino esters are treated with an equimolar mixture of 100% nitric acid and ammonium nitrate, or with nitrogen dioxide in ether, insoluble blue oils, identified as α-nitro-α-nitroso esters (I), are formed in excellent yield.



I

The new compounds (I, R=alkyl) are characterized by low-intensity absorption bands at 630–635 mμ. Their infrared spectra show two bands (NO, NO_2) in the 6.3μ region. They are sensitive to light, oxygen, heat, and prolonged exposure to

(1) (a) This work was performed under the auspices of the U. S. Atomic Energy Commission. (b) Presented before the Organic Section of the American Chemical Society at the 134th meeting, Chicago, September 1958.

(2) V. M. Rodionov, I. V. Machinskaya, and V. M. Belikow, *Akad. Nauk S.S.S.R., Inst. Org. Khim. Sintezy Org. Soedinenii Sbornik I*, 117 (1950).

(3) M. Conrad and A. Schulze, *Ber.*, **42**, 739 (1909).

(4) J. Schmidt and A. Haid, *Ann.*, **377**, 23 (1910); J. Schmidt and K. T. Widman, *Ber.*, **42**, 1896 (1909).

(5) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

(6) D. C. Iffland and G. X. Criner, *J. Am. Chem. Soc.*, **75**, 4047 (1953); D. C. Iffland and T. Yen, *J. Am. Chem. Soc.*, **76**, 4083 (1954).

(7) (a) V. Meyer, *Ber.*, **9**, 701 (1876); G. Born, *Ber.*, **29**, 93 (1896). (b) V. Meyer, *Ann.*, **175**, 120 (1875).

(8) H. Rheinboldt and M. Dewald, *Ber.*, **60**, 250 (1927).

(9) R. Scholl, *Ber.*, **21**, 506 (1888).

(10) W. Charlton, J. C. Earl, J. Kenner, and A. A. Luciano, *J. Chem. Soc.*, 30 (1932).

(11) R. Scholl and K. Landsteiner, *Ber.*, **29**, 89 (1896).

(12) G. Ponzio and F. Biglietti, *Gazz. chim. ital.*, **64**, 861 (1934).

(13) R. Scholl, *Ber.*, **23**, 3490 (1890).

water, but may be stored for several weeks at temperatures below 10°. They have been postulated as unstable intermediates in the conversion of α-nitro esters to α-oximino esters with sodium nitrite in aqueous ethanol.[14] This theory is now supported

$$RCH(NO_2)COOEt + NO_2^- \longrightarrow RC(=NOH)COOEt + NO_3^-$$

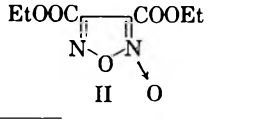
by the observation that the pure α-nitro-α-nitroso esters react with 50% aqueous alcoholic sodium nitrite to give α-oximino esters in good yield.

Oxidation with air, oxygen (especially when catalyzed by light), chromic oxide, or peroxytrifluoroacetic acid converts the α-nitro-α-nitroso esters (I) to α,α-dinitro esters prepared previously by another procedure.[15] These dinitro esters are formed also when the α-nitro-α-nitroso esters (I) are permitted to react with 100% nitric acid and ammonium nitrate without stirring.

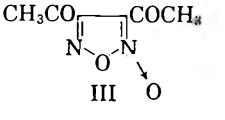
Ethyl oximinoacetate reacts exothermically with gaseous nitrogen dioxide giving ethyl nitrooximinoacetate and its decomposition product 3,4-dicarbethoxyfuroxan (II).[16] With 100% nitric acid and ammonium nitrate the same initial products are probably formed; the nitrolic acid, however, is further oxidized and dinitroacetate is isolated.[17] 3,4-Dicarbethoxyfuroxan (II) is the only insoluble product when ethyl aminooximinoacetate is nitrated under the same conditions.

Oximino esters with negative substituents, such as ethyl chlorooximinoacetate and ethyl oximinomalonate, are converted in good yields to the corresponding α-nitro esters by 100% nitric acid and ammonium nitrate.

With other oximino compounds the nitrating mixture of 100% nitric acid and ammonium nitrate has proved less advantageous. Thus, acetone oxime gives the known 3,4-diacetylfuroxan (III), which also is formed from α-oximinoacetone by the action of N_2O_4 in ether.[18] Ethyl α-oximinoacetoacetate



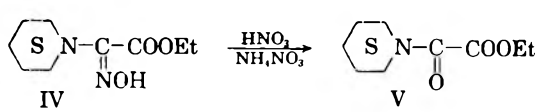
II



III

reacts to give essentially the same mixture of ethyl dinitroacetate and 3,4-dicarbethoxyfuroxan (II) as is obtained from ethyl oximinoacetate. Under milder conditions (HNO_3, d. 1.2) it yields a mixture of ethyl nitrooximinoacetate and II.[19]

A still different type of reaction occurs with ethyl piperidinooximinoacetate (IV) which is converted to ethyl α-oxopiperidineacetate (V) by nitric acid and ammonium nitrate.



IV V

α-Oximino acids (VI, R = alkyl) under similar conditions undergo simultaneous nitration and decarboxylation to dinitroparaffins (VII) which are

$$RC(=NOH)COOH + HNO_3 + NH_4NO_3 \longrightarrow RCH(NO_2)_2 + CO_2$$

VI VII

isolated in small yields. Oximinocyanoacetic acid and β-amino-β-oximinopropionic acid have given only water-soluble nitration products.

EXPERIMENTAL[20]

Ethyl α-nitro-α-nitrosopropionate. (a) Ammonium nitrate (80.0 g., 1.0 mole) was added with stirring to 100% nitric acid (63.0 g., 1.0 mole) at room temperature, and the suspension was cooled to 20°. A blue oil formed immediately when ethyl α-oximinopropionate (13.1 g., 0.1 mole) was added in small portions. The mixture was stirred at 23–25° for 2.5 hr. and poured on ice. The oil was taken up in methylene chloride, washed with water, and dried over sodium sulfate at 5°. After removal of the solvent under reduced pressure a blue oil (14.6 g., 83%) remained which had n_D^{25} 1.4218, λ_{max} 630 mμ, ε6.8 (in cyclohexane), λ(C=O) 5.69μ, λ(NO_2) 6.31, 7.42μ, and λ(N=O) 6.40μ.

Anal. Calcd. for $C_5H_8N_2O_5$: C, 34.10; H, 4.57. Found: C, 34.34; H, 4.58.

(b) Nitrogen dioxide was added slowly to a solution of ethyl α-oximinopropionate (13.1 g., 0.1 mole) in ether (100 ml.), contained in an ice bath. The mixture was allowed to stand for 1 hr. and was distilled under reduced pressure below 20°, finally at 1 mm. The residual blue oil (16.5 g., 94%), n_D^{25} 1.4260,[21] had an infrared spectrum identical with the above ester.

Ethyl α-nitro-α-nitrosobutyrate. The nitration of ethyl α-oximinobutyrate (7.2 g., 0.05 mole) with 100% nitric acid (0.5 mole) and ammonium nitrate (0.5 mole) at 20° under identical conditions gave 8.8 g. (93%) of blue oil with n_D^{25} 1.4250, λ_{max} 635 mμ, ε8.3 (in cyclohexane), λ(C=O) 5.69μ, λ(NO_2) 6.30, 7.41μ, λ(NO) 6.41μ.

Anal. Calcd. for $C_6H_{10}N_2O_5$: C, 37.88; H, 5.30. Found: C, 37.84; H, 4.99.

The α-nitro-α-nitroso esters were insoluble in water and dissolved in ethanol, methanol, chloroform, acetic acid, benzene, and cyclohexane. They were unchanged in contact with water below room temperature but decomposed slowly on standing in water at 25°, yielding colorless oils containing dinitro esters.

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(15) L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **23**, 1340 (1958).

(16) L. Bouveault and A. Wahl, *Bull. soc. chim.*, [3] **31**, 679 (1904).

(17) More recent evidence indicates that the nitrolic acid is an intermediate also in the reaction of ethyl bromoacetate with sodium nitrite in dimethylformamide [N. Kornblum and W. M. Weaver, *J. Am. Chem. Soc.*, **80**, 4333 (1958)]. Depending on the temperature, this may be then degraded to oxalic acid or 3,4-dicarbethoxyfuroxan. The isolation of pseudonitroles or nitrolic acids in the nitration of α-oximino esters appears to depend on the solubility of these compounds. They may be isolated when they are insoluble, as are the esters I, R = alkyl, but will react further when they are soluble in the reaction mixture.

(18) W. S. Mills, *Chem. News*, **88**, 228 (1903).

(19) M. Jowitschitsch, *Ber.*, **28**, 1215 (1895); **39**, 785 (1906).

(20) All temperatures are uncorrected. Microanalyses by M. Naranjo.

(21) The high refractive index in this sample is attributed to the presence of a small amount of dinitro ester.

Ethyl α-oximinobutyrate from ethyl α-nitro-α-nitrosobutyrate. When a solution of sodium nitrite (1.72 g., 0.025 mole) in 10 ml. of water was added to a blue solution of ethyl α-nitro-α-nitrosobutyrate (1.58 g., 0.0083 mole) in 10 ml. of 95% ethanol, the color changed to green immediately. It was yellow after 5 min. at 25°. The mixture was allowed to stand at 25° for 16 hr., diluted with 50 ml. of water, and extracted with ether. The extract was dried over sodium sulfate, filtered, and evaporated at 50 mm., leaving 1.0 g. (83%) of pale yellow oil which crystallized in colorless needles from hexane-petroleum ether, the needles melting at 59–60°. Melting point, mixed melting point, and infrared spectrum were identical with those of pure ethyl α-oximinobutyrate (lit. m.p. 58°).[22]

Oxidation of ethyl α-nitro-α-nitrosobutyrate. Ethyl α-nitro-α-nitrosobutyrate was oxidized to ethyl α,α-dinitrobutyrate under various conditions (Table I). The products were extracted with methylene chloride or chloroform, dried, and distilled to remove the solvents. They gave identical infrared spectra which also agreed with that of an authentic specimen,[15] boiled at 45–50° (0.1–0.2 mm.), and had analytical values corresponding to the dinitro ester.

TABLE I

OXIDATION OF ETHYL α-NITRO-α-NITROSOBUTYRATE

Method	Yield, %	n_D^{25} of Dinitro Ester
Chromium trioxide in HOAc at 15°	25	Not detd.
Peroxytrifluoroacetic acid[5]	47	1.4342
Air oxidation[a]	64	1.4330
Oxygen and GE 135W lamp[a]	78	1.4356
Nitric acid and ammonium nitrate[b]	42	1.4348

[a] The gas was introduced into the liquid ester through a dispersion disk.

[b] The α-nitro-α-nitrosobutyrate was not isolated in this case. The stirrer was stopped when the blue oil was formed from the oximino ester and the mixture was allowed to warm exothermically.

Nitration of other oximino compounds. Each of the following compounds was added with stirring at 20° to a five- to ten-fold excess of an equimolar mixture of 100% nitric acid and ammonium nitrate. The reaction mixtures were stirred at 20–25° for 2 ± 0.5 hr., poured on ice, and extracted with methylene chloride. The extracts were washed with ice water, dried over sodium sulfate, and distilled.

(a) *Ethyl oximinomalonate* gave a 74% yield of ethyl nitromalonate, b.p. 50° (0.08 mm.), n_D^{25} 1.4272, λ(C=O) 5.69, λ(NO_2) 6.35, 7.31μ.

Anal. Calcd. for $C_7H_{11}NO_6$: C, 40.99; H, 5.40; N, 6.83. Found: C, 41.30; H, 5.86; N, 6.74.

Nitration of ethyl oximinomalonate with 100% nitric acid and concentrated sulfuric acid gave only a small yield of impure nitro ester.

Ethyl α-chloro-α-oximinoacetate yielded 51% of ethyl α-chloro-α-nitroacetate, b.p. 45° (0.03 mm.), n_D^{25} 1.4358, λ(C=O) 5.67, λ(NO_2) 6.31, 7.41μ.

Anal. Calcd. for $C_4H_6ClNO_4$: C, 28.66; H, 3.60; N, 8.36. Found: C, 28.72; H, 3.63; N, 8.20.

(c) *Ethyl α-oximinoacetoacetate* and *ethyl oximinoacetate* both gave mixtures of ethyl dinitroacetate and 3,4-dicarbethoxyfuroxan (II) which were separated by extraction with 20% aqueous sodium carbonate solution. 3,4-Dicarbethoxyfuroxan boiled at 90° (0.1 mm.) and had n_D^{25} 1.4730; yield 56 and 24%, λ(C=O) 5.73μ, λ(C=N) 6.15μ. Ethyl dinitroacetate was regenerated from its yellow sodium salt solution by acidification with concentrated hydrochloric acid at 0°. The ester was recovered in 31 and 11% yield, respectively, by extraction with methylene chloride and evaporation of the solution. It boiled at 40° (0.5 mm.) and had n_D^{25} 1.4322, λ(C=O) 5.65μ, and λ(NO_2) 6.31, 7.51μ.

Anal. Calcd. for $C_4H_6N_2O_6$: C, 26.98; H, 3.40; N, 15.74. Found: C, 27.09; H, 3.25; N, 15.07.

(d) *Ethyl aminooximinoacetate* furnished a 31% yield of 3,4-dicarbethoxyfuroxan (II), b.p. 90° (0.05 mm.), n_D^{25} 1.4730, λ_{max} 270 mμ (log ε 3.63) in ethanol.

Anal. Calcd. for $C_8H_{10}N_2O_6$: C, 41.76; H, 4.38; N, 12.18. Found: C, 42.09; H, 4.39; N, 11.79.

(e) *Ethyl piperidinooximinoacetate* (IV)[23] was converted to ethyl α-oxopiperidineacetate (V) both by the above nitrating agent and by nitrogen dioxide in chloroform in yields of 33–65%. The product was twice distilled from a molecular still and boiled at 75° (0.05 mm.), n_D^{25} 1.4724; λ(C=O) 5.76 and 6.03μ.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.33; H, 8.10; N, 7.56. Found: C, 58.39; H, 8.18; N, 6.92.

Its infrared spectrum was identical with that of an authentic specimen, prepared from ethyl oxalate and piperidine.[24]

(f) *Acetone oxime* gave a 35% yield of 3,4-diacetylfuroxan (III), b.p. 65° (0.1 mm.), n_D^{25} 1.5032, λ(C=O) 5.83μ, λ(C=N) 6.24μ, λ_{max_1} 221 mμ (log ε 3.94), λ_{max_2} 272 mμ (log ε 3.82) in ethanol.

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.37; H, 3.55; N, 16.47. Found: C, 42.43; H, 3.38; N, 16.08.

(g) *α-Oximinopropionic acid* yielded 1,1-dinitroethane (29%), which was converted to the hydrazine salt, m.p. 137–138°.[15]

Anal. Calcd. for $C_2H_8N_4O_4$: C, 15.79; H, 5.26. Found: C, 15.44; H, 5.55.

(h) *α-Oximinobutyric acid* furnished 1,1-dinitropropane in 29% yield. Its hydrazine salt melted at 99–100°.[15]

Anal. Calcd. for $C_3H_{10}N_4O_4$: C, 21.69; H, 6.06. Found: C, 22.30; H, 6.47.

Absorption spectra. Infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrophotometer, ultraviolet absorption spectra with a Beckman DR spectrophotometer.

LOS ALAMOS, N. MEX.

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[CONTRIBUTION FROM WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

Degradation of Corticosteroids. III.[1,2] Catalytic Hydrogenation of Cortisol

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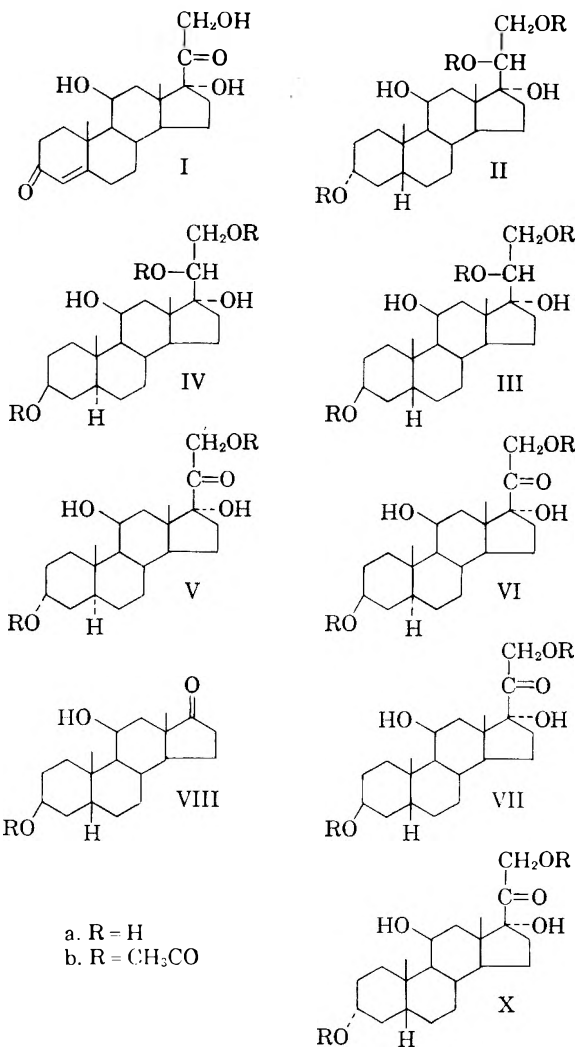
The catalytic hydrogenation of cortisol gave complicated mixtures, which were difficult to resolve, instead of the expected equatorial allo isomer. Hydrogenation in glacial acetic acid with platinum oxide gave 39% of 3α,11β,17α,20β,21-pentahydroxypregnane, 27% of 3β,11β,17α,20β,21-pentahydroxypregnane, and only 9.5% of 3β,11β,17α,20β,21-pentahydroxyallo pregnane. Hydrogenation of cortisol in glacial acetic acid with rhodium (5%) on alumina gave 13.5% of 3β,11β,17α,21-tetrahydroxyallopregnan-20-one, 32% of 3β,11β,17α,21-tetrahydroxypregnan-20-one, 26.5% of 3α,11β,17α,21-tetrahydroxyallopregnan-20-one, 18% of 3α,11β,17α,21-tetrahydroxypregnan-20-one and 1% of 3β,11β-dihydroxyetiocholan-17-one. Evidence is presented for the hydrogen bonding of carbonyls at C-20 with water of crystallization.

For the past few years we have been investigating the biosynthetic origin of carbon atoms of the corticosteroid nucleus. Cortisol-C^{14} was biosynthesized from acetate-1-C^{14} and methods had to be devised for the degradation and isolation of individual carbons of the steroid nucleus. One of the approaches explored for the opening of ring D was to hydrogenate cortisol to an alcohol saturated in ring A, and to cleave the side chain and open ring D of the derived 17-ketosteroid. It has been reported that steroidal 4-en-3-ones having an 11β-hydroxy, an 11-ketone or unsaturation at $C^{9(11)}$ or C^{11} on hydrogenation yield almost exclusively allo-isomers.[3] When the reduction proceeds to the alcohol stage, an equatorial hydroxyl (3β) group is formed. It was hoped that on hydrogenation of cortisol satisfactory yields of a single isomer of the allo series would be obtained. With this in mind studies were undertaken on the catalytic hydrogenation of cortisol in glacial acetic acid with two catalysts: platinum oxide and rhodium (5%) on alumina. Contrary to expectation, in both cases, complex mixtures, difficult to resolve, were obtained. Certain of our results differ profoundly from those previously reported.[3]

A solution of cortisol (I) in glacial acetic acid was shaken for 16 hours in an atmosphere of hydrogen with platinum oxide.[4] The reaction



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(2) This investigation was supported by grants from the American Cancer Society Inc. P-102 and P-103. Presented at the 134th Meeting of the American Chemical Society, Chicago, 1958.

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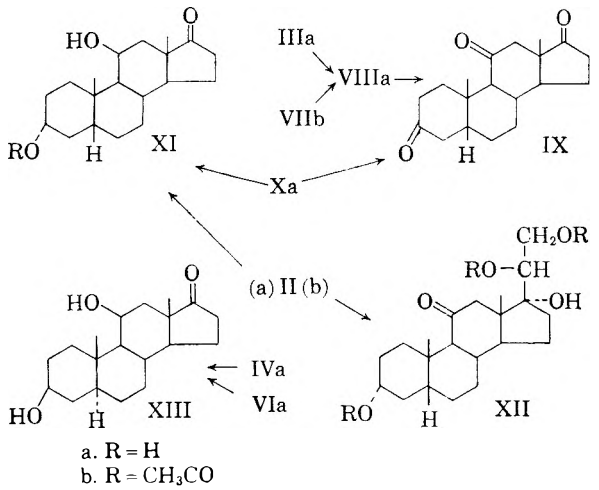
(4) Purchased from Baker and Co., Inc., Newark, N. J.

mixture was processed as described in the experimental part and $3\alpha,11\beta,17\alpha,20\beta,21$-pentahydroxypregnane (IIa, 39%), $3\beta,11\beta,17\alpha,20\beta,21$-pentahydroxypregnane (IIIa, 27%), $3\beta,11\beta,17\alpha,20\beta,21$-pentahydroxyallopregnane (IVa, 9.7%) were isolated.

The major product (IIa) was obtained in two forms as the anhydrous pentol $C_{21}H_{36}O_5$ m.p. 261–263° (19%), and the monohydrate $C_{21}H_{36}O_5 \cdot H_2O$ m.p. 166–170° (20%). On recrystallization from methanol the monohydrate was converted to the anhydrous pentol. Acetylation of IIa gave a sirupy triacetate IIb which was oxidized[5] to XIIb and then saponified[6] to the free alcohol XIIa. The rotational increment on acetylation XIIb → XIIa $\Delta[M]_D$ + 409° is consistent with a 20β hydroxyl.[7] Finally, cleavage of the side chain[8] of IIa gave the known $3\alpha,11\beta$-dihydroxyetiocholan-17-one and completes the proof of the assigned structure.



The second product was the previously undescribed pentol IIIa. The substance (m.p. 242–244°) analyzed for $C_{21}H_{36}O_5$ and its infrared spectrum had bands at 3600, 3450, and 1022 (axial hydroxyl) cm.$^{-1}$. Acetylation gave a triacetate IIIb ($C_{21}H_{42}O_8$, m.p. 153–155°) which had a complex group of bands in the C—O—C stretching region, 1285, 1270, 1239, 1205 cm.$^{-1}$, characteristic of axial acetoxy compounds.[9–11] The rotational increment on acetylation IIIb → IIIa $\Delta[M]_D$ + 285, is consistent with a 20β hydroxy function. Oxidation of IIIa with sodium bismuthate gave VIIIa (m.p. 259–261°), the infrared spectrum of which differed from those of the known $3\alpha,11\beta$-dihydroxyetiocholan-17-one, $3\alpha,11\beta$-dihydroxyandrostan-17-one and $3\beta,11\beta$-dihydroxyandrostan-17-one. Oxidation of VIIIa with chromium trioxide pyridine complex[5] gave IX identical in every respect with a sample of etiocholane-3,11,17-trione prepared from $3\alpha,11\beta,17\alpha$,21-tetrahydroxypregnan-20-one.

The pentol IVa was obtained as the monohydrate (9.7%) $C_{21}H_{36}O_5 \cdot H_2O$ and showed a double melting point at 159–163° with resolidification and remelting at 215–216°. The structure of the substance was proven by the identity of the infrared spectra of the free alcohol IVa and of the triacetate IVb (m.p. 204–208°) with those of authentic samples.[12]

The preponderance of cis isomers formed on hydrogenation of cortisol with platinum oxide in acetic acid was surprising and to our knowledge has not been previously reported. It has been assumed that 11β-hydroxy functions prevent the adsorption of the β side of the steroids on the surface of the catalyst[3e,f] and consequently the hydrogen atoms must enter from the α side and form the alloisomers. The results reported in this paper seem to indicate that other factors, besides the steric hindrance of the 11β-hydroxyl, may be influencing the course of the reaction. This assumption finds support in the reported observations that modification of conditions of hydrogenation profoundly influences the stereochemistry of the resulting products.[13–16] The isolation of relatively large amounts of $3\beta,11\beta,17\alpha,20\beta,21$-pentahydroxypregnane is of interest. Although the formation of the thermodynamically less stable axial compounds could be expected according to Barton's modified Auwers-Skita rule,[17] the substance seems not to have been previously described.

A solution of cortisol (I) in glacial acetic acid was shaken for 3 hr. in an atmosphere of hydrogen with

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rhodium (5%) on alumina until the gas uptake became very slow. The reaction mixture was processed as described in the epxerimental part and 3β,11β,17α,21-tetrahydroxyallopregnan-20-one (VIa, 13.5%), 3β,11β,17α,21-tetrahydroxypregnan-20-one (VIIa, 32%), 3α, 11β, 17α, 21-tetrahydroxyallopregnan-20-one (Va, 26.5%), 3α,11β,17α,21-tetrahydroxypregnan-20-one (Xa, 18%) and 3β,11β-dihydroxyetiocholan-17-one (VIIIa,1%) were isolated.

The equatorial alcohol VIa (13.5%) was obtained in two form as the tetrahydro derivative $C_{21}H_{34}O_5$, m.p. 221–224°, and as the hemihydrate $C_{21}H_{34}O_5 \cdot {}^1/_2\ H_2O$, m.p. 211–214°. The infrared spectra of the two forms differed in the carbonyl region and in the 1450–1200 cm.$^{-1}$ region. However, both products moved identically when chromatographed on paper.[18] Their solutions in sulfuric acid gave identical spectra,[19] on acetylation identical esters were obtained and finally on cleaving the side chain both gave XIII establishing thus the assigned structures. The infrared spectrum of the anhydrous sample had a single carbonyl band at 1705 cm.$^{-1}$ and the hemihydrate had two distinct bands at 1710 and 1690 cm.$^{-1}$. The intensity of the 1690 cm.$^{-1}$ band varied from 80–100% of the 1710 cm.$^{-1}$ band. The presence of the 1690 cm.$^{-1}$ band in the hydrated sample indicates a partial hydrogen bonding of the ketone at C-20 with the water of hydration.

The apparently not yet described VIIa was isolated as the hemihydrate $C_{21}H_{34}O_5 \cdot {}^1/_2H_2O$, m.p. 135–138°, in 32% yield. The structure assignment of the substance is based on elementary analysis, purple coloration with blue tetrazolium,[20] infrared spectrum and on oxidative cleavage of the side chain to VIIIa.

In addition to the two described products the known 3α,11β,17α,21-tetrahydroxyallopregnan-20-one (Va), m.p. 244–245°, (26.5% yield) and 3α,11β,17α,21-tetrahydroxypregnan-20-one (Xa), m.p 207–209°, (18% yield) were isolated and identified by comparison of their infrared spectra with those of authentic samples. In all hydrogenation experiments with rhodium (5%) on alumina small amounts 1–1.5% of 3β,11β-dihydroxyetiocholan-17-one (VIIIa) were formed.

Hydrogenation of cortisol in acetic acid solution with rhodium (5%) on alumina catalyst led to the reduction of the conjugated carbonyl function in ring A and the formation of the "tetrahydro" derivatives. The dihydroxy acetone moiety remained essentially unchanged. In some experiments up to 9% of various 20β-hydroxy pentols were obtained. It seems possible that the formation of the small amounts of 17-ketosteroid was an artifact and the cleavage of the dihydroxyacetone moiety occurred on the alumina which supported the rhodium catalyst. Transformations of steroids on alumina were previously observed.

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EXPERIMENTAL[21]

Hydrogenation of cortisol with platinum oxide catalyst. A mixture of 4 g. of cortisol, 150 ml. of glacial acetic acid (Mallinkrodt Analytical Reagent, Dichromate Test) and 560 mg. of platinum oxide[4] was shaken 16 hr. in an atmosphere of hydrogen. The catalyst was filtered, washed with acetone, and the solvents removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with 2*N* sodium carbonate, water, then dried over sodium sulfate, and the solvent distilled leaving 4.4 g. of a glass. A portion of the glass (1.1 g.), equivalent to 1 g. of cortisol, was dissolved in ethyl acetate and on concentration of the solution a white semi-solid residue separated out. The residue was digested three times with small amounts of hot ethyl acetate leaving 424 mg. of a mixture of solids (*Fraction A*), m.p. 147–159° which was subsequently fractionally crystallized. Concentration of the combined mother liquors gave 206 mg. (in four crops) of a homogeneous product, m.p. 212–222° (*Fraction B*). Finally, the remaining mother liquor was evaporated to dryness and carefully chromatographed on silica gel (*Chromatography 1*). The column (60 × 3 cm.) was eluted with benzene, mixtures of benzene-ethyl acetate, ethyl acetate, mixtures of ethyl acetate-methanol and methanol. Eluates of 50 ml. were collected.

Hydrogenation of cortisol with rhodium (5%) on alumina catalyst. To a pre-reduced mixture of 100 ml. of glacial acetic acid (Mallinkrodt Analytical Reagent, Dichromate Test) and 550 mg. of rhodium (5%) on alumina catalyst[4] 2 g. of cortisol was added and the suspension was shaken in an atmosphere of hydrogen. The reaction was stopped after 3 hr. after 2.1 mols. of hydrogen had been absorbed and the gas uptake had almost ceased. The reaction mixture was processed as described above and on concentration of the ethyl acetate solution 535 mg. of solids, m.p. 205–233° was obtained. The mother liquor was distilled to dryness and the residue was chromatographed on silica gel (*Chromatography 2*). The column (50 × 2 cm.) was eluted with benzene, mixtures of ethyl acetate-benzene, ethyl acetate, mixtures of methanol-ethyl acetate and methanol. Eluates of 50 ml. were collected.

3α,11β,17α,20β,21-Pentahydroxypregnane (IIa). The above described *Fraction A* was fractionally crystallized from mixtures of methanol-ethyl acetate and eight crops of crystalline solids were collected. The first crop was IIa monohydrate and the second the anhydrous IIa. The subsequently obtained crops 3–8 were 3β,11β,17α,20β,21-pentahydroxyallopregnane (IVa).

(21) The eluates from the chromatography columns were assayed by infrared spectroscopy on a Perkin-Elmer Infracord Spectrometer. The yields reported are based on the weights of products eluted from the chromatography columns. Melting points were determined on a Fisher-Johns hot stage and are reported as read. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. Ultraviolet absorption spectra were determined by means of a Cary Model 11 MS spectrophotometer. Optical rotations were determined in methanol in a 1-dm. semimicro tube. Infrared spectra were obtained from material incorporated into rectangular potassium bromide prisms[11] on a Perkin-Elmer 12C spectrometer.

A. Isolation of IIa monohydrate. *a.* The first crop obtained on fractional crystallization of *Fraction A* gave 200 mg. of IIa, m.p. 164–168°.

The sample was recrystallized twice from methanol-ethyl acetate, m.p. 166–170°; $[\alpha]_D^{20}$ +28.8° (*c*, 0.5618), $[M]_D$ +111°; ultraviolet $\lambda_{max.}^{MeOH}$ none; infrared $\nu_{max.}^{KBr}$ 3550, 1039 (equatorial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{36}O_5 \cdot H_2O$: C, 65.25; H, 9.91. Found: C, 65.02; H, 9.71.

B. Isolation of anhydrous IIa. *a.* The second crop obtained on fractional crystallization of *Fraction A* gave 98 mg. of IIa, m.p. 230–235°. *b. From Chromatography 1.* Fractions 128–138, which were eluted with a mixture of methanol-ethyl acetate (1:9) yielded 94.2 mg. of IIa. The combined residue was crystallized from methanol and gave IIa, m.p. 253–257°.

The infrared spectra of both forms of IIa were essentially identical.

A sample was recrystallized from methanol, m.p. 261–263°; $[\alpha]_D$ +28° (*c*, 0.6433); $[M]_D$ +103°; ultraviolet: $\lambda_{max.}^{MeOH}$ none; infrared $\nu_{max.}^{KBr}$ 3580, 1039 (equatorial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85; Found: C, 68.14; H, 9.63.

The triacetate IIb was prepared in the usual manner but could not be crystallized.

3β,11β,17α,20β,21-Pentahydroxypregnane (IIIa). A. The previously described *Fraction B* gave 206 mg. of IIIa, m.p. 212–222°.

B. *From Chromatography 1.* Fractions 88–144 which were eluted with a mixture of ethyl acetate-benzene (17:3), gave 68.9 mg. of IIIa, m.p. 210–224°.

A sample was recrystallized from methanol-ethyl acetate, m.p. 242–244°. $[\alpha]_D^{22}$ +27.6° (*c*, 0.6450); $[M]_D$ +102°; ultraviolet $\lambda_{max.}^{MeOH}$ none; $\nu_{max.}^{KBr}$ 3600, 3450, 1022 (axial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 69.10; H, 9.78.

The triacetate IIIb was prepared in the usual manner and was recrystallized from ethyl acetate, m.p. 153–155°. $[\alpha]_D^{22}$ +78.3° (*c*, 0.8406); $[M]_D$ +387°; ultraviolet: $\lambda_{max.}^{MeOH}$ none; $\nu_{max.}^{KBr}$ 3600, 1285, 1270, 1239, 1205 (axial acetate), 1028 (axial acetoxy) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_8$: C, 65.56; H, 8.56. Found: C, 65.59; H, 8.25.

3β,11β,17α,20β,21-Pentahydroxyallopregnane (IVa). A. Crops 3–8 obtained on fractional crystallization of *Fraction A* yielded 72 mg. of IVa, m.p. 200–208°.

B. *Chromatography 1.* Fractions 116–124, which were eluted with ethyl acetate, yielded 24.5 mg. of IVa, m.p. 140–144°. The infrared spectra of both samples were identical with that of authentic IVa.[12]

A sample was recrystallized from methanol and showed a double melting point first at 159–163° then resolidified and melted again at 215–216°. $[\alpha]_D^{22}$ +9.8 (*c*, 0.5555) $[M]_D$ +38°; ultraviolet: $\lambda_{max.}^{MeOH}$ none; infrared: $\nu_{max.}^{KBr}$ 3530, 1043 (equatorial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{36}O_5 \cdot H_2O$: C, 65.25; H, 9.91. Found: C, 65.18; H, 10.01.

The triacetate IVb was prepared in the usual manner; m.p. 204–208°; infrared: $\nu_{max.}^{KBr}$ 3600, 1270, 1028 (equatorial hydroxyl) cm.$^{-1}$. The infrared spectrum was identical with that of authentic IVb.[12]

3α,11β,17α,21-Tetrahydroxyallopregnan-20-one (Va). The three crystalline crops (535 mg.) obtained following the hydrogenation of cortisol in the presence of rhodium (5%) on alumina were Va, m.p. 210–233°.

A sample was recrystallized from methanol, m.p. 244–245°. $[\alpha]_D^{21}$ +59.7° (*c*, 0.3356); $[M]_D$ +219°; ultraviolet: $\lambda_{max.}^{MeOH}$ no selective absorption in the 200–240 mμ region; infrared: $\nu_{max.}^{KBr}$ 3500, 1715, 1005 (axial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.24; H, 9.26.

The diacetate Vb was prepared in the usual manner; m.p. 188–190°, $[\alpha]_D^{19}$ +65.3° (*c*, 0.5605 in methanol); $[M]_D$ +295°; infrared: $\nu_{max.}^{KBr}$ 3600, 1750, 1720, 1265, 1028 (axial acetoxy) cm.$^{-1}$.

3β,11β,17α,21-Tetrahydroxyallopregnan-20-one (VIa). *Chromatography 2.* Fractions 96–107, which were eluted with a mixture of benzene-ethyl acetate (1:1), gave 274 mg. of VIa. Crystallization of the product from acetone gave a first crop m.p. 211–215° and a second crop m.p. 220–222°.

A. The lower melting product was recrystallized, m.p. 215–216°; ultraviolet: $\lambda_{max.}^{MeOH}$ no specific absorption in the 200–240° mμ region: infrared: $\nu_{max.}^{KBr}$ 3540, 3480, 1705, 1690, 1048 (equatorial hydroxyl) cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O_5 \cdot {}^1/_2H_2O$: C, 67.17; H, 9.40. Found: C, 67.40; H, 9.55.

Drying of a sample of the hydrate for 16 hr. at 80° at 0.01 mm. pressure or 3 hr. at 165–170° at 0.01 mm. pressure did not remove the water. Sublimation of the hydrate gave the anhydrous VIa.

B. The higher melting, second crop, was recrystallized twice to give a solid m.p. 221–224°; $[\alpha]_D^{20}$ +61.8° (*c*, 0.6509); $[M]_D$ +216°; ultraviolet: $\lambda_{max.}^{MeOH}$ none in the 220–240 mμ region; infrared: $\nu_{max.}^{KBr}$ 3540, 3480, 1710, 1048 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.46; H, 9.35.

Both alcohols, VIa, were acetylated in the usual manner to yield the same diacetate VIb m.p. 203–206°. Infrared: $\nu_{max.}^{KBr}$ 3600, 1750, 1718, 1245, 1030 cm.$^{-1}$

Paper chromatography of 3β,11β,17α,21-tetrahydroxyallopregnan-20-one (VIa).[18] The anhydrous and hemihydrate samples were chromatographed on paper in the chloroform-formamide system. Both samples showed identical mobilities and a mixture of the two could not be separated.

3β,11β,17α,21-Tetrahydroxypregnan-20-one (VIIa). *Chromatography 2.* Fractions 74–95 which were eluted with a mixture of ethyl acetate-benzene (1:1), gave 635 mg. of VIIa, m.p. 131–138°. A sample was recrystallized from ethyl acetate, m.p. 135–138°; $[\alpha]_D^{22}$ +54.5° (*c*, 0.5288); $[M]_D$ +205; ultraviolet: $\lambda_{max.}^{MeOH}$ no selective absorption in the 200–240 mμ region; infrared: $\nu_{max.}^{KBr}$ 3520, 1712, 1025 (axial hydroxyl).

Anal. Calcd. for $C_{21}H_{34}O_5 \cdot {}^1/_2H_2O$: C, 67.17; H, 9.40. Found: C, 66.85; H, 9.39.

3α,11β,17α,21-Tetrahydroxypregnan-20-one (Xa). *Chromatography 2.* Fractions 108–167 which were eluted with a mixture of benzene-ethyl acetate (1:1), gave 357 mg. of Xa. A sample was crystallized from ethyl acetate methanol, m.p. 207–209°. The infrared spectrum had bands at ν_{max}^{KBr} 3550, 1705, and 1040 cm.$^{-1}$ and was identical to that of authentic Xa.

3β,11β-Dihydroxyetiocholan-17-one (VIIIa). A. *Chromatography 2.* Fractions 58–66 which were eluted with a mixture of ethyl acetate-benzene (1:1), gave 22 mg. of VIIIa.

B. A solution of 50 mg. of 3β,11β,17α,20β,21-pentahydroxypregnane (IIIa) in 2 ml. of aqueous acetic acid (1:1) was shaken 16 hr. with 500 mg. of sodium bismuthate. The excess reagent was reduced with a 10% solution of sodium bisulfite, then diluted with water and extracted thoroughly with ether. The extract was washed with 1 *N* sodium hydroxide, then with a 25% saline solution and dried over sodium sulfate. The removal of the solvent left 43.3 mg. of crystalline VIIIa, m.p. 218–225°.

C. A portion of 3β,11β,17α,21-tetrahydroxypregnan-20-one (VIIa) was treated with sodium bismuthate as above to yield a crystalline residue of VIIIa, m.p. 251–253°. The infrared spectra of the three crystalline samples and of the mother liquor of "C" were identical.

A sample was recrystallized from methanol ethyl acetate, m.p. 259–261°; $[\alpha]_D^{22}$ +82.4° (c, 0.5181 in methanol); $[M]_D^{22}$ +252°; infrared: $\nu_{max.}^{KBr}$ 3600, 3550, 3400, 1728, 1026 (axial hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.88. Found: C, 74.07; H, 9.90.

The alcohol VIIIa was acetylated in the usual manner to yield VIIIb. The crystalline structure of the acetate

changed at 204–209° and the substance melted at 212–215°; $[\alpha]_D^{18}$ +86.5° (c, 0.4108); $[M]_D$ +301°; infrared: $\nu_{max.}^{KBr}$ 3600, 1740, 1257, 1240, 1023 (axial acetoxy) cm.$^{-1}$.

Etiocholane-3,11,17-trione (IX). A. To a solution of 93 mg. of authentic 3α,11β,17α,21-tetrahydroxypregnan-20-one (X) in 3 ml. of glacial acetic acid a solution of 237 mg. of chromium trioxide in 0.4 ml. of glacial acetic acid and 0.1 ml. of water was added and the mixture was left for 16 hr. at room temperature. The reaction mixture was processed in the usual manner and the residue was dissolved in a mixture of ethyl acetate and ether. After two weeks in the refrigerator, 22 mg. of IX m.p. 128–131° separated.

B. A solution of 15 mg. of 3β,11β-dihydroxyetiocholan-17-one (VIIIa) in 0.5 ml. of pyridine was added to a suspension of 20 mg. of chromium trioxide in 0.2 ml. of pyridine and the mixture was left for 16 hr. at room temperature. The product was recovered in the usual manner and was crystallized as above to yield 2 mg. of IX, m.p. 129–131°, infrared: $\nu_{max.}^{KBr}$ 1745, 1705 cm.$^{-1}$.

3α,11β-Dihydroxyethicholan-17-one (XIa). A. The side chain of IIa was cleaved with sodium bismuthate and the steroid was recovered as previously described. The residue was crystallized from ethyl acetate to produce XIa.

B. Authentic 3α,11β,17α,21-tetrahydroxypregnan-20-one was oxidized as above to yield XIa.

The infrared spectra of both samples were identical. The recrystallized sample showed a m.p. 239–241°; infrared: $\nu_{max.}^{KBr}$ 3620, 1715, 1031 (equatorial hydroxyl).

3α,20β,21-Triacetoxy-17α-hydroxypregnan-11-one (XIIb). The sirupy triacetate IIb, 40 mg., was dissolved in pyridine, 0.5 ml., and oxidized for 16 hr. at room temperature with a suspension of 70 mg. of chromium trioxide in 0.7 ml. of pyridine. The reaction mixture was processed as previously described to yield 29 mg. of XIIb, m.p. 197–200°. Recrystallization from ethyl acetate-neohexane raised the m.p. to 202–203°; $[\alpha]_D^{20}$ +104° (c, 0.6561); $[M]_D$ +513°; infrared; $\nu_{max.}^{KBr}$ 3600, 1738, 1698, 1245, 1026 (equatorial acetoxy) cm.$^{-1}$.

3α,17α,20β,21-Tetrahydroxypregnan-11-one (XIIa). A solution of 10 mg. of potassium bicarbonate in 0.1 ml. of water was added to a solution of 10 mg. of XIIb in 0.5 ml. methanol. The air was replaced with nitrogen and the mixture was left for 16 hr. at room temperature. After the addition of a drop of acetic acid the volatile components were removed *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water and dried over sodium sulfate. On concentration the solution gave 4.5 mg. of XIIa, m.p. 240–245°; $[\alpha]_D^{21}$ +28.4° (c, 0.2047); $[M]_D$ +104°; infrared: $\nu_{max.}^{KBr}$ 3550, 1700, 1045 cm.$^{-1}$.

3β,11β-Dihydroxyandrostan-17-one (XIII). A. A solution of 30 mg. of IVa in 15 ml. of methanol was treated with 6 ml. of a stock solution of sodium metaperiodate[3i,1b] and was left for 120 min. in the dark at room temperature. The reaction mixture was processed as previously described[1b] to yield 20 mg. of XIII. The product was recrystallized from ethyl acetate, and showed a m.p. 225–228°.

B. A portion of VIa was oxidized with sodium bismuthate and the 17-ketosteroid was isolated in the usual manner.

The infrared spectra of both samples were identical with that of authentic XIII.[12]

Spectra of 3β,11β,17α,21-tetrahydroxyallopregnan-20-one (VIa), *of* VIa-*hemihydrate and of the diacetate* VIb *in sulfuric acid solution.* The solutions and the spectra were prepared as described by E. Caspi and M. M. Pechet.[19] The spectra were identical and changed in an identical manner with time.

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SHREWSBURY, MASS.

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY AND CHEMISTRY DEPARTMENT, CLARK UNIVERSITY]

Synthesis of Radioactive Dehydroepiandrosterone[1,2]

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A method for the synthesis of dehydroepiandrosterone-4-C^{14} using testosterone-4-C^{14} as starting material and 17-yl sulfite as an intermediate is described. Also described is specifically tritiated dehydroepiandrosterone, obtained by the reduction of 7α-bromodehydroepiandrosterone acetate.

Endocrinological studies on the metabolism of dehydroepiandrosterone prompted us to study the preparation of radioactive dehydroepiandrosterone whereby highest specific activity might be obtained. We are reporting here the synthesis of dehydroepiandrosterone-C^{14} labelled in position 4 and of dehydroepiandrosterone-H^3 labelled mostly in position 7.

The only previously published method for the preparation of isotopically labelled dehydroepiandrosterone (dehydroepiandrosterone-16-C^{13}) by E. B. Hershberg *et al.*[3] was rather involved, requiring the preparation and use of diazomethane C^{14}. Furthermore a few reports[4] on the bio-oxidation of ring D justified the elaboration of a ring A, B, or C labelled dehydroepiandrosterone.

(1) Presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 1958.

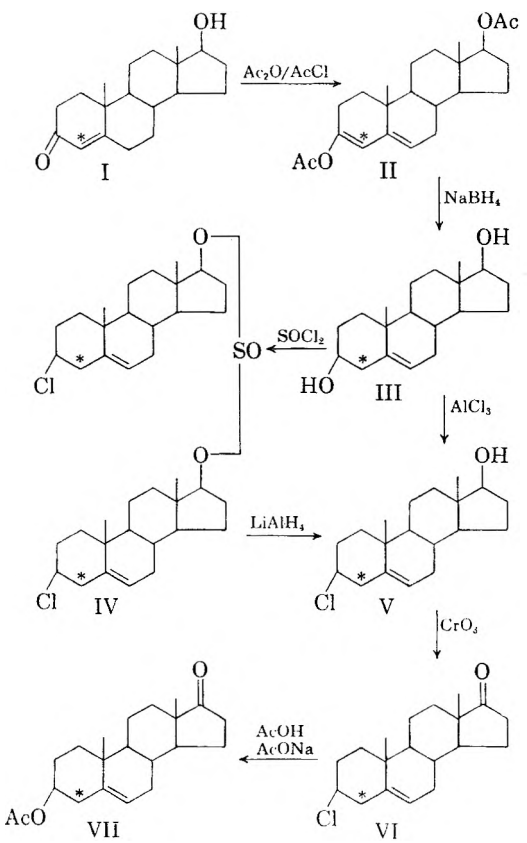
(2) This investigation was supported in part by research grants USPH C-231 and A-2672.

(3) E. B. Hershberg, E. Schwenk, and E. Stahl, *Arch. Biochem.* 19, 300 (1948).

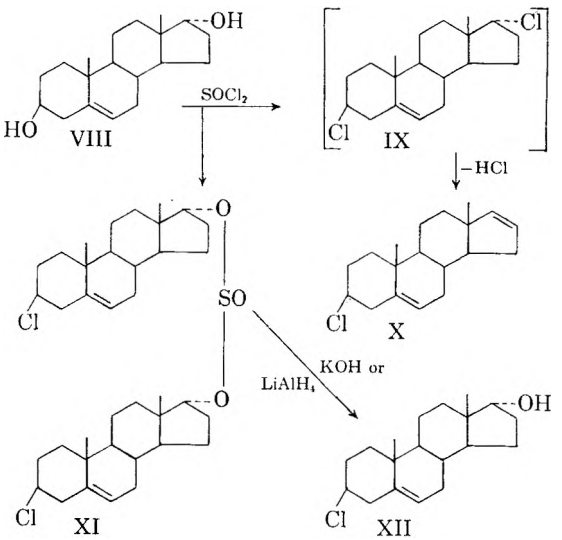
(4) R. D. H. Heard, R. Jacobs, V. O'Donnell, F. G. Peron, J. C. Saffran, S. S. Solomon, L. M. Thompson, H. Willoughby, and C. H. Yates, *Recent Progress in Hormone Research*, 9, 386, (1954).

Since the readily available testosterone-4-C^{14} (I) can easily be transformed to either androst-4-ene-3,17-dione or to androst-5-ene-3β,17β-diol, the main problem of this synthesis consists of either a selective reduction of the 3-ketone (with concomitant shift of the double bond to the 5,6-position), or of the selective oxidation of the 17-hydroxyl group. The latter was carried out as follows:

Testosterone-4-C^{14} (I) was converted to its enol diacetate (II) (with acetic anhydride and acetyl chloride) and the crude reaction product was reduced with sodium borohydride in methanol. The reduced product was refluxed with methanolic hydrochloric acid to hydrolyze residual 17-acetate and eliminate the allylic alcohols which are always obtained as by-products from the hydride-reduction of the enol acetate. The resulting mixture was then chromatographed on silica gel whereby androst-3,5-dien-17β-ol-4-C^{14} and androst-5-ene-3α,-17β-diol-4-C^{14} were separated from the desired androst-5-ene-3β,17β-diol-4-C^{14} (III). The latter product, on treatment with thionyl chloride, yielded bis(3β-chloroandrost-5-en-17β-yl)-sulfite-4,4′-C^{14} (IV). The chloroester was cleaved with lithium aluminum hydride, with retention of the homoallylic chlorine, and the resulting 3β-chloroandrost-5-en-17β-ol-4-C^{14} (V)[5] was oxidized with chromic oxide in acetic acid (the short duration of the oxidation made it unnecessary to protect the double bond by bromination) to 3β-chloroandrost-5-en-17-one-4-C^{14} (VI). This product gave the desired dehydroepiandrosterone-4-C^{14} as its acetate (VII) after refluxing with anhydrous sodium acetate in acetic acid.



In connection with the formation of the above mentioned sulfite ester, the reaction of androst-5-ene-3β,17α-diol with thionyl chloride was examined. As already described, the more[6] hindered 17β-hydroxyl (III) (pseudo equatorial conformation) reacts with thionyl chloride to give the 17β-sulfite ester, while the less[6] hindered 17α-hydroxyl (VIII) (pseudo axial) gives as main product the extremely unstable 17α-chloro compound (IX). The latter could not be isolated as such, but its Δ^{16}-analog (X) was obtained after spontaneous elimination of the elements of hydrochloric acid. In addition very little 17α-sulfite ester (XI) was also isolated. This ester could be hydrolyzed with lithium aluminum hydride or with a methanolic potassium hydroxide solution to the 17α-alcohol.



The striking difference in behavior of the 17α- and 17β-hydroxyl towards thionyl chloride is noteworthy and probably due to differences in steric factors.

Tritiated dehydroepiandrosterone was prepared by catalytic reduction of 7α-bromodehydroepiandrosterone acetate with tritium. We found, however, that more than the calculated amount of tritium had entered; we shall report at a later date on the position and amount of tritium introduced.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Analyses were performed by

(5) This compound could also be obtained though in lower yield, from the corresponding diol by the action of anhydrous aluminum chloride, causing selective replacement of the 3β-hydroxyl group: J. Broome, B. R. Brown, and G. H. R. Summers, *J. Chem. Soc.*, 2071 (1957).

(6) In this pentacyclic alcohol the pseudo equatorial hydroxyl is indeed more hindered (mainly from the 18-methyl group) than the pseudo axial 17α-hydroxyl as can readily be seen from inspection of a molecular model.

Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Ultraviolet absorption spectra were determined in methanol by means of a Cary Model 11 MS spectrophotometer. Optical rotations were determined in a 1-dm. semimicro tube. The infrared spectra were obtained from a pressed potassium bromide prism and taken on a Perkin-Elmer Model 12C spectrometer. All chromatographic separations were made on Davison Silica Gel mesh 100–200.

Testosterone-4-C^{14} (I). This material was prepared following exactly the procedure given by G. I. Fujimoto.[7]

Testosterone enol diacetate-4-C^{14} (II). This substance was prepared as described by U. Westphal.[8] The crude product was recrystallized once from methanol which contained a few drops of triethylamine and melted then at 145–151°, $[\alpha]_D^{23}$ − 147° (chloroform), ultraviolet maximum λ 239 mμ (ε 15100).

Androst-5-ene-3β,17β-diol-4-C^{14} (III). A solution of 1.5 g. of testosterone enol diacetate-4-C^{14} in 10 ml. methanol was added to a suspension of 1 g. of sodium borohydride in 30 ml. of methanol and allowed to stand with occasional shaking at 25° for one day. One additional gram of sodium borohydride was added in portions while the reaction mixture stood for an additional day. Then the mixture was evaporated to dryness, the residue taken up in chloroform, and the chloroform extract washed successively with 2*N* hydrochloric acid, water, 2*N* sodium carbonate solution and again with water. The residue which remained after evaporation of the chloroform was dissolved in 50 ml. of 95% ethanol, 1 ml. of concentrated hydrochloric acid was added, and the resulting solution refluxed under nitrogen for 2 hr. This solution was again evaporated to dryness, extracted with chloroform, the chloroform extract washed with water, 2*N* sodium carbonate solution and water. After drying and evaporation, the residue was dissolved in little benzene and chromatographed. The benzene fractions gave some crystallized material, consisting, most likely, of androsta-3,5-dien-17β-ol-4-C^{14}. The benzene-ethyl acetate fractions gave first a small amount of androst-5-ene-3α,17β-diol-4-C^{14}, melting at 199–205°, and then androst-5-ene-3β,17β-diol-4-C^{14}, melting at 175–178° (not depressed on admixture to authentic material). The yield was 35%.

Bis(3β-chloroandrost-5-en-17β-yl) sulfite-4,4′-C^{14} (IV). To 500 mg. of androst-5-ene-3β,17β-diol-4-C^{14} were added 10 ml. of thionyl chloride and the mixture was shaken for one minute with moisture excluded (until all solid material was dissolved). The solution was evaporated to dryness and the residue stored in a vacuum desiccator over solid sodium hydroxide for 2 days. The remaining crystals, which were now free from the last traces of thionyl chloride, were recrystallized from large amounts of acetone and melted at 231–232° with slow decomposition; yield 82%; $[\alpha]_D^{20}$ − 122° ± 3° (*c*, 0.895 in chloroform); ultraviolet maximum: none; infrared maxima: ν_{max} 3540, 1439, 767, 760 (—Cl), 1200 (sulfite), 822 (trisubstituted double bond), 894 (five ring), 802 (six ring) cm.$^{-1}$.

Anal. Calcd. for $C_{38}H_{56}O_3Cl_2S$: C, 68.75; H, 8.50; Cl, 10.68; S, 4.83. Found: C, 68.93; H, 8.50; Cl, 10.65; S, 4.62.

3β-Chloroandrost-5-en-17β-ol-4-C^{14} (V). A suspension of 305 mg. of bis(3β-chloro-androst-5-en-17β-yl) sulfite-4,4′-C^{14} in 150 ml. ether containing 900 mg. lithium aluminum hydride was refluxed overnight in a dry atmosphere. Then ethyl acetate was added dropwise to the reaction mixture until the excess hydride was consumed. Addition of saturated sodium sulfate solution and then of solid anhydrous sodium sulfate produced a dry ether solution, which was decanted. The residue was extracted several times with ethyl acetate, the extracts added to the ether solution and the combined solutions finally evaporated to dryness. Chromatography of the residue gave, with the benzene-ethyl acetate eluates, colorless prisms, melting 160–163°, $[\alpha]_D^{23}$ −41° ± 3° (*c*, 1.11 in chloroform); ultraviolet maximum: none; infrared maxima: ν_{max} 3350, 1465, 1440, 870, 821, 800, 764 cm.$^{-1}$. Kuwada and Miyasaki[9] give m.p. of 163°.

3β-Chloroandrost-5-en-17-one-4-C^{14} (VI). To the solution of 120 mg. of 3β-chloroandrost-5-en-17β-ol-4-C^{14} in 15 ml. acetic acid was added 1.5 equivalents chromium oxide in 5 ml. 90% aqueous acetic acid and the mixture was allowed to stand for 10 min. at room temperature. Then 5 drops of methanol were added, the solution evaporated to dryness and the residue extracted with benzene. The benzene extract was washed with water, dried and evaporated. Upon chromatography the benzene-ether eluates gave the desired chloro ketone in 81% yield; melting point 155–157° (same melting point on admixture with authentic material).

Dehydroepiandrosterone acetate-4-C^{14} (VII). Three g. of fused powdered sodium acetate was added to a solution of 80 mg. of 3β-chloroandrost-5-en-17-one-4-C^{14} in 30 ml. of acetic acid and the mixture was refluxed for 18 hr. The reaction mixture was extracted with benzene, and the benzene solution washed with 2*N* sodium carbonate solution. The acetate, obtained after evaporation of the benzene, was chromatographed and 76 mg. of dehydroepiandrosterone acetate-4-C^{14}, m.p. 169–171° (unchanged upon admixture with authentic material), was obtained from the benzene-ethyl acetate eluate.

Reaction of thionyl chloride with androst-5-ene-3β,17α-diol.[10] *3β-Chloroandrosta-5,16-diene* (X), *bis(3β-chloroandrost-5-en-17α-yl) sulfite* (XI), *and 3β-chloroandrost-5-en-17α-ol* (XII). To 550 mg. of finely powdered androst-5-ene-3β,17α-diol were added 5 ml. of thionyl chloride and the reaction mixture, with exclusion of atmospheric moisture, immediately cooled to −70°. After all crystals were dissolved (approx. 3 min.), the solution was evaporated to dryness *in vacuo* at −20° and stored for 2 weeks in a vacuum desiccator over solid sodium hydroxide. However, as soon as the crude semicrystalline product was exposed to atmospheric moisture, a pungent gas escaped. The product was chromatographed without any attempt at recrystallization. The hexane eluates furnished, in a yield of 16%, 3β-chloroandrosta-5,16-diene. The analytical sample which was sublimed at $35°_{0.01}$ had a m.p. of 74–76°; $[\alpha]_D^{21}$ −115° ± 3° (*c*, 1.385 in acetone); ultraviolet maximum: none; infrared maxima: ν_{max} 3500, 1440, 872, 839, 817, 805, 760, 725 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}Cl$: C, 78.45; H, 9.36; Cl, 12.19. Found: C, 78.24; H, 9.62; Cl, 12.00.

From the benzene eluates were obtained, in a yield of 7%, bis(3β-chloroandrost-5-en-17α-yl) sulfite, m.p. 235–236°, with instantaneous decomposition; $[\alpha]_D^{20}$ −36° ± 4° (*c*, 1.00 in chloroform); ultraviolet maximum: none; infrared maxima: ν_{max} 1460, 1440, 1205, 877, 829, 764, 730 cm.$^{-1}$.

In another run the crude reaction product was treated with 5% methanolic potassium hydroxide solution for 2 hr. at 25°, the mixture then extracted with ether, washed with water, dried, evaporated, and chromatographed. The hexane fractions gave the above described 3β-chloroandrosta-5,16-diene and from the benzene-ether fractions a third compound was isolated in a yield of 11%, namely 3β-chloroandrost-5-en-17α-ol, m.p. 140–141°; $[\alpha]_D^{20}$ −82° ± 3° (*c*, 0.815 in chloroform); ultraviolet maximum: none; infrared maxima: ν_{max} 3450, 1460, 1435, 823, 760 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.47; Cl, 11.48. Found: C, 74.25; H, 9.49; Cl, 10.98.

The same compound was also obtained from the reduction of bis(3β-chloroandrost-5-en-17α-yl) sulfite with lithium aluminum hydride.

7α-Bromo-3β-ol-androst-5-en-17-one acetate. This material was prepared exactly as described by Antonucci *et al.*[11]

(7) G. I. Fujimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951).

(8) U. Westphal, *Chem. Ber.*, **70**, 2128 (1936).

(9) S. Kuwada and M. Miyasaki, *J. Pharm. Soc. Japan*, **57**, 234 (1937).

(10) Kindly donated by Dr. Horst Witzel, Schering A. G., Berlin.

(11) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).

Dehydroepiandrosterone acetate-7α(?)-H[3].[12] The solution of 103 mg. of 7α-bromo-3β-hydroxyandrost-5-en-17-one acetate was added to the suspension of 1075 mg. of 5% palladium on calcium carbonate which was prereduced. The mixture was shaken with 5 ml. hydrogen to which 2 curies of tritium were added for 1 hr. The reduction mixture was filtered, the filtrate evaporated, and the residue hydrolyzed with methanolic *N* sodium hydroxide solution at room temperature overnight. The hydrolyzed product was worked up and reacetylated. Purification of the acetate by chromatography yielded 48 mg. (57%) of crystalline dehydroepiandrosterone acetate-7α-H[3] with the benzene-ethyl acetate eluates. After recrystallization from methanol it melted at 168–171° and its infrared absorption spectrum was identical[13] with the spectrum of authentic material. The specific radioactivity of this sample was 3.5 mC per mg. On subsequent hydrolysis followed by reacetylation the specific activity remained unchanged.

SHREWSBURY AND WORCESTER, MASS.

(12) Compare D. K. Fukushima, S. Lieberman and B. Praetz, *J. Am. Chem. Soc.*, **72**, 5205 (1950).

(13) The relatively low tritium concentration does not produce changes in the fingerprint region.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Utilization of Gas Phase Chromatography for Identification of Volatile Products from Alkaline Degradation of Herqueinone

JAMES CASON AND EDWIN R. HARRIS

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Low molecular weight carbonyl compounds may be conveniently identified by gas chromatography of their oximes. By use of di-2-ethylhexyl phthalate as partitioning agent, there may be identified in presence of each other the aldehydes with 2–4 carbons, acetone, butanone, and 3-methyl-2-butanone. From the alkaline degradation of herqueinone, the only volatile carbonyl component detected by this method was acetaldehyde. The volatile acids from alkaline degradation of herqueinone, also examined by gas chromatography, have been found to be a mixture of formic, acetic, and isobutyric acids.

In an earlier publication[1] from this laboratory, there was reported an examination of the volatile carbonyl component obtained by heating herqueinone, the red pigment from *Penicillium herquei*, with aqueous alkali. Although the 2,4-dinitrophenylhydrazone originally precipitated from the aqueous distillate agreed rather well in properties with the derivative of acetaldehyde, it was concluded from chromatography experiments that the derivative must be either a mixture, or some other substance than the derivative of acetaldehyde. In a simultaneous publication[2] by Raistrick and co-workers, it was reported that the volatile carbonyl component is acetaldehyde, on the basis of the properties of the 2,4-dinitrophenylhydrazone. Since our earlier results based on chromatography on silicic acid and on Bentonite were probably obscured[3] by decomposition or isomerization of the hydrazone, this carbonyl component has been reexamined by use of gas phase chromatography.

Since acetaldehyde is inconveniently volatile, certain derivatives were considered for use in gas chromatography, and the oxime was found to be well adapted for gas chromatography of low molecular weight carbonyl compounds. A procedure has been developed for formation of this derivative from an aqueous solution of 5–25 mg. of the carbonyl compounds. As shown in Table I, the several compounds examined have sufficiently different retention times to permit their detection.

TABLE I

RETENTION TIMES OF OXIMES IN GAS PHASE CHROMATOGRAPHY

Oxime	Retention Time[a] (min.: sec.)
Acetaldehyde	3:35
Acetone	4:45
Propionaldehyde	5:10
Isobutyraldehyde	6:45
Butanone	7:55
n-Butyraldehyde	9:10
3-Methyl-2-butanone	10:55

[a] Retention time, which is given in minutes and seconds, was taken as time elapsing between injection and maximum in peak. The column was 2 meters × 8 mm. o.d., packed with 30–60 mesh Celite firebrick impregnated with 3% di-2-ethylhexyl phthalate; temperature, 88°; helium flow rate, 35 ml./min.

When the volatile neutral material from alkaline degradation of herqueinone was converted to the oxime and subjected to gas chromatography, a single peak was observed with the retention time of acetaldoxime; no other peak was observed after lapse of 55 minutes. Thus, our observations based on gas chromatography are in accord with the report of the British investigators[2] that acetaldehyde is the only steam-volatile carbonyl component

(1) R. E. Harman, J. Cason, F. H. Stodola, and A. L. Adkins, *J. Org. Chem.*, **20**, 1260 (1955).

(2) J. A. Galarraga, K. G. Neill, and H. Raistrick, *Biochem. J.*, **61**, 456 (1955).

(3) Work to be published in *J. Am. Chem. Soc.* on the alterations of phenylhydrazones has been carried out by Professor H. Rapoport and R. J. O'Connor in this department.

TABLE II

GAS PHASE CHROMATOGRAPHY OF ESTERS AND ACIDS

Compound	Retention Time[a] (min.:sec.)	% Yield[b]
Methyl acetate	6:10	
Methyl propionate	9:45	
Methyl isobutyrate	12:30	
Methyl trimethylacetate	14:55	
Methyl *n*-butyrate	17:30	
Methyl esters of acids from degradation[c]	6:15	1.3 ± 0.5
	12:25	28 ± 3
Butyl formate	[d]	
Butyl acetate	14:40	
Butyl isobutyrate	36:10	
Dibutyl ether	22:50	
Butyl esters of acids from degradation	[d]	1.0 ± 0.5
	15:00	3.0 ± 0.3
	24:10	
	38:20	53 ± 5
Formic acid	14:20	
Acetic acid	16:35	
Propionic acid	30:00	
Isobutyric acid	46:00	
Trimethylacetic acid	59:00	
n-Butyric acid	59:00	
Acids from degradation	14:05	2.9 ± 0.3
	16:35	2.2 ± 0.3
	46:30	42 ± 5

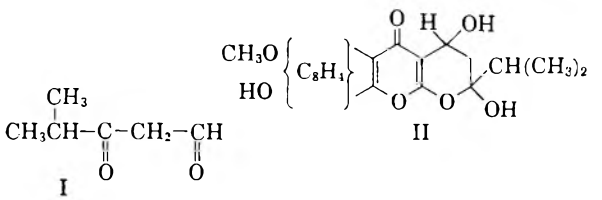
[a] Column used for the methyl esters was 4 m. × 8 mm. o.d.; partitioning agent, 3% di-2-ethylhexyl phthalate on 30–60 mesh Celite firebrick; temp., 50°, helium flow, 42 ml./min. Column used for the butyl esters was 2 m. × 9 mm. o.d.; partitioning agent, 40% high vacuum silicone grease on 30–60 mesh Chromosorb; temp., 76°; helium flow, 75 ml./min. Column used for the acids was 2 m. × 8 mm. o.d.; partitioning agent, 35% on 30–60 mesh Chromosorb of the mixture: 8 parts silicone oil DC 550, 1 part stearic acid, 1 part phosphoric acid; temp. 103°; helium flow, 115 ml./min. [b] Yields, calculated as moles of acid per mole of herqueinone, were determined by comparison of areas under the tracings from degradation products with areas under the tracings of known amounts of known compounds taken under the same conditions. The free acids and methyl esters were the product of the first degradation described in the Experimental section; the butyl esters were the product of the second degradation described. [c] Methyl formate could not be determined for it was under the large band from ether used as solvent. Methyl acetate was on the edge of this band, so the uncertainty in the measurement was relatively large, as indicated. In another chromatography at 19°, the methyl acetate band with retention time of 11:45 was resolved from ether; yield was calculated as 1.8 ± 0.2%. [d] At 76°, butyl formate was not resolved from the large band resulting from excess butyl alcohol used in esterification. At 58°, the butyl formate band appeared on the trailing edge of the butyl alcohol band, at 14:30. Comparison of area with that of a known sample of butyl formate (retention time, 14:45) indicated a yield of 1 ± 0.5% of formic acid, based on herqueinone.

recovered from alkaline degradation of herqueinone.

Failure to find 3-methyl-2-butanone, formed in acid degradation of herqueinone,[1,2] in the distillate from alkaline degradation does not unequivocally prove that this ketone is not a degradation product; however, it probably is not formed in significant amounts. When 1.0 millimole of acetaldehyde and 0.25 millimole of 3-methyl-2-butanone were added to 1*N* alkali, and the mixture was then heated to boiling and distilled, neither compound could be detected in the distillate. In contrast, however, when a solution of 1.0 millimole of the aldehyde and 0.5 millimole of the ketone was added slowly beneath the surface of the distilling alkaline solution, 86% of the 3-methyl-2-butanone was recovered.

Although it was reported previously[1] that volatile acid is liberated during alkaline degradation of herqueinone, the nature of the acid was not investigated. This volatile acid has now been examined by utilization of gas phase chromatography of the free acid, its methyl ester, and its butyl ester. As shown by the data in Table II, the principal component of this acid mixture is isobutyric acid, although small amounts of formic and acetic acids are also present. It is of interest that the yields of acetaldehyde and isobutyric acid are comparable.

It seems highly probable that the isopropyl group in the isobutyric acid from alkaline degradation of herqueinone arises from the same carbon atoms as does the isopropyl group in the 3-methyl-2-butanone obtained by acid degradation. This follows from the fact that hydrolysis of herqueinone to yield 3-methyl-2-butanone would give $C_{15}H_{12}O_7$ as the residual fragment. Hydrolytic cleavage of isobutyric acid from this fragment would leave $C_{11}H_6O_6$, a rather improbable formula. If there be only one potential isopropyl group in herqueinone, the equivalent yields of acetaldehyde and isobutyric



II

I

acid, along with the very low yields of formic and acetic acids, indicate presence in herqueinone of some structure which may give rise to structure I (or its parts) on alkaline hydrolysis. If the formyl group in structure I should be generated by a chain-cleavage step such as the reverse aldol condensation, then a different direction of chain cleavage might account for the formation of 3-methyl-2-butanone in acid degradation. Although such a partial structure as II could give rise to I (as well as small amounts of acetic acid) and is consistent with other properties of herqueinone, there is not yet available sufficient evidence to allow any firm conclusions concerning the basic ring structures present in herqueinone.

TABLE III

PHYSICAL PROPERTIES OF OXIMES

Oxime of	B.P., °C./mm. Hg Obsd.	B.P., °C./mm. Hg Lit.	n_D^{25} (Obs.)	n_D (°C.) (Lit.)
Acetaldehyde	114/760	114–115/760[a]	1.4230	1.4257 (20.4)[b]
Propionaldehyde	39–42/33	77/100[c]	1.4288	1.4287 (20)[d]
n-Butyraldehyde	65–67/22	67/16.5[e]	1.4333	1.4367 (20)[f]
Isobutyraldehyde	53–54/21	139/760[a]	1.4252	1.4302 (20.5)[b]
Acetone	133/760	135/728[g]	m.p. 57–59°	m.p. 59–60°[g]
Butanone	47–48/18.5	152/763[d]	1.4367	1.4428 (20)[d]
3-Methyl-2-butanone	74.5/21	158–160/760[h]	1.4414	

[a] J. Petraczek, *Ber.*, **15**, 2784 (1882). [b] J. W. Brühl, *Z. physik. Chem.*, **16**, 214 (1895). [c] E. Bourgeois and J. Dambmann, *Ber.*, **26**, 2860 (1893). [d] C. Trapesonzjanz, *Ber.*, **26**, 1432 (1893). [e] S. Yamada, I. Chibata, and R. Tsurui, *Pharm. Bull. (Tokyo)*, **2**, 59 (1954); *Chem. Abstr.*, **50**, 11132 (1956). [f] A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 542 (1952). [g] V. Meyer and A. Janny, *Ber.*, **15**, 1324 (1882). [h] P. Karrer, M. Gisler, E. Horlacher, F. Locher, W. Mäder, and H. Thomann, *Helv. Chim. Acta*, **5**, 478 (1922).

EXPERIMENTAL[4]

Preparation of oximes on small scale. To a solution of 10–100 mg. of the carbonyl compound in 10 ml. of water was added 3.13 g. (45 mmoles) of hydroxylamine hydrochloride. To this solution was added 2.39 g. (22.5 mmoles) of anhydrous sodium carbonate sufficiently slowly to allow control of effervescence. This mixture was extracted continuously for 1 hr. with ether which had been distilled from sulfuric acid and stored over sodium. After the extract had been dried over sodium sulfate, ether was distilled through the column until only about 1 ml. of solution remained. The column was allowed to drain for a few minutes, then the residual solution was transferred by use of a syringe to a 2-ml. volumetric flask. Ether used to wash the distillation flask was added to bring the volume to 2 ml., and this solution was used for injection in gas phase chromatography.

Oximes used to determine the retention times recorded in Table I were prepared on a larger scale and purified by distillation. Properties are found in Table III. Those oximes which were distilled at reduced pressure were found to decompose to some extent when distillation at atmospheric pressure was undertaken.

Esters used for determining retention times recorded in Table II were commercial products, except in the instances of trimethylacetic acid and isobutyric acid, in which cases commercial acids were directly esterified.

Alkaline hydrolysis of herqueinone. A solution of 744 mg. (2 mmoles) of herqueinone (isolated as previously described[1] and purified by chromatography) in 100 ml. of *N* aqueous sodium hydroxide was directly steam-distilled in a slow stream of nitrogen. During the first few seconds of distillation the odor of acetaldehyde was observed, and this was soon replaced with the odor of aldol. The distillate was collected in 4-ml. portions in ice-cooled receivers. The first 6 portions of distillate (24 ml.) gave a positive test for aldehyde with 2,4-dinitrophenylhydrazine, while the seventh portion was negative; so the first 24 ml. was treated in the manner described above for formation of oximes on a small scale. Quantitative gas phase chromatography indicated a 20% yield of acetaldehyde (based on one mole of acetaldehyde per mole of herqueinone), and no band was observed except that with the retention time of acetaldehyde.

After carbonyl components had been distilled, as described above, the alkaline aqueous solution was acidified with sulfuric acid to *p*H 2, and distillation was continued as water was added at about the rate it was distilled. The distillate was collected in 4 portions whose volumes were respectively 230, 60, 90, and 50 ml. Titration of these samples with 0.1*N* sodium hydroxide, using phenolphthalein as indicator, gave consumption of 10.65, 0.48, 0.38, and 0.00 ml. of alkali. Thus, total yield of acids distilled amounted to 1.15 meq. or 58% of one mole per mole of herqueinone degraded. The first 3 portions of distillate were combined, the *p*H was adjusted to 13, and the volume reduced by distillation to about 10 ml. The concentrated solution was acidified with sulfuric acid and continuously extracted with ether for 20 hr. The extract was concentrated under a column and eventually made up to a 2-ml. volume for injection in gas chromatography, following the procedure described under preparation of oximes. Chromatography was with the silicone oil–phosphoric acid–stearic acid partitioning agent, as recorded in Table II.

The solution remaining after chromatography of free acids (about 95% of the total) was allowed to react with 1.5 mmoles of diazomethane[5] for about 2 hr. The resultant solution was centrifuged to remove a small gelatinous precipitate, then made up to 5 ml. for gas chromatography as recorded for methyl esters in Table II.

In a second run, utilizing 372 mg. (1 mmole) of herqueinone, the pigment was dissolved in about 10% of the alkaline solution and added slowly to the boiling solution of the remainder of the base. To ensure recovery of acetaldehyde, ice water was circulated through the condenser. Gas chromatography indicated a yield of 50 ± 5% of acetaldehyde. The yield of acids in this run, by titration, was 59%. The solution of the acid salts obtained as described for the first run was evaporated to dryness under reduced pressure, and esters were prepared by heating the salts at 100° for 1 hr. with 1.5 ml. of *n*-butyl alcohol containing 20% by weight of concentrated sulfuric acid. The reaction mixture was dissolved in 10 ml. of ether and extracted once with water, twice with 7% sodium bicarbonate solution, and once with saturated sodium chloride solution. After the solution had been dried and concentrated to 2.6 ml. it was used for injection in gas chromatography (cf. Table II).

Distillation of 3-methyl-2-butanone and acetaldehyde from alkaline solution. (*a*) A mixture of 1 mmole of acetaldehyde and 0.25 mmole of 3-methyl-2-butanone was added to 50 ml. of cold *N* aqueous sodium hydroxide. The mixture was heated to boiling and distilled in an atmosphere of nitrogen until 10 ml. of distillate had been collected. The distillate

(4) Boiling points are uncorrected; distillations were carried out through a 65-cm. column of a simple Podbielniak design, with heated jacket and partial reflux head. Partitioning agents and dimensions of columns for gas phase chromatography are indicated in Tables I and II.

(5) The diazomethane solution, prepared according to F. Arndt, *Org. Syntheses*, Coll. Vol. II, 165 (1943), was not distilled but was assayed by titration.

was processed as described for small scale preparation of oximes. Gas chromatography indicated no carbonyl components in the distillate.

(*b*) A sample of 0.25 mmole of 3-methyl-2-butanone was distilled as described under (*a*). Gas chromatography indicated a recovery in the distillate of 0.2 mmole of the ketone.

(*c*) A solution of 1 mmole of acetaldehyde and 0.5 mmole of 3-methyl-2-butanone in 10 ml. of water was added beneath the surface of 50 ml. of a distilling *N* solution of aqueous alkali. Rate of addition was about equal the rate of distillation, and the procedure was as in (*a*) except for the gradual addition to the distilling solution. Gas chromatography indicated a recovery in the first 10 ml. of distillate of 75% of the acetaldehyde and 86% of the ketone.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO.]

(+)-2,3-Diaminosuccinic Acid

F. A. HOCHSTEIN

Received November 3, 1958

(+)-2,3-Diaminosuccinic acid has been found in the fermentation beers of *Streptomyces rimosus*. This is the first reported isolation of a diaminosuccinic acid from a natural source.

Diaminosuccinic acid has long been known as a synthetic substance. The first preparations of *dl*- and *meso*- forms were reported as early as 1893, and many syntheses have been effected since that time.[1,2] There is no record of the isolation of this material from natural sources, though it has been reported to be a product of enzymatic synthesis from hydrazine and fumaric acid by pig liver and *E. coli* preparations.[3]

We wish to report here the isolation of an optically active form of diaminosuccinic acid from the fermentation beers of *Streptomyces rimosus*, an actinomycete better known as the producer of the antibiotic Terramycin.[4] When the acidified filtered beers were adjusted to *p*H 2–4, the crude acid in some cases precipitated directly as white crystals of the dihydrate, which decomposes without melting at 240–260°. The pure anhydrous compound shows $[\alpha]_D^{25}$ +28° in 5% sodium hydroxide.

The structure of the new compound follows from its elemental analysis, $C_4H_8N_2O_4$, and from its chemical and physical properties. Titration shows it to be a dibasic acid, pK_a 6.7 and 9.1. The amine nature of the two nitrogen atoms is evident from the ready formation of the dibenzoyl and di-2-naphthalenesulfonyl derivatives. The compound shows only end absorption in the ultraviolet spectrum. The infrared spectrum, (KBr) which shows strong bonded NH and OH absorption at 3–3.5μ, and broad bonded carbonyl absorption at 6.1μ, is entirely consistent with this structure. Our product is identical to synthetic *dl*-2,3-diaminosuccinic acid on two paper chromatography systems.

We were unable to detect diaminosuccinic acid in either the raw broth prior to fermentation, or in acid hydrolysates of the protein source (soy bean meal). It seems evident that diaminosuccinic acid is therefore an elaboration product of *S. rimosus*, and is not merely liberated from the vegetable protein. This conclusion is strengthened by the observation that the yields of acid (1–2 g./l.) would account for 10% of the total protein nitrogen introduced in the fermentation media.

Qualitative (paper chromatographic) examination of the beers from several strains of *S. rimosus* all showed the presence of diaminosuccinic acid. However, two strains of *S. aureofaciens* yielded no detectable quantities of diaminosuccinic acid.

EXPERIMENTAL

Isolation of (+)-2,3-diaminosuccinic acid. Streptomyces rimosus was grown for 96 hr. at 28° with aeration in a medium containing only 4% soybean meal, and 0.5% sodium nitrate. (Other media may also be used.)

Two l. of the broth were adjusted to *p*H 2 with HCl, filtered from mycelia, and readjusted to pH 4. After refrigerated storage (2–5°) for one week, 1.36 g. of crude (+) diaminosuccinic acid was separated by filtration. Twenty g. of the crude product isolated in a similar manner was purified by solution in 400 ml. of 5% aqueous hydrochloric acid at 80°, treatment with 2 g. "Darco G-60" charcoal, and filtration. On addition of 10*N* sodium hydroxide, precipitation started at *p*H 1, and appeared to be substantially complete at *p*H 4. The suspension was cooled to 5° overnight and 18 g. of white crystals were recovered by filtration. Paper chromatographic examination on a methyl ethyl ketone–acetic acid-water 3:1:1 system showed substantially one component, which gave an abnormal gray-violet ninhydrin color on spraying with detection reagent and heating the paper. A methanol-pyridine–water 8:2:1 system showed a single component with R_f between that of *meso*- and of (+)-diaminopimelic acid.

Two grams of once recrystallized diaminosuccinic acid was dissolved in 300 ml. of boiling water and cooled to 5° to yield 1.8 g. of a pure hydrated diaminosuccinic acid. Drying overnight at 20 mm. and room temperature over calcium

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(1) J. M. Farchy and J. Tafel, *Ber.*, **26**, 1980 (1893) and J. Tafel and H. Stern, *Ber.*, **38**, 1589 (1905).

(2) H. McKennis, Jr., and A. S. Yard, *J. Org. Chem.*, **23**, 980 (1958) have reported a recent study. They give an excellent series of references to chemical and biochemical work through 1957.

(3) K. P. Jacobsohn and M. Soares, *Enzymologia*, **1**, 183 (1936).

(4) Terramycin is the registered trade name of Charles Pfizer and Co. for the antibiotic oxytetracycline.

chloride yielded the dihydrate (18% volatile found, calcd. 19.0%) which was further dried at 100°, 0.1 mm. to constant weight (6 hr.) for analysis.

The anhydrous compound has $[\alpha]_D^{25}$ +28° (*c*, 2 in 5% NaOH) $[\alpha]_D^{25}$ +59° (*c*,2 in 5% HCl). It decomposes without melting over a broad range, 240–290°, depending on rate of heating. Titration of an aqueous solution indicates a dibasic acid, pK_a 6.7, and 9.1, eq. wt. 72 and 156. (Calcd., eq. wt. 74 and 148.1.)

Anal. Calcd. for $C_4H_8N_2O_4$: C, 32.43; H, 5.44; N, 18.91. Found C, 32.42; H, 5.23; N, 18.89.

The ultraviolet absorption spectrum in water solution shows only end absorption, ϵ = 38 at 220 mμ. The infrared absorption spectrum (KBr pellet) shows bonded OH and NH absorption at 3–3.5μ, and a very broad carbonyl absorption band at 6–6.2μ.

A quantitative analysis (paper chromatography–ninhydrin) of the broth indicates the presence of about 1–2 g. of (+)-2,3-diaminosuccinic acid per liter of the broth examined. Unfermented broths showed no diaminosuccinic acid.

Acid stability of diaminosuccinic acid. A solution containing 2% diaminosuccinic acid in 10% aqueous HCl was heated under reflux for 24 hr. Aliquots were withdrawn at 2, 6, and 24 hr. Neutralization to *p*H 3 yielded crystalline acid in each case.[5] Paper chromatographic examination of the samples indicated that slight decomposition to other ninhydrin positive substances had occurred at 6 hr.; definite decomposition was detectable at 24 hr. A sample of the soybean meal used in the fermentation was hydrolyzed in 10% hydrochloric acid at reflux for 24 hr. Paper chromatographic examination of the hydrolysates showed no diaminosuccinic acid.

N,N'-Dibenzoyl-(+)-2,3-diaminosuccinic acid. One-half g. of (+)-diaminosuccinic acid, was dissolved in 9 ml. of 5% sodium hydroxide, cooled to 0°, and 1 ml. of benzoyl chloride added to the stirred solution. After standing at room temperature overnight, the solution was acidified to *p*H 2 with HCl, and the resulting suspension was extracted twice with an equal volume of ether to yield 0.8 g. of crude dibenzoyldiaminosuccinic acid. This crude product was twice crystallized from 5 ml. ethanol by addition of water. The pure product, 0.35 g., melts at 164–166° with softening and darkening from 158°. It was dried for 2 hr. at 80°, 0.05 mm. for analysis. $[\alpha]_D^{25}$ +109° (*c*, 1 in MeOH).

Anal. Calcd. for $C_{18}H_{16}N_2O_6 \cdot H_2O$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.51; H, 4.89; N, 7.71.

N,N'-di-2-Napthalenesulfonyl-(+)-2,3-diaminosuccinic acid. Two hundred mg. of (+)-diaminosuccinic acid in 27 ml. 1*N* sodium hydroxide was stirred with 1.2 g. 2-naphthalenesulfonyl chloride in 5 ml. ether. Three 2.7-ml. portions of *N* NaOH were added at 1, 3, 4 hr. The aqueous phase was separated, acidified, and the crude product, 0.55 g. was crystallized twice from ethanol-water and dried at 26°, 0.01 mm. for analysis. The product obtained in this way melted at 190–195° with much prior decomposition. This m.p. is dependent on rate of heating. This substance did not analyze satisfactorily.

Anal. Calcd. for $C_{24}H_{20}N_2S_2O_8 \cdot {}^1/_2\ H_2O$. C, 53.70; H, 3.95; N, 5.21. Found: C, 53.78; H, 4.38; N, 5.90.

The corresponding *dl* derivative melts at 200°, the *meso* derivative at 234°.[1]

Examination of S. aureofaciens beers. Beers from the fermentations of two strains of *S. aureofaciens* in media containing corn steep liquor as the proteinacious ingredient were filtered and examined directly by chromatography on a methyl isobutyl ketone-acetic acid–water system. No (+)-2,3-diaminosuccinic acid could be detected. A standard containing 0.1% diaminosuccinic acid gave a strong positive test in the same run.

Acknowledgments. I am indebted to Dr. F. W. Tanner, Jr., for the fermentation broths, to Mr. M. J. Lynch for the paper chromatographic studies, and to Dr. R. L. Wagner and his associates for the physical measurements and analyses. I wish to thank Mr. A. Adriansen for his competent technical assistance. Dr. A. S. Yard kindly provided the *dl*-2,3-diaminosuccinic acid for comparison.

BROOKLYN 6, N. Y.

(5) R. Kuhn and F. Zumstein, *Ber.*, **59**, 479 (1926), state that *dl*-diaminosuccinic acid is converted to the *meso* form after 3 hrs. reflux in 15% hydrochloric acid. A similar conversion may have occurred here, but was not evident from the paper chromatograms.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE]

Reaction of Ethylene Dibromide with Triethylamine and the Restoring Action of Some Alkanebis(triethylammonium) Ions upon Sodium-Deficient Nerve Fibers

FREDERICK VIDAL

Received December 19, 1958

It is shown that the reaction of ethylene dibromide with triethylamine yields no ethylenebis(triethylammonium bromide-contrary to the reports in the literature. The only crystalline products obtained are triethylamine hydrobromide and 1) bromoethane-2-triethylammonium bromide.

The synthesis and properties of the ethylenebis(triethylammonium halides), prepared in the course of studies on neurophysiological problems, are reported. The bisquaternary ammonium salts were formed by quaternization of *N,N,N',N'*-tetraethylethylenediamine with ethyl halide. In addition to the bisquaternary ammonium compounds mixed tertiary-quaternary ammonium salts, ethane-1-diethylamino-2-triethylammonium halides, were also isolated, whose properties are described.

For many years this laboratory has been engaged[1] in testing the neurophysiological effects of different nitrogenous basic compounds on nerve fibers. Some of these onium ions, of which the tetraethylammonium ion may be regarded as one of the prototypes, restore the ability to conduct impulses in sodium-deficient nerve fibers.

In order to study the biological activities of the

alkanebis(triethylammonium chlorides) in this system, we prepared the corresponding compounds containing polymethylene chain lengths of C_2, C_3, C_5, and C_{10}. The reaction of α,ω-alkene dibromides with triethylamine yielded the 3-, 5-, and 10-carbon members.[2,3] However, the 2-carbon member could not be obtained employing this method, despite a claim[4] that ethylenebis(triethylammonium bromide) can be synthesized by the addition of ethylene dibromide to triethylamine.

The reaction of ethylene dibromide with triethylamine in ethanol, performed in a pressure bomb according to Lucius,[4] yielded in our laboratory two crystalline products. One of them was identified as triethylamine hydrobromide, which previously had been claimed to be ethylenebis(triethylammonium bromide). This compound and its picrate showed no depression in melting points when mixed with the corresponding triethylamine salts and its bromine analysis checked with the theoretically required value. The second crystalline product of this synthesis was 1-bromoethane-2-triethylammonium bromide.[5] The nitrogen: bromine ratio of this salt was 1:2 and only one half of the total bromine was ionically bound. Furthermore, the reaction was accompanied by formation of a gas which presumably was vinyl bromide.

We also obtained the same crystalline reaction products either by heating under reflux in an open flask[2] or by simply allowing the starting materials to stand at room temperature for several weeks. In neither instance were we able to detect any ethylenebis(triethylammonium bromide).

Our findings are in agreement with these of Hofmann[6] who could not obtain the bisquaternary ammonium compound by reacting ethylene dibromide with triethylamine. It is also known that the expected bisquaternary ammonium salts are not always produced by the reaction of ethylene dibromide with tertiary amines.[7] Furthermore, it has recently been demonstrated that the reaction of ethylene dibromide with trimethylamine yielded a mixture of products. One of these was actually identified as tetramethylammonium bromide[8] and was not, as had been previously claimed, ethylenebis(trimethylammonium bromide).

Authentic ethylenebis(triethylammonium halides) were obtained by a two-step process. At first we prepared *N,N,N′,N′*-tetraethylethylenediamine according to the procedure of Laasko and Reynolds.[9] Quaternization of this bistertiary amine was achieved by refluxing the base for several hours with ethyl bromide or ethyl iodide in ethanol, yielding ethylenebis(triethylammonium halide). In addition to this bisquaternary ammonium salt a mixed tertiary-quaternary ammonium compound, ethane-1-diethylamino-2-triethylammonium halide, was also isolated. On further reaction with ethyl halide the latter product yielded the desired bisquaternary ammonium halide. Ethylenebis(triethylammonium bromide) could be quantitatively converted to the corresponding dichloride by adsorbing on the cation exchange resin Dowex 50-WX8 and eluting with 3*N* hydrochloric acid.

The reason for the failure to obtain the bisquaternary ammonium compound in the reaction between ethylene dibromide and triethylamine in all probability is due to steric hindrance in the final product. An inspection of a Courtauld model of ethylenebis(triethylammonium) ion clearly shows almost complete restriction of C—C rotation as a result of the relatively bulky triethylammonium groups in close proximity with one another. It is therefore not surprising that the addition of one molecule of triethylamine to the dibromide with the subsequent formation of the isolated monoquaternary compound proceeds smoothly. On the other hand, the addition of the second molecule of triethylamine to this intermediate is greatly impeded resulting in a negligible yield of the diquaternary ammonium bromide. The isolation of triethylamine hydrobromide from the reaction mixture indicates that hydrogen bromide is also formed. It is split off from the unreacted ethylene dibromide under the conditions of the experiment with the simultaneous production of vinyl bromide.

The neurophysiological results of some of the onium ions tested are shown in Table I. It will be seen that with the exception of ethane-1-diethylamino-2-triethylammonium chloride whose activity was dubious, all the other compounds were able to restore conduction of impulses in sodium-deficient bullfrog splanchnic nerve fibers. However, the restoring ability of tetraethylammonium ion was greater than the activity of the alkanebis(triethylammonium) ions. Furthermore, it can be seen that ethylenebis(triethylammonium chloride) restored the ability to conduct impulses to more fibers than triethylammonium chloride.

Full details of the neurophysiological experiments, the methods used, and the results obtained will be reported elsewhere.

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(8) A. P. Gray and T. B. O'Dell, *Nature*, **181**, 634 (1958).

(9) T. M. Laasko and D. D. Reynolds, *J. Am. Chem. Soc.*, **73**, 3518 (1951).

TABLE I

RELATIVE ABILITY OF ONIUM IONS TO RESTORE CONDUCTION OF IMPULSES IN SODIUM-DEFICIENT NERVE FIBERS

Compound	Degree of Restoring Ability
Ethane-1-diethylamino-2-triethylammonium chloride	X?
N,N,N',N'-tetraethylethylenediamine hydrochloride	X
Triethylammonium chloride	XX
Ethylenebis(triethylammonium) chloride	XXX
Pentamethylenebis(triethylammonium) chloride	XXXX
Decamethylenebis(triethylammonium) chloride	XXXX
Tetraethylammonium chloride	XXXXX

EXPERIMENTAL[10-12]

Reaction of triethylamine with ethylene dibromide.[4] (*a*) A mixture of 22.5 g. triethylamine, 45 g. ethylene dibromide, and 30 ml. absolute ethanol was heated for 6 hr. in a pressure bottle to 80–90°. During this period the pressure rose constantly. After cooling the solution to room temperature the crystalline material was removed by filtration and recrystallized from ethanol; 21 g. of white product, m.p. 247–249°,[13] were obtained. A mixed melting point with a sample of ethylenebis(triethylammonium bromide), prepared by a different method (see below), showed a marked depression. But it showed no depression in a mixed melting point with triethylamine hydrobromide.

Anal. Calcd. for $C_{14}H_{34}Br_2N_2$: Br, 40.96; for $C_6H_{16}BrN$: Br, 43.88. Found: Br, 43.99.

With saturated aqueous picric acid triethylamine picrate, m.p. 173–175°, was obtained. A mixed melting point with an authentic sample was not depressed.

Upon addition of ether to the alcoholic filtrate from triethylamine hydrobromide, a solid material precipitated which after recrystallization from propanol-ether yielded 3.1 g. 1-bromoethane-2-triethylammonium bromide, m.p. 216–217°, (reported[4] m.p. 241–242°).

Anal. Calcd. for $C_8H_{19}Br_2N$: C, 33.24; H, 6.63; Br^-, 27.65; Br (total), 55.29; N, 4.84. Found: C, 33.34; H, 6.67; Br^-, 27.82; Br (total), 54.68; N, 4.73.

This salt yielded with saturated aqueous picric acid 1-bromoethane-2-triethylammonium picrate as a slightly soluble crystalline salt, m.p. 141–143°.

Examination of the mother liquor from 1-bromoethane-2-triethylammonium bromide failed to reveal ethylenebis(triethylammonium bromide) or any other substance.

(*b*) Triethylamine (125 g.), 63 g. ethylene dibromide, and 50 ml. ethanol were refluxed in an open flask[2] for 24 hr. The crystalline products were isolated as described above. 24 g. triethylamine hydrobromide and 3.9 g. β-bromoethyltriethylammonium bromide were thus obtained.

(*c*) A mixture of 20.5 g. triethylamine and 16.3 g. ethylene dibromide was allowed to stand at room temperature for 2 weeks in a stoppered container. On working it up as described in (*a*), 1.3 g. triethylamine hydrobromide and 2.9 g. 1-bromoethane-2-triethylammonium bromide were isolated. In both experiments (*b* and *c*) no ethylenebis(triethylammonium bromide) was found.

Preparation of 1-bromoethane-2-triethylammonium chloride. Six grams of 1-bromoethane-2-triethylammonium bromide was dissolved in 60 ml. water and stirred with 18 g. of silver chloride at room temperature. The slurry was filtered and the filtrate evaporated *in vacuo* to dryness. The residue was recrystallized twice from propanol-ether to yield 1-bromoethane-2-triethylammonium chloride, m.p. 224–226° (dec.).

Anal. Calcd. for $C_8H_{19}BrClN$: Br, 32.67; Cl, 14.50. Found: Br, 32.90; Cl, 14.51.

Preparation of ethylenebis(triethylammonium) iodide. *N,N,N',N'*-tetraethylethylenediamine[9] (17.2 g., 0.1 mole) in 15 ml. ethanol and 33 g. (0.21 mole) ethyl iodide were refluxed for 2 hr. Upon cooling to room temperature, the precipitate which formed was filtered and washed with ethanol, m.p. 228–230° (dec.). After several recrystallizations of the crude material from water, 17.4 g. (35.5%) of ethylenebis(triethylammonium iodide), m.p. 236–238° (dec.), were obtained. This salt is slightly soluble in cold water, soluble in hot water, and practically insoluble in methanol.

Anal. Calcd. for $C_{14}H_{34}I_2N_2$: C, 34.72; H, 7.07; I, 52.42; N, 5.78. Found: C, 34.55; H, 7.21; I, 52.57; N, 5.69.

A *picrate* was prepared in aqueous solution and recrystallized from methanol. Ethylenebis(triethylammonium picrate) melted at 244–245°.

Anal. Calcd. for $C_{26}H_{38}N_8O_{14}$: C, 45.47; H, 5.58; N, 16.32. Found: C, 45.64; H, 5.83; N, 16.12.

After concentrating the combined aqueous mother liquors of the ethylenebis(triethylammonium iodide) recrystallizations to a small volume and subsequent cooling, 0.2 g. (0.5%) ethane-1-diethylammonium-2-triethylammonium diiodide, m.p. 193–194° (dec.), was obtained.

Isolation of ethane-1-diethylamino-2-triethylammonium iodide. Ether was added to the alcoholic mother liquor which remained after filtration of the bisquaternary ammonium iodide until a white precipitate started to separate. The precipitate was filtered, washed with ether, and dried *in vacuo*, m.p. 89–92°. Recrystallization from acetone-ether gave 14.3 g. (43.5%) ethane-1-diethylamino-2-triethylammonium iodide, m.p. 90.5–92.5°. This product is very soluble in water, ethanol, and acetone, insoluble in ether.

Anal. Calcd. for $C_{12}H_{29}IN_2$: C, 43.90; H, 8.90; I, 38.66, N, 8.53. Found: C, 43.91; H, 8.87; I, 38.55; N, 8.57.

A *picrate* was prepared from this monoiodide. Ethane-1-diethylammonium-2-triethylammonium dipicrate was precipitated as a sparingly soluble crystalline salt. On recrystallization from methanol, its m.p. was 186–188°.

Anal. Calcd. for $C_{24}H_{34}N_8O_{14}$: C, 43.77; H, 5.20; N, 17.02. Found: C, 43.95; H, 5.29; N, 17.31.

Preparation of ethane-1-diethylammonium-2-triethylammonium diiodide. This salt was prepared by adding the theoretical amount of hydriodic acid to an aqueous solution of ethane-1-diethylamino-2-triethylammonium iodide. Removal of the solvent under reduced pressure and recrystallizing the residue twice from propanol, gave the desired product, m.p. 194–195° (dec.).

Anal. Calcd. for $C_{12}H_{30}I_2N_2$: I, 55.64. Found: I, 55.79.

This diiodide yielded with picric acid, ethane-1-diethylammonium-2-triethylammonium dipicrate, m.p. 186–188°.

Formation of ethylenebis(triethylammonium iodide) from ethane-1-diethylamino-2-triethylammonium iodide (I). A mixture of 6.5 g. (0.02 mole) (I), 11 g. (0.07 mole) ethyl iodide, and 15 ml. ethanol was refluxed for 8 hr. The precipitate which formed upon cooling was removed by filtration and washed with ethanol. Recrystallization from water yielded 5.1 g. (53%) ethylenebis(triethylammonium) iodide m.p. 236–238° (dec.).

After concentrating the ethanolic filtrate and subsequent cooling, a product precipitated. Removal of the solid by filtration and recrystallizing it from propanol, gave 2.0 g. (22%) of ethane-1-diethylammonium-2-triethylammonium diiodide, m.p. 193–195° (dec.). By adding ether to this last alcoholic mother liquor, 1.5 g. (23%) of material precipi-

(10) All melting points are corrected. Determinations were made with the Kofler block.

(11) Microanalysis for C, H, and N were carried out by Mr. T. Bella of this Institute.

(12) The halogen of the quaternary halides was determined as ionic halid by the Volhard method. The nonionic bromine was determined by the Carius method.

(13) Lucius[4] reported m.p. 245–246° and a good analysis for ethylenebis(triethylammonium bromide).

tated. This was identified as unchanged starting material (ethane-1-diethylamino-2-triethylammonium iodide).

Preparation of ethylenebis(triethylammonium bromide). Eight and six-tenths grams (0.05 mole) *N, N, N', N'*-tetraethylethylenediamine,[9] 13 g. (0.12 mole) ethyl bromide, and 8 ml. ethanol were refluxed for 12 hr. The solid material which formed on cooling was filtered and the precipitate washed with ethanol and dried *in vacuo*, m.p. 228–235° (dec.). After several recrystallizations from ethanol, 2.2 g. (11.3%) ethylenebis(triethylammonium bromide) were obtained, m.p. 243–244° (dec.). A mixed melting point with the product obtained according to the procedure of Lucius[4] showed a depression, m.p. 225–230° (dec.).

Anal. Calcd. for $C_{14}H_{34}Br_2N_2$: C, 43.08; H, 8.78; Br, 40.95; N, 7.18. Found: C, 42.93; H, 8.89; Br, 40.82; N, 7.31.

After concentrating the alcoholic mother liquor of ethylenebis(triethylammonium bromide) and subsequent cooling, 0.5 g. (2.8%) ethane-1-diethylammonium-2-triethylammonium dibromide precipitated. This salt was purified by recrystallization from propanol-acetone and had a m.p. 204–205° (dec.).

Anal. Calcd. for $C_{12}H_{30}Br_2N_2$: Br, 44.13. Found: Br, 43.83.

Upon adding aqueous picric acid to this dibromide, ethane-1-diethylammonium-2-triethylammonium dipicrate, m.p. 186–188°, was formed. It was identified by a mixed melting point with the sample prepared above.

Ethane-1-diethylamino-2-triethylammonium bromide. All the solvent from the ethanolic mother liquor which remained after filtration of ethane-1-diethylammonium-2-triethylammonium dibromide was removed *in vacuo*. The oily residue did not solidify on cooling. Yield was 11.9 g. (84.5%). This oil was soluble in acetone, insoluble in ether and gave a positive Br^- test. A picrate was prepared in ethanol which was identified by a mixed melting point, as ethane-1-diethylammonium-2-triethylammonium dipicrate, m.p. 186–188°.

Preparation of ethane-1-diethylammonium-2-triethylammonium dibromide. By adding the theoretical amount of hydrobromic acid to an aqueous solution of this oily residue, evaporating the water *in vacuo*, and recrystallizing the residue from propanol-acetone, a white crystalline material was obtained, m.p. 205–206° (dec.). This product was shown to be ethane-1-diethylammonium-2-triethylammonium dibromide. The oil was therefore ethane-1-diethylamino-2-triethylammonium bromide.

Preparation of ethylenebis(triethylammonium chloride). A solution of ethylenebis(triethylammonium bromide) was chromatographed over the cation exchange resin DOWEX 50-WX8, 200–400 mesh, used in hydrogen form. The column was eluted with 3*N* hydrochloric acid, the effluent collected, the solvent evaporated *in vacuo*, and the residue crystallized from propanol-acetone. Ethylenebis(triethylammonium chloride) had a m.p. 278–279° (dec.).

Anal. Calcd. for $C_{14}H_{34}Cl_2N_2$: Cl, 23.53. Found: Cl, 23.42.

This dichloride gave with picric acid ethylenebis(triethylammonium picrate), m.p. 244–245°.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

Synthesis of Chromones. II. Some Derivatives of 7-Hydroxy-2-methylchromone

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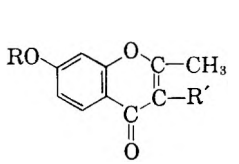
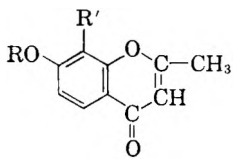
7-Hydroxy-2-methylchromone has been synthesized by an improved method and a number of its derivatives have been prepared.

An earlier publication[1] which may be considered as Part I of this series deals with the chemistry of some naturally occurring chromones and reports the synthesis of 5-methoxy-, and 5,8-dimethoxy-2-methylchromones. The present communication deals with the synthesis of a number of derivatives of 7-hydroxy-2-methylchromone.

7-Hydroxy-2-methylchromone[2] (I) has been synthesized by an improved method using the Kostanecki reaction, with the intermediate, 7-acetoxy-3-acetyl-2-methylchromone (II), isolated in good yield and characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Hydrolysis of II using aqueous sodium carbonate gave rise to I, which gave its 2,4-dinitrophenylhydrazone during twenty four hours.

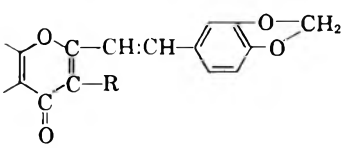
Methylation of I using excess diazomethane gave its methyl ether (III) which yielded its 2,4-dinitrophenylhydrazone during twenty-four hours.





I. R = R′ = H
II. R = R′ = $COCH_3$
III. R = CH_3; R′ = H
VI. R = $COCH_3$; R′ = H

IV. R = H; R′ = CHO
V. R = $COCH_3$; R′ = CHO
VII. R = H; R′ = $COCH_3$



VIII. R = H or $COCH_3$

Condensation of I using hexamine in glacial acetic acid produced 8-formyl-7-hydroxy-2-methylchromone (IV), as pale yellow rectangular plates, characterized by an intense red ferric color and the ready formation of its 2,4-dinitrophenylhydrazone. Its acetate V was prepared, which was further characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Acetylation of I using

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(2) St. V. Kostanecki and A. Rozycki, *Ber.*, **34**, 106 (1901).

acetic anhydride and pyridine gave its acetoxy derivative[2] VI which underwent smooth migration when heated with anhydrous aluminum chloride giving rise to 8-acetyl-7-hydroxy-2-methylchromone (VII), characterized by the ready formation of its 2,4-dinitrophenylhydrazone.

A number of piperonylidene derivatives of the type VIII of 2-methylchromones, just reported, have been synthesized.

EXPERIMENTAL

7-Hydroxy-2-methylchromone (I). A mixture of reacetophenone (5 g.), acetic anhydride (15 ml.), and anhydrous sodium acetate (10 g.) was boiled under reflux at 180–185° for about 6 hr. The cooled reaction mixture was then decomposed with ice water and the brown solid that had separated out crystallized from methanol, when it appeared as yellow plates, m.p. 126–127°, identified as *7-acetoxy-3-acetyl-2-methylchromone* (II), by its insolubility in alkali and the ready formation of its 2,4-dinitrophenylhydrazone, which on crystallization from ethyl acetate–petroleum ether (b.p. 40–60°) appeared as yellow needles, m.p. 268–269°. Yield, 3.5 g.

Anal. Calcd. for $C_{20}H_{16}N_4O_8$: C, 54.5; H, 3.6. Found: C, 54.6; H, 3.8.

Five g. of II were boiled gently under reflux using sodium carbonate solution (50 ml., 10%), during 1 hr. The clear solution thus obtained was acidified with concentrated hydrochloric acid and the precipitated solids filtered and dried. The dry solids were macerated with methanol when a crisp solid, mainly consisting of I, was obtained. This type of separation was found to be advantageous as it removed traces of 7-hydroxy-3-acetyl-2-methylchromone during alcoholic treatment. Yield: 2 g. A sublimed sample of I (245°/0.01 mm.) melted at 254–255°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.5. Found: C, 68.3; H, 4.8.

The 2,4-dinitrophenylhydrazone of I appeared as deep red rectangular prisms, m.p. 320° (from ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}N_4O_6$: C, 53.9, H, 3.4. Found: C, 54.2; H, 3.5.

7-Hydroxy-2(3',4'-methylenedioxystyryl)chromone. I (1 mole) was condensed with piperonal (1 mole) using alcoholic sodium ethoxide by gentle boiling on a water bath for about 1 hr. On working up the reaction product, the compound appeared as yellow rectangular plates (from methanol), m.p. 225–226°. A sublimed sample (220°/0.01 mm.), however, melted at 227–228°. In alcoholic and concentrated sulfuric acid solutions, the compound exhibited a blue fluorescence.

Anal. Calcd. for $C_{18}H_{12}O_5$: C, 70.1; H, 3.9. Found: C, 70.4; H, 4.1.

7-Methoxy-2-methylchromone (III). This compound, prepared by methylating I, using excess diazomethane in ether, melted at 112–13° and formed its 2,4-dinitrophenylhydrazone during 24 hr., which appeared as orange-red prisms (from ethyl acetate), m.p. 173–74°.

Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.1; H, 3.7. Found: C, 55.4; H, 3.9.

7-Methoxy-2(3',4'-methylenedioxystyryl)chromone. Prepared by the condensation of III with piperonal using alcoholic sodium ethoxide, it appeared as bright yellow rectangular plates (from ethyl acetate), m.p. above 300°. In alcoholic and concentrated sulfuric acid solutions, it exhibits a pale blue fluorescence.

Anal. Calcd. for $C_{19}H_{14}O_5$: C, 70.8; H, 4.3. Found: C, 71.1; H, 4.6.

8-Formyl-7-hydroxy-2-methylchromone (IV). To a solution of I (1 g.) in glacial acetic acid (40 ml.), hexamine (4 g.) was added and the resulting solution heated on a boiling water bath for 6 hr. The reaction mixture was then decomposed by the addition of hot hydrochloric acid (20 ml., 1:1) and heating continued for another 0.5 hr. It was then diluted with water to about 200 ml. and extracted with a large volume of ether, and the ether extract washed with a solution of sodium bicarbonate to remove acid impurities. Removal of the solvent left a yellow residue which appeared as pale yellow rectangular plates, m.p. 171–172°, after one crystallization from petroleum ether (b.p. 40–60°). A sublimed sample (165°/0.01 mm.), however, melted at 173–174°. In alcoholic solution, it gave an intense red ferric color.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.9. Found: C, 65.0; H, 4.2.

IV readily gave its 2,4-dinitrophenylhydrazone during 15 min., which on crystallization from ethyl acetate appeared as deep red short rectangular plates, m.p. 306°.

Anal. Calcd. for $C_{17}H_{12}N_4O_7$: C, 53.1; H, 3.1. Found: C, 53.5; H, 3.1.

8-Formyl-7-hydroxy-2(3',4'-methylenedioxystyryl)chromone. This was prepared using IV and piperonal following the procedure adopted earlier. It appeared as bright yellow rectangular plates and prisms (on crystallization from methanol), m.p. 262–263°. A sublimed sample (250°/0.01 mm.) had the same m.p. It exhibits a blue fluorescence in alcoholic and concentrated sulfuric acid solutions.

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 67.8; H, 3.6. Found: C, 67.9; H, 3.8.

8-Formyl-7-acetoxy-2-methylchromone (V). This was prepared from IV using acetic anhydride and pyridine and crystallized from methanol as colorless rectangular plates, m.p. 159–160°.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.5; H, 4.1; Found: C, 63.6; H, 4.2.

It readily gave its 2,4-dinitrophenylhydrazone, which appeared as red needles, m.p. 301–302° after one crystallization from ethyl acetate.

Anal. Calcd. for $C_{19}H_{14}N_4O_8$: C, 53.5; H, 3.2. Found: C, 53.9; H, 3.5.

8-Formyl-7-acetoxy-2(3',4'-methylenedioxystyryl)chromone. This was prepared using V and piperonal adopting the procedure described earlier. It appeared as bright orange-yellow prisms (from alcohol), m.p. above 300°. In alcoholic and concentrated sulfuric acid solutions, it exhibits a blue fluorescence.

Anal. Calcd. for $C_{21}H_{14}O_7$: C, 66.6; H, 3.7. Found: C, 67.0, H, 4.1.

8-Acetyl-7-hydroxy-2-methylchromone (VII). A mixture of 7-acetoxy-2-methylchromone (1 g.) and powdered anhydrous aluminum chloride (2 g.) was heated on a metal bath at 120° and when the reaction mixture had melted, the temperature was raised slowly to 140° and kept at that temperature for 10 min. Decomposition of the cooled reaction product using hydrochloric acid, while cooling, gave the compound as a pale yellow solid, which appeared as colorless stout needles when recrystallized from methanol, m.p. 191–192°. A sublimed sample had the same melting point. With alcoholic ferric chloride, it gave an intense red color.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.3; H, 4.8.

This readily gave its 2,4-dinitrophenylhydrazone, which appeared as yellow needles on crystallization from ethyl acetate–petroleum ether (b.p. 40–60°), m.p. 284–285°.

Anal. Calcd. for $C_{18}H_{14}N_4O_7$: C, 54.3, H, 3.5. Found: C, 54.6; H, 3.7.

WALTAIR, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

Synthesis of Chromones. III. Furano and Pyrono Derivatives of Chromone

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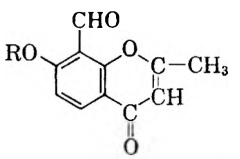
Starting from 8-formyl-7-hydroxy-2-methylchromone, the synthesis of 2-methylfurano(7,8,2′,3′)chromone is effected. Its 3-acetyl derivative was synthesized using 5-acetyl-4-hydroxybenzofuran. A number of α-, and γ-pyrono derivatives of 2-methylchromone of the type A and B have also been synthesized starting from 8-formyl- and 8-acetyl-7-hydroxy-2-methylchromones respectively.

A previous paper[1] deals with the synthesis of some derivatives of 7-hydroxy-2-methylchromone. The present communication reports the synthesis of 2-methylfurano(7,8,2′,3′)chromone (I) and 2-methyl-3-acetylfurano(7,8,2′,3′) chromone (II) and some α-, and γ-pyrono derivatives of 2-methylchromone.

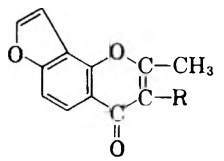
8-Formyl-7-hydroxy-2-methylchromone[1] (III) was condensed with ethyl bromoacetate, yielding 8-formyl-7-*O*-carbethoxymethyl-2-methylchromone (IV) as a liquid, characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Hydrolysis of IV with dilute alkali in the cold gave the corresponding carboxylic acid (V), while hydrolysis using strong hot alkali gave I, cyclization and decarboxylation taking place simultaneously during the course of hydrolysis. Compound I could also be produced by cyclizing V using acetic anhydride and anhydrous sodium acetate. Alternative methods of synthesis of I have also been explored. Karanjic acid[2] (VI) was converted into its methyl ester VII and subsequently condensed with acetone in presence of sodium under the conditions of the Claisen reaction, yielding 5-ω-acetylaceto-4-hydroxybenzofuran (VIII). Attempts to cyclize VIII to produce I brought about decomposition of the diketone, resulting in the isolation of VI. The other easily available starting material was 5-acetyl-4-hydroxybenzofuran (IX) which was obtained (1) from hydrolysis of pongamol[3] and (2) by its synthesis using 2,4 - dihydroxy - 3 - formylacetophenone[4] and passing through the stage: 4-*O*-carbethoxymethyl-3-formyl-2-hydroxyacetophenone its carboxy derivative and cyclization with decarboxylation.

When IX was condensed with acetic anhydride and anhydrous sodium acetate under the conditions of the Kostanecki reaction, II was obtained, further characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Deacetylation of II to yield I could not be achieved.

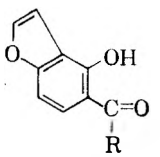
Condensation of III with acetic anhydride and sodium acetate under the conditions of the Perkin reaction, yielded 2-methyl-α-pyrono(7,8,6′,5′) chromone (X), while condensation with diethyl malonate, ethyl acetoacetate, and cyanoacetic ester gave 3′-carbethoxy, 3′-acetyl or 3′-cyano-2-methyl-α-pyrono(7,8,6′,5′) chromones, XI, XII, and XIII, respectively. Hydrolysis of XI with alkali yielded the 3′-carboxy derivative. These α-pyrono-chromones are colorless crystalline substances exhibiting prominent visible fluorescence effects in alcoholic, alkaline alcoholic, and concentrated sulfuric acid solutions.



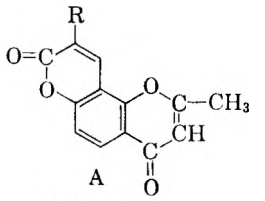
III. R = H
IV. R = CH_2COOEt
V. R = CH_2COOH



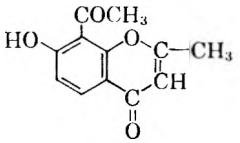
I. R = H
II. R = $COCH_3$



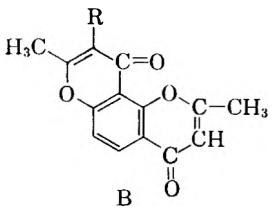
VI. R = OH
VII. R = OCH_3
VIII. R = CH_2COCH_3
IX. R = CH_2



X. R = H
XI. R = COOEt or COOH
XII. R = $COCH_3$
XIII. R = CN



XIV



XV. R = $COCH_3$
XVI. R = H

Condensation of 8-acetyl-7-hydroxy-2-methylchromone (XIV) with acetic anhydride and anhydrous sodium acetate under the conditions of the Kostanecki reaction yielded 2,2′-dimethyl-3′-acetyl-γ-pyrono(7,8,6′,5′) chromone (XV) char-

(1) Ch. Bheemasanakara Rao, G. Subramanyam, and V. Venkateswarlu, *J. Org. Chem.*, **24**, 683 (1959).

(2) T. R. Seshadri and V. Venkateswarlu, *Proc. Ind. Acad. Sci.* (A), **13**, 404 (1941); **17**, 16 (1943). D. B. Limaye, *Abstr. Indian Sci. Cong.*, 118 (1925) and 151 (1926); *Rasāyanam*, 1 (1936) and 119 (1937).

(3) Ch. Bheemasankara Rao and V. Venkateswarlu, *Current Sci. (India)*, **35**, 357 (1956).

(4) H. A. Shah and R. C. Shah, *J. Chem. Soc.*, 133 (1939).

acterized by the ready formation of its 2,4-dinitrophenylhydrazone. XV underwent smooth deacetylation on boiling with aqueous sodium carbonate giving 2,2′-dimethyl-γ-pyrono(7,8,6′,5′) chromone (XVI).

EXPERIMENTAL

2-Methylfurano(7,8,2′,3′)chromone (I). III (2 g.) in dry acetone (50 ml.), ethyl bromoacetate (1.2 ml.), and anhydrous potassium carbonate (10 g.) was boiled under reflux on a water bath for 12 hr. On working up the product, IV was obtained as a liquid characterized by the formation of its 2,4-dinitrophenylhydrazone during the first 5 min., which on recrystallization from ethyl acetate appeared as deep orange-red rectangular plates, m.p. 218–19° (dec.).

Anal. Calcd. for $C_{21}H_{18}N_4O_9$: C, 53.7; H, 3.8. Found: C, 53.9; H, 4.1.

Hydrolysis of IV. (*a*) *With cold dilute alkali.* IV (1 g.) was suspended in potassium hydroxide solution (20 ml., 2%) and left overnight at the laboratory temperature. Acidification of the deep orange solution thus obtained, precipitated V as a yellow solid which on crystallization from methanol appeared as yellow rectangular plates and prisms, m.p. 188–89° (dec.).

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.5; H, 3.8. Found: C, 59.6; H, 4.0.

(V) yielded, during the first 5 min., its 2,4-dinitrophenylhydrazone, which on crystallization from ethyl acetate appeared as deep red prisms, m.p. 220–21°.

Anal. Calcd. for $C_{19}H_{14}N_4O_9$: C, 51.5; H, 3.2. Found: C, 51.6; H, 3.5.

(*b*) *With hot strong alkali.* The ester (IV, 1 g.) was heated with aqueous potassium hydroxide (25 ml., 10%) for 0.5 hr. on a boiling water bath, followed by acidification using dilute sulfuric acid, when (I) separated out as a pale yellow solid. Recrystallized from methanol, it appeared as pale yellow slender prisms, m.p. 105–106°. It was insoluble in sodium bicarbonate solution and did not react with 2,4-dinitrophenylhydrazine hydrochloride.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.0; H, 4.0. Found: C, 72.1; H, 4.2.

Cyclization of (V). A mixture of V (0.5 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (10 ml.) was boiled under reflux for about 2 hr. Decomposition of the cooled reaction mixture with water gave (I) as a pale yellow solid. Recrystallized from methanol, it appeared as pale yellow prisms, m.p. 105–106°. A mixed melting point with a sample of (I) obtained earlier was undepressed.

5-ω-Acetylaceto-4-hydroxybenzofuran (VIII). Sodium powder (1 g.) in dry ether was added with cooling to a mixture of methyl ester of karanjic acid[2] (1 g.) and dry acetone (5 ml.). There was brisk reaction followed by the formation of a fluffy solid. The reaction mixture was then boiled under reflux for about 4 hr. Any excess sodium was then decomposed using small quantities of methanol and the mixture decomposed using dilute acetic acid. The residue obtained was crystallized from petroleum ether when it appeared as colorless needles, m.p. 224–225°, giving a green ferric coloration turning blue in alcoholic solution. A mixed melting point with karanjic acid was considerably depressed. This diketone in ether solution when shaken with an aqueous solution of copper acetate precipitated the copper complex, which on crystallization from chloroform appeared as dull green crystals melting above 300°.

Anal. Calcd. for $C_{12}H_{10}O_4$; C, 66.1; H, 4.6. Found: C, 65.9; H, 4.7.

5-Acetyl-4-hydroxybenzofuran (IX). Pongamol (1 g.) was boiled under reflux for 8 hr. using methyl alcoholic potassium hydroxide (30 ml., 8%). As much of the alcohol as possible was then removed by evaporation, the liquid residue diluted with water, cooled and extracted with ether (A). The aqueous alkaline solution (B) was worked up separately. The ether solution (A) on evaporation left a residue which solidified during the course of 24 hr. Recrystallized from petroleum ether (b.p. 40–60°), it appeared as rectangular plates, m.p. 58–59°, with no positive ferric reaction. This was identified as 5-acetyl-4-methoxybenzofuran by comparison with an authentic sample synthesized earlier[3] and by the preparation of its 2,4-dinitrophenylhydrazone which appeared as orange-red prisms (from alcohol), m.p. 215–16°.

Anal. Calcd. for $C_{17}H_{14}N_4O_6$: N, 15.1. Found: N, 15.0.

Demethylation of 5-acetyl-4-methoxybenzofuran using hydriodic acid in acetic anhydride gave a small quantity of (IX). The aqueous alkaline extract (B) was acidified with dilute sulfuric acid and the precipitated solid extracted with ether, the ether extract washed with aqueous sodium bicarbonate, and the residue obtained after removal of the solvent recrystallized from petroleum ether (b.p. 40–60°), m.p. 86–87°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.5. Found: C, 68.2; H, 4.6.

By synthesis. 2,4-Dihydroxy-3-formylacetophenone[4] (1 g.) dissolved in anhydrous acetone (25 ml.) was boiled under reflux on a water bath after addition of ethyl bromoacetate (1 ml.) and anhydrous potassium carbonate (10 g.). On working up, 4-O-carbethoxymethyl-3-formyl-2-hydroxyacetophenone was obtained as colorless rectangular plates and prisms (from methanol), m.p. 84–85°. Yield, 0.6 g.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. Found: C, 58.4; H, 5.4.

This (1 g.) on hydrolysis using boiling aqueous alkali (20 ml., 2%) during 0.5 hr., followed by acidification gave the carboxylic acid as colorless plates (from ethyl acetate), m.p. 163–164°. Yield, 0.4 g.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 55.6; H, 4.2. Found: C, 55.6; H, 4.3.

Cyclization of the above carboxylic acid (0.5 g.) using acetic anhydride (5 ml.) and anhydrous sodium acetate (2 g.) by boiling under reflux during 0.5 hr. gave (IX) as pale yellow needles, m.p. 86–87°. A mixed melting point with the sample obtained earlier was undepressed.

2-Methyl-3-acetylfurano(7,8,2′,3′)chromone (II). A mixture of IX (0.5 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (10 ml.) was boiled under reflux at 180–185° for about 6 hr. The residue obtained after working up was crystallized from methanol–petroleum ether (b.p. 40–60°) when it appeared as pale yellow needles, m.p. 118–119° with no positive ferric reaction.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.6; H, 4.4.

This readily formed a 2,4-dinitrophenylhydrazone, which on crystallization from ethyl acetate appeared as orange-red prisms, m.p. 283–284°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.9; H, 3.3. Found: C, 57.1; H, 3.5.

α- and γ-Pyronochromones. 2-Methyl-α-pyrono(7,8,6′,5′)-chromone. A mixture of III (1 g.), acetic anhydride (10 ml.), and freshly fused sodium acetate (2 g.) was gently boiled under reflux for 10 hr. The cooled reaction mixture was then decomposed using ice water and the solid that had separated out was filtered, dried, and recrystallized from methanol when it appeared as colorless rectangular plates, m.p. 233–234°. A sublimed sample had the same melting point. In alcoholic solution, it exhibits a weak violet fluorescence which becomes deeper on the addition of alkali. In concentrated sulfuric acid, it dissolved to give a colorless solution with a weak blue fluorescence.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.4; H, 3.5. Found: C, 68.6; H, 3.7.

2-Methyl-3′-acetyl-α-pyrono(7,8,6′,5′)chromone. Condensation of III (0.5 g.) and ethyl acetoacetate (0.32 g.) in presence of piperidine gave the required compound as pale yellow plates (from ethyl acetate–petroleum ether, b.p. 40–60°), m.p. 241–242°. It dissolved in alcohol and alcoholic alkali forming pale yellow solutions having a pale blue fluorescence, while in concentrated sulfuric acid, it gave a

pale orange-yellow solution with a green fluorescence having a bluish tinge.

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.7; H, 3.7. Found: C, 67.0; H, 4.1.

2-Methyl-3'-cyano-α-pyrono(7,8,6',5')chromone. Condensation of III (0.5 g.) with ethyl cyanoacetate (0.28 g.) in presence of piperidine gave the compound which appeared as pale yellow plates, m.p. 196–197° (dec.). In alcohol and concentrated sulfuric acid solutions, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_7NO_4$: C, 66.4; H, 2.8. Found: C, 66.7; H, 3.1.

2-Methyl-3'-carbethoxy-α-pyrono(7,8,6',5')chromone. III (0.5 g.) was condensed with diethyl malonate (0.4 g.) in presence of piperidine and the resulting product crystallized from methanol when it appeared as colorless prisms, m.p. 205–206°. In alcohol, it gave a pale yellow solution with a pale greenish blue fluorescence and with alcoholic alkali deeper greenish blue was observed. In concentrated sulfuric acid it exhibits a weak violet fluorescence.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.0; H, 4.0. Found: C, 64.1; H, 4.2.

2-Methyl-α-pyrono(7,8,6',5')chromone-3'-carboxylic acid. Saponification of the above ester using methanolic alkali in the cold during 24 hr., followed by acidification gave the carboxylic acid, which on crystallization from methanol appeared as colorless rectangular prisms, m.p. 257–258° (dec.). It dissolved easily in sodium bicarbonate solution. In alcoholic solution, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_8O_6$: C, 61.8; H, 2.9. Found: C, 62.0; H, 3.1.

2,2'-Dimethyl-3'-acetyl-γ-pyrono(7,8,6',5')chromone (XV). A mixture of XIV (1 g.), anhydrous sodium acetate (2 g.), and acetic anhydride (5 ml.) was boiled under reflux at 180–185° for about 6 hr. The product obtained after working up was crystallized from methanol when it appeared as colorless plates and prisms, m.p. 184–185° (dec.). A sublimed sample, however, melted at 185–186° (dec.). It gave no ferric coloration in alcoholic solution.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2. Found: C, 67.8; H, 4.3. This compound readily gave its 2,4-dinitrophenylhydrazone which on crystallization from ethyl acetate–petroleum ether (b.p. 40–60°) appeared as deep yellow plates and prisms, m.p. 243–244° (dec.).

Anal. Calcd. for $C_{22}H_{16}N_4O_8$: C, 56.9; H, 3.5. Found: C, 56.8; H, 3.7.

2,2'-Dimethyl-γ-pyrono(7,8,6',5')chromone (XVI). 0.5 g. of XV was dissolved in aqueous sodium carbonate solution (2*N*, 50 ml.) and gently boiled under reflux for about 3 hr. The product when worked out was found to be a mixture of (XVI) and its corresponding diketone and hence the product was directly employed for complete cyclization. A solution of the mixture (0.25 g.) in absolute alcohol (5 ml.) containing concentrated hydrochloric acid (2 drops) was refluxed for 5 min. and the solvent removed by evaporation. The residue was then crystallized from methanol when it appeared as yellow prisms, m.p. 260–261°, having no positive reaction with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.6; H, 4.3.

WALTAIR, INDIA

[CONTRIBUTION FROM UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY]

Studies on the Constitution, Stereochemistry, and Synthesis of Aegeline,[1] an Alkaloidal-Amide of *Aegle marmelos* Correa

A. CHATTERJEE, S. BOSE, AND S. K. SRIMANY

Received September 11, 1958

Aegeline, a neutral product of *Aegle marmelos* Correa, is shown to have the formula $C_{18}H_{19}O_3N$. It is proved to be *N*-β-hydroxy-β-*p*-methoxyphenylethylcinnamamide from the studies of its acid hydrolysis, hydramine fission, periodic acid oxidation, and other degradative experiments, and also by its synthesis. The stereochemistry and steric stability of the compound are discussed. The characteristic features observed in its ultraviolet and infrared spectra, particularly in the —C=C— stretching region and the "trans band region" at 990–965 cm.$^{-1}$ establish the *trans* configuration of aegeline.

The leaves of *Aegle marmelos* Correa were reported as a source of aegeline, m.p. 176° (yield, 0.09%) by Chatterjee and Bose.[2] The substance showed absorption in the ultraviolet region (λ_{max} at 217 mμ, log ε 4.5328, 223 mμ, log ε 4.5177, and 275 mμ, log ε 4.6053) and contained an alcoholic function. It was earlier believed to be a neutral non-nitrogenous compound from its elementary analysis but later a careful examination of its infrared spectrum (Table I) revealed that aegeline was a conjugated amide. This observation accorded with the ultraviolet spectra measurements which were closely similar to those of *trans-N*-methylcinnamamide (λ_{max} at 216, 222, and 273 mμ, log ε 4.2863, 4.2077, and 4.4038, respectively) thus indicating that the substance did contain nitrogen.[3] In further consonance with this fact, aegeline evolved a strong base having methylamine-like odor when fused with alkali. Thereby, serious doubt was raised as to the correctness of the formula $C_{18}H_{18}O_4$ originally proposed. Several elementary analyses now carefully performed clearly demonstrated that aegeline must possess the formula $C_{18}H_{19}O_3N$. The present communication concerns the studies on its constitution, synthesis, stereochemistry, and steric stability.

For the isolation of aegeline, the previous ether extraction method[2] was followed with some modification. The ethereal mother liquor left after the

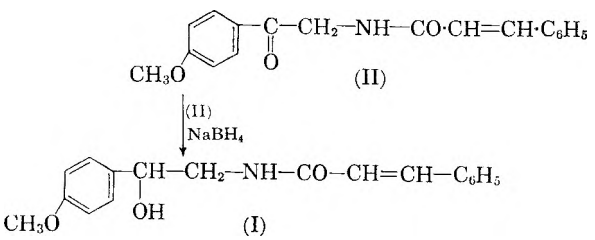
(1) Following the convention for terminology, the suffix *e* has been added to aegelin.

(2) A. Chatterjee and S. Bose, *J. Indian Chem. Soc.*, 29, 425 (1952).

(3) A. Chatterjee and S. K. Srimany, *Congress Handbook XVIth International Congress of Pure and Applied Chemistry*, Part II, p. 199 (1957).

removal of aegeline was freed from the solvent, taken up in benzene, and on subsequent chromatographic resolution on alumina using ethylacetate as the eluent yielded more aegeline, the over-all yield being 0.12%. The compound was freely soluble in chloroform, moderately in acetone, alcohol, and ethyl acetate, and sparingly in benzene, and contained a methoxyl group. It did not form salts with mineral or organic acids because of its insolubility in these reagents, thereby rendering alkaloid tests impossible with aegeline. Acetylation of the compound with acetic anhydride-pyridine yielded a monoacetate, m.p. 124°, with strong infrared alcoholic acetate absorption (λ_{max}^{Nujol} 1724 and 1235 cm.$^{-1}$). Microhydrogenation with Adam's catalyst in ethanol yielded a dihydro derivative, $C_{18}H_{21}O_3N$, m.p. 140°. Upon alkali fusion aegeline decomposed to give several products from which anisic acid and benzoic acid were isolated and identified. Prolonged alkali fusion demethylated anisic acid. With periodic acid aegeline formed benzaldehyde and anisaldehyde in a fairly good yield.

Upon hydrolysis with concentrated hydrochloric acid according to the method of Crombie[4] aegeline furnished anisaldehyde, cinnamic acid, and a mixture of two volatile bases. One of them formed a picrate, m.p. 208–209° which appeared to be the picrate of methylamine. Further characterization of the basic components is in progress. Simultaneous formation of anisaldehyde and the elimination of the nitrogen atom from aegeline during hydrolysis with hydrochloric acid emphasized that the compound had suffered hydramine fission and its basic fragment was β-hydroxy-β-*p*-methoxy-phenylethylamine derivative. Liberation of cinnamic acid coupled with the facts stated above made formula I[5] very probable. This unsaturated acylamido alcohol structure I for aegeline was finally substantiated by a simple and straightforward synthesis. ω-trans-cinnamoylamino-*p*-methoxy acetophenone (II) was synthesized according to the method of Lister and Robinson[6] with some modification. The latter upon reduction with sodium borohydride furnished aegeline (I).



It appeared of interest to study the geometrical configuration of aegeline because of its being a conjugated amide. Zechmeister[7,8] in his excellent work on the stereochemistry of carotenoids and diphenylpolyenes had shown that a definite correlation does exist between spatial configuration of organic molecules and their spectra (both ultraviolet and infrared). Similar observations were also made by Crombie[9–11] during the investigation of geometrical stereochemistry of unsaturated vegetable amides. Thereby, spectroscopic methods were applied by the present authors for the diagnosis of the configuration concerned. The spectral data were interpreted according to Zechmeister and Crombie.

The ultraviolet spectrum of aegeline, exhibited λ_{max} at 217, 223, and 275 mμ, log ε 4.5328, 4.5177, and 4.6053, respectively, which were indicative of trans-double bond to the carboxyamide grouping in I. This assignment was in agreement with the infrared spectrum of the compound. The latter showed a strong absorption at "trans-band region" (an intense band at 982 cm.$^{-1}$ with a shoulder at 990 cm.$^{-1}$, which was due to out-of-plane deformation vibration of the olefinic bond —CH=CH). Such stereochemically significant bands were found to be missing in dihydroaegeline. The facts stated above together with the absence of an absorption maximum of medium intensity at 818 cm.$^{-1}$ (for *cis*) in the infrared spectrum of the compound and the —C=C— stretching vibration discernible at 1665 cm.$^{-1}$ characteristic of trans α,β-unsaturated amides[10] clearly indicated the presence of α,β-trans linkage in aegeline. All the spectroscopical data cited here compared well with those of herclavin[12] (trans-*N*-2-*p*-methoxyphenylethyl-*N*-methylcinnamamide) and trans-*N*-methylcinnamamide (Table I) showing thereby that aegeline is indeed trans-*N*-β-hydroxy-β-*p*-methoxy-phenyl ethylcinnamamide. The amide (I) was found to exhibit considerable resistance to stereomutation. Thermal treatment and iodine-catalyzed irradiation with ultraviolet light for sixty-four hours failed to induce any stereochemical alteration in the molecule. This was in conformity with conclusions based upon molecular models. On a static model no inhibition of coplanarity was discernible with the *trans* configuration about the double bond, but with *cis* there was severe steric hindrance which forced the phenyl nucleus out of plane as observed with *cis*-cinnamic acid. This spatial conflict and the large amount of energy necessary for *trans-cis* rotation of the double bond appeared to be responsible for the steric stability of the compound.

(4) L. Crombie, *J. Chem. Soc.*, 995 (1955).

(5) When the structure determination of aegeline was complete, a preliminary note concerning its constitution was published (R. N. Chakravarty and B. Das Gupta, *Chem. & Ind. (London)*, 1632 (1955) confirming some of the results of the present authors.

(6) J. Lister and R. Robinson, *J. Chem. Soc.* 1297 (1912).

(7) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944).

(8) K. Lunde and L. Zechmeister, *Acta Chem. Scand.*, **8**, 1421 (1954).

(9) L. Crombie, *J. Chem. Soc.*, 1007 (1955).

(10) L. Crombie, *J. Chem. Soc.*, 4338 (1952).

(11) L. Crombie, *J. Chem. Soc.*, 2760, 2767 (1957).

(12) L. Crombie, *J. Chem. Soc.*, 995 (1955).

TABLE I

(Infrared data in cm.$^{-1}$)

Aegeline	Herclavin	Trans-*N*-methyl-cinnamamide
3250	1655	3280
3060	1610	3100
2830	1576	2860
1665	1509	1660
1627	1036	1625
1580	1027	1580
1520	991	1500
1062	982	983
1040		
990		
982		

Noteworthy was the behavior of aegeline toward polarized light. It contains an asymmetric carbon atom but is optically inactive. A review of the literature shows that when asymmetric carbon atoms are present, the rotatory power is obviously dependent on *cis-trans* isomerism.[7]

It therefore, seems that the linkage of the *trans*-cinnamoyl group to the optically active *N*-β-hydroxy-β-*p*-methoxyphenylethylamine causes an inversion at the asymmetric centre thereby producing racemic compound or it might be that the optically active bases (the enantiomorphs) themselves are unstable and readily racemise as observed in the case of vasicine.[13] Further investigation in this line is in progress.

EXPERIMENTAL

Isolation of aegeline from Aegle marmelos correa. Powdered sun-dried leaves (5000 g.) were extracted with ether (8000 ml.) in a Soxhlet apparatus for 72 hr. The deep green extract was concentrated to 500 ml, washed with 1% hydrochloric acid and 5% sodium hydroxide to remove bases, phenolic and acidic components. The ether solution after washing with water and drying over anhydrous sodium-sulphate was kept in the refrigerator for a fortnight when crude aegeline (3.6 g.) separated out. The adherent chlorophyll and gummy matters were removed by treating the crude mass with benzene and acetone (P). Fairly pure aegeline, m.p. 173–175°, thus obtained crystallized from ethanol in shining flakes. The mother liquor (P) was freed from the solvent, dissolved in benzene and chromatographed on 4000 g. of alumina. Elution with ethyl acetate (200 ml.) yielded homogeneous aegeline, m.p. 176° (2.4 g.) which upon crystallization from ethanol and ethyl acetate did not show any change in melting point.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.72; H, 6.39; N, 4.71; methoxyl, 10.44; active hydrogen, 0.34; mol. wt., 297. Found: C, 72.34, 72.40; H, 6.18, 6.26; N, 4.79; methoxyl, 10.46; active hydrogen, 0.31; mol. wt., 296.8 (Rast).

Monoacetylaegeline. A solution of 0.2 g. of aegeline in 2 ml. of acetic anhydride was refluxed with 2 drops of dry pyridine on water-bath for 4 hr. The reaction product was poured into water containing ice chips whereupon monoacetylaegeline separated out. It crystallized from ethyl acetate in colorless plates, m.p. 124°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.79; H, 6.19; N, 4.13; methoxyl, 9.14. Found: C, 70.59; H, 6.27; N, 4.11; methoxyl, 9.21.

(13) E. Späth, F. Kuffner, and N. Platzer, *Ber.*, **68**, 1384 (1935).

Dihydroaegeline. Aegeline (0.3 g.) upon hydrogenation with Adam's catalyst (0.09 g.) for 2 hr. in an aldehyde-free ethanolic solution (30 ml.) showed an uptake of one molar equivalent of hydrogen. The solution was freed from the catalyst and upon removal of the solvent dihydroaegeline (0.25 g.) was obtained. It crystallized from ethanol and ethyl acetate in colorless plates, m.p. 140°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.30; H, 7.01; N, 4.58.

Ozonolysis of Aegeline. Ozonized oxygen was passed through aegeline (0.25 g.), dissolved in 10 ml. of ethyl acetate and 2 ml. of acetic acid, for 50 min., the solution being kept cooled to −75°. The ozonide thus formed was decomposed reductively by adding a mixture of magnesium powder (0.5 g.) and 10 ml. of aqueous acetic acid (1:1) and keeping it overnight. The decomposition product was diluted with water (50 ml.) and shaken with chloroform (30 ml. × 3).

The aqueous layer was removed and the organic layer was washed twice with HCl (2*N*) to remove the basic material. The chloroform layer was washed with water, dried over anhydrous sodium sulphate and distilled in an atmosphere of nitrogen. The residual oil was rapidly dissolved in 2 ml. of ethanol and treated with Brady's reagent. After 40 hr. the crude 2,4-dinitrophenylhydrazone of benzaldehyde was collected and dissolved in a mixture of benzene and ethyl acetate (1:1). The solution was chromatographed on Brockmann alumina. The faster running zone was eluted with benzene. The eluents upon evaporation and crystallization from ethanol yielded 45 mg. of DNPH, m.p. 233°. After two further crystallizations from the same solvent, it formed shining orange-red crystals, m.p. 234–35°, undepressed when mixed with benzaldehyde-2,4-dinitrophenylhydrazone, m.p. 235°.

Anal. Calcd. for $C_{13}H_{10}O_4N_4$: N, 19.58. Found: N, 19.72.

Periodate oxidation of the amide. Two grams of periodic acid was added to a methanolic solution (150 ml.) of 0.15 g. of neutral compound. After 4 hr. the mixture was steam-distilled. Benzaldehyde and anisaldehyde distilled over and they were extracted out from the distillate (800 ml.) with ether (250 ml. × 4) which was subsequently washed with a little sodium bisulfite to remove iodine. The ether extract on evaporation left anisaldehyde and benzaldehyde which with 2,4-dinitrophenylhydrazine gave orange-red crystals. These melted over a long range 225–247°. The crude derivative was dissolved in 15 ml. of benzene-ethyl acetate (1:1) and chromatographed on alumina. Elution with benzene (45 ml.) yielded 80 mg. of 2,4-dinitrophenylhydrazone of benzaldehyde, m.p. 234°, and with ethyl acetate (30 ml.) 40 mg of DNPH of anisaldehyde, m.p. 250°.

Acid hydrolysis of aegeline. An ethanolic solution (5 ml.) of aegeline (0.5 g.) was heated at 120° in an oil bath for 60 hr. in a sealed tube with 5 ml. of concentrated hydrochloric acid. The product was diluted with 50 ml. of water and extracted with ether (A) (100 ml. × 3). Evaporation of the aqueous phase (B) gave a residue which upon decomposition with alkali liberated a gas. It was absorbed in 10 ml. of aqueous solution of 2*N* hydrochloric acid. The latter upon evaporation was dissolved in 1 ml. of water in which a few drops of aqueous solution of picric acid were added when a crystalline precipitate separated. It partly melted at 208–9° and decomposed when further heated. It did not depress the melting point of methylamine picrate, m.p. 209–10° when admixed but its further purification has not been possible.

The ether layer (A) was washed with water and shaken with an aqueous solution of sodium-bicarbonate from which cinnamic acid (0.159 g.) was isolated upon acidification with hydrochloric acid.

Anal. Calcd. for $C_9H_8O_2$: C, 72.97; H, 5.40. Found: C, 73.12; H, 5.32.

The ether layer (A) left after the removal of cinnamic acid was freed from the solvent, yielded anisaldehyde upon evap-

oration. The aldehyde was dissolved in 3 ml. of alcohol and gave 60 mg. of a derivative with 2,4-dinitrophenylhydrazine. An ethyl acetate solution (10 ml.) of the derivative was chromatographed on alumina and eluted with 45 ml. of benzene and with 30 ml. of ethyl acetate. The ethyl acetate eluents afforded deep-red crystals of pure anisaldehyde 2,4-dinitrophenylhydrazone, m.p. 250° which was crystallized from ethanol.

Anal. Calcd. for $C_{14}H_{12}O_5N_4$: N, 17.72. Found: N, 17.90.

Alkali fusion of the amide. Aegeline (1.0 g.) was fused with potassium hydroxide (6.0 g.) in a nickel crucible at 250° for 30 min. on a metal bath, when a base having a strong odor like methylamine was evolved. The mass was cooled and digested with 200 ml. of water in which 10.0 g. of solid ammonium chloride was added. The reddish brown solution was filtered and the aqueous alkaline filtrate was shaken up with ether (200 ml. × 5). The organic layer left no residue upon evaporation. The aqueous alkaline solution was cooled and acidified with hydrochloric acid. The turbid solution was subsequently extracted with ether (100 ml. × 3) which was washed with water and dried over anhydrous sodium sulphate. The ether solution upon evaporation yielded a mixture of anisic and benzoic acids (0.20 g.) which were separated by fractional sublimation and subsequent crystallizations from dilute ethanol. Anisic acid (30 mg.), m.p. 184° showed no depression in the mixture melting point with its authentic sample.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.26; methoxyl, 20.39. Found: C, 63.29; H, 5.32; methoxyl, 20.45.

Benzoic acid melted at 121°. No change in m.p. was observed when mixed with an authentic sample of benzoic acid.

Anal. Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.91. Found: C, 69.06; H, 4.86.

Synthesis of aegeline. The starting material for the synthesis was ω-amino-*p*-methoxyacetophenone hydrochloride, the latter being obtained by the prolonged hydrolysis (16 hr.) of ω-phthalimido-*p*-methoxyacetophenone[14] (crystallized from hot benzene) with concentrated hydrochloric acid at the reflux temperature. Hydrolysis in a sealed tube gave ω-amino-*p*-hydroxyacetophenone hydrochloride.

ω-amino-*p*-methoxyacetophenone hydrochloride (1.0 g.) obtained from acid hydrolysate was dissolved in minimum quantity of water (3 ml.) in which 3 ml. of an aqueous solution of hydrated stannic chloride (1.24 g.) containing 1 ml. of hydrochloric acid was added. The mixture was stirred when crystalline precipitate (2.0 g.) appeared. It was collected, dissolved in 20 ml. of hot water, cooled to about 37°, and stirred with 2.0 g. of molten cinnamoyl chloride. A cold aqueous solution of potassium hydroxide (25 ml., 10%) was added dropwise to the mixture. When the solution turned red, addition of alkali was stopped and stirring was continued until the solution became colorless. Further alkali was similarly added. The red coloration persisted when the addition of alkali was just complete. This procedure prevented the formation of pyrazine derivative.

ω-Cinnamoylamino-*p*-methoxyacetophenone separated, were collected after 2 hr., washed with water, and crystallized from ethylacetate in colorless shining flakes, m.p. 153–54°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.22; H, 5.76; N, 4.74. Found: C, 73.01; H, 5.58; N, 4.60.

Sodium borohydride (5.0 g.) was added to a methanolic solution (50 ml.) of ω-cinnamoylamino-*p*-methoxyacetophenone (0.5 g.). After 24 hr. the alcoholic solution was concentrated, treated with 100 ml. of water and shaken with ether (200 ml. × 3). The organic layer was washed with water, dried over anhydrous sodium sulfate, and distilled. The residue crystallized from ethylacetate in shining flakes, m.p. 176° (yield 60%), which were identical with natural aegeline in every respect.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.72; H, 6.39; N, 4.71; methoxyl, 10.44. Found: C, 72.38; H, 6.22; N, 4.80; methoxyl, 10.49.

Acknowledgment. Our grateful thanks are due to Dr. L. Marion, National Research Council, Ottawa, Canada, for the infrared spectra and Dr. A. Hofmann, Sandoz. AG., Switzerland, for valuable comments.

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(14) F. Tutin, *J. Chem. Soc.* 2508 (1910).

Notes

A department for short papers of immediate interest.

Synthesis of Pyrazinoic Acid

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Considerable interest is attached to the synthesis of pyrazinoic acid since this compound is used in the preparation of the tuberculostat pyrazinamide.[1] The acid was formerly obtained in low yield by the oxidation of methylpyrazine with potassium permanganate[2] or by the monodecarboxylation of pyrazine-2,3-dicarboxylic acid.[3] The synthesis of the latter compound requires several steps. We wish to report two new simple syntheses of pyrazinoic acid which now make this acid a readily available material.

One method, consisting of the oxidation of methyl pyrazine with selenious acid in pyridine, gave the desired acid in 64% yield. There are several examples of the oxidation of activated methyl groups in a nitrogen heterocyclic compound to the corresponding carboxylic acid with selenium dioxide.[4,5]

The second synthesis is the oxidation of ethylpyrazine in water with potassium permanganate which gave a 48% yield of pyrazinoic acid. Ethylpyrazine was synthesized by a series of steps[6] similar to those used by Kitchen and Hanson[7] in the synthesis of methylpyrazine. Ethylenediamine was reacted with 1,2-butylene oxide to give *N*-(2-hydroxybutyl)ethylenediamine which was then cyclized to 2-ethylpiperazine by heating the substituted diamine at 105° for 2 hours in aqueous solution in the presence of Raney nickel.[8] Dehydrogenation of 2-ethylpiperazine to ethylpyrazine in 57% yield (and 19% recovery of starting material) was effected over copper chromite catalyst at 360° in aqueous rather than in a benzene solution.[7]

EXPERIMENTAL[9]

Ethylpyrazine, b.p. 152–153°/760 mm., had n_D^{25} 1.4969. *Anal.* Calcd. for $C_6H_8N_2$: C, 66.64; H, 7.46; N, 25.91. Found: C, 66.87; H, 7.56; N, 26.20.

Pyrazinoic acid. A. To 5 l. of pyridine was added a solution of 1.25 kg. (11.3 moles) of selenium dioxide in 500 ml. of water. Four hundred and forty grams (4.7 moles) of methylpyrazine was added and the mixture was refluxed with stirring for 10 hr. while selenium precipitated. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in 3 l. of 2.5*N* sodium hydroxide. Decolorizing carbon, 50 g., was added and the mixture was stirred overnight. Acidification of the filtrate with one liter of 7.5*N* hydrochloric acid precipitated pyrazinoic acid which was filtered and washed well with water. The dissolution of the pyrazinoic acid in aqueous alkali, treatment with decolorizing carbon, and subsequent acidification was repeated and gave finally 372 g., (64%) of a light tan product, m.p. 219° dec. (m.p. 229–230° dec.)[2] and neut. equiv. 121.4 (calcd. 124.1). The infrared spectrum was identical with that of a sample prepared from methylpyrazine according to Stoehr.[2] The methyl ester, prepared by the Fischer method, melted at 59.5–60.5° (m.p. 61–62°).[10] For purposes of economy in large runs, 92% of the selenium was recovered (as selenium dioxide) from the precipitated selenium and the mother liquors containing selenious acid.[11]

B. A solution of 54 g. (0.5 mole) of ethylpyrazine in 750 ml. of water was treated portionwise with 315 g. (2.0 moles) of solid potassium permanganate in 12 hr. while the mixture was kept at room temperature with slight cooling. After an additional 8 hr. of stirring, the precipitated manganese dioxide was removed by filtration and the filtrate was acidified with 60 ml. of concentrated hydrochloric acid. The precipitated pyrazinoic acid was filtered and washed well with water. The yield was 29.7 g. (48%) of pure white crystals, m.p. 218.5–219° dec., with neut. equiv. 123.8 (calcd. 124.1). There was no depression in the melting point when samples of pyrazinoic acid from both methods A and B were mixed. The methyl ester, m.p. 59.5–60.5° was prepared as noted in method A.

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(1) E. P. Jordan, *Modern Drug Encyclopedia and Therapeutic Index*, 7th ed., Drug Publications Inc., New York, N. Y., 1958, p. 952.

(2) C. Stoehr, *J. prakt. Chem.*, (2) **51**, 468 (1895).

(3) W. L. McEwen, U. S. Patent **2,675,384** [*Chem. Abstr.*, **49**, 4730 (1955)].

(4) C. W. Larson, Ph.D. dissertation, Polytechnic Institute of Brooklyn, May 1949.

(5) D. Jerchel, J. Heider, and H. Wagner, *Ann.*, **613**, 153 (1958).

(6) These preparations were by Dr. Moses Cenker, Wyandotte Chemicals Corp.

(7) L. J. Kitchen and E. S. Hanson, *J. Am. Chem. Soc.*, **73**, 1838 (1951).

(8) W. K. Langdon, Canadian Patent **557,792**, May 20, 1958.

(9) All melting points are uncorrected.

(10) T. I. Fand and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1345 (1952).

(11) N. Rabjohn, *Org. Reactions*, **5**, 344 (1949).

Microbiological Transformation of Steroids. VII. 15β-Hydroxylation

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Although hydroxylations of steroids by fungi have been demonstrated for a variety of positions

and substrates, few bacterium-induced hydroxylations have been disclosed so far.[1] We have now found that 4-pregnene-17α,21-diol-3,20-dione (I) (Reichstein's Compound S) and progesterone (II) are converted to 4-pregnene-15β,17α,21-triol-3,20-dione (III) and 4-pregnen-15β-ol-3,20-dione (IV),[1] respectively, by the action of *Bacillus megaterium* (Schering 41[1a]).[2] Bernstein and his coworkers,[3] in a preliminary communication, described the preparation of III by the action of a fungus of the *Spicaria* genus and provided evidence for this assignment of structure. We had reached similar conclusions about the structure of III on the basis of experiments which parallel in part those of Bernstein.

Reichstein's S (I), when incubated with *B. megaterium* in a yeast extract medium, afforded *ca.* 50% yield of III, isolated by chloroform extraction and purified by crystallization from acetone. Analysis indicated the presence of one additional hydroxyl group. Oxidation of III with sodium bismuthate[3a] gave a 17-ketosteroid (V) (carbonyl bands at 5.77 and 6.01μ in the infrared spectrum containing an hydroxyl group, which, upon further oxidation with chromic acid, gave an hydroxyl-free steroid (VI) with carbonyl bands at 5.68, 5.78, and 5.98 μ in the infrared spectrum. Since no absorption bands corresponding to a saturated, six-membered ring carbonyl could be demonstrated, and since study of the band at 5.78 μ indicated that two five-membered ring carbonyl groups were probably present (the D ring carbonyl band was more intense than the A ring carbonyl band), the entering hydroxyl group was placed at position 15 or 16.

From the literature[1,4] the changes in molecular rotation for hydroxylation at 15 and 16 are given as $\Delta M_D^{16\alpha OH-H}$ -64,[4a] $\Delta M_D^{16\beta OH-H}$ $+38$,[4b] $\Delta M_D^{15\alpha OH-H}$ $+87$ and $\Delta M_D^{15\beta OH-H}$ -114 (average of values for ΔM^{15} for 15α- and 15β-hydroxyprogesterone and 15α- and 15β-hydroxydesoxycortiscosterone). The change in molecular rotation from I to III was -138 units. From this it was inferred that the most likely possibilities for the position of the entering hydroxyl group were 15β and 16α.

The physical constants of V, m.p. 203–205°, $[\alpha]_D^{25}$ + 120° (ethanol) are notably different from those reported for 4-androstene-16α-ol-3,17-dione,[1] m.p. 185–187°, $[\alpha]_D$ + 194°. Microbiological reduction of V with *Saccharomyces cerevisiae*[5] afforded VIa, m.p. 220–222°, $[\alpha]_D^{25}$ + 57° (ethanol), which contrasts with 4-androstene-16α,17β-diol-3-one,[1,6] m.p. 183–184°[1] or 191–192°.[6] $[\alpha]_D$ + 76°[1] or + 80°.[6] Consequently, 16α is rejected as a likely position for the entering hydroxyl group.

It was reasoned that the presence of a β-diketone structure in VI should permit ready titration with strong base. Potentiometric titration with 0.25*N* sodium hydroxide was carried out in 50% aqueous dimethyl sulfoxide, affording a molecular weight value of 303, in excellent agreement with the theory (300). Hence, the position of the entering hydroxyl in III is fixed as 15β.

Fried[1] has observed that the 15β-hydroxyl group in IV is not readily acylable. A mixture of acetic anhydride and pyridine did not acetylate V at room temperature in significant yield, only unreacted V being recovered from the reaction. Although III may be diacetylated with acetic anhydride in pyridine the second acetyl group enters with some reluctance. From a mixture of III with a large excess of acetic anhydride in pyridine after fifteen hours at room temperature some 21-monoacetate of III (VII) was isolated in addition to a major yield of 15β,21-diacetate (VIII). Selective acetylation of III with one mole of acetic anhydride was readily effected and the resulting VII was then oxidized to 4-pregnene-17α,21-diol-11,15,20-trione 21-acetate (IX) with chromic acid. Hence, III behaves in a manner consistent with its assigned structure.

Following an argument of Reichstein's,[7] we supposed that the degradation of III to the corresponding 17β-carboxylic acid by the action of potassium periodate should lead to lactone formation involving the 15β-hydroxyl group. We carried out this degradation and isolated a carboxylic acid (X), which was readily soluble in dilute sodium hydroxide, and which was esterified by diazomethane to a methyl ester. Hence, for compounds in this series, the argument is not valid. It is possible that the steric hindrance, which inhibits acetylation, is one of the factors operating here as well.

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(1) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Rec. Prog. Hor. Res.*, XI, 149 (1955) describe the 14α-hydroxylation of progesterone with *B. cereus*.

(1a) Schering 41 now bears the ATCC number 13368.

(2) W. J. McAleer, T. H. Stoudt, *et al.*, *Arch. Biochem.*, **73**, 127 (1958) have reported independently the 15β-hydroxylation of progesterone with *B. megaterium;* in the same paper they also describe 11α-hydroxylation of progesterone with *B. cereus* strains. The strain of *B. megaterium* employed by us is not the same as that employed by the Merck group.

(3) S. Bernstein, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *Chem. & Ind. (London)*, 111 (1956).

(3a) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(4) (a) D. Perlman, E. Titus, and J. Fried, *J. Am. Chem. Soc.*, **74**, 2126 (1952); (b) A. Wettstein, *Experientia*, **XI**, 465 (1955). The configurational assignments for 15α- and 15β-hydroxydesoxycorticosterone, given originally by C. Meystre, E. Vischer, and A. Wettstein, *Helv. chim. Acta*, **38**, 381 (1955), were incorrect and are reversed in the *Experientia* article.

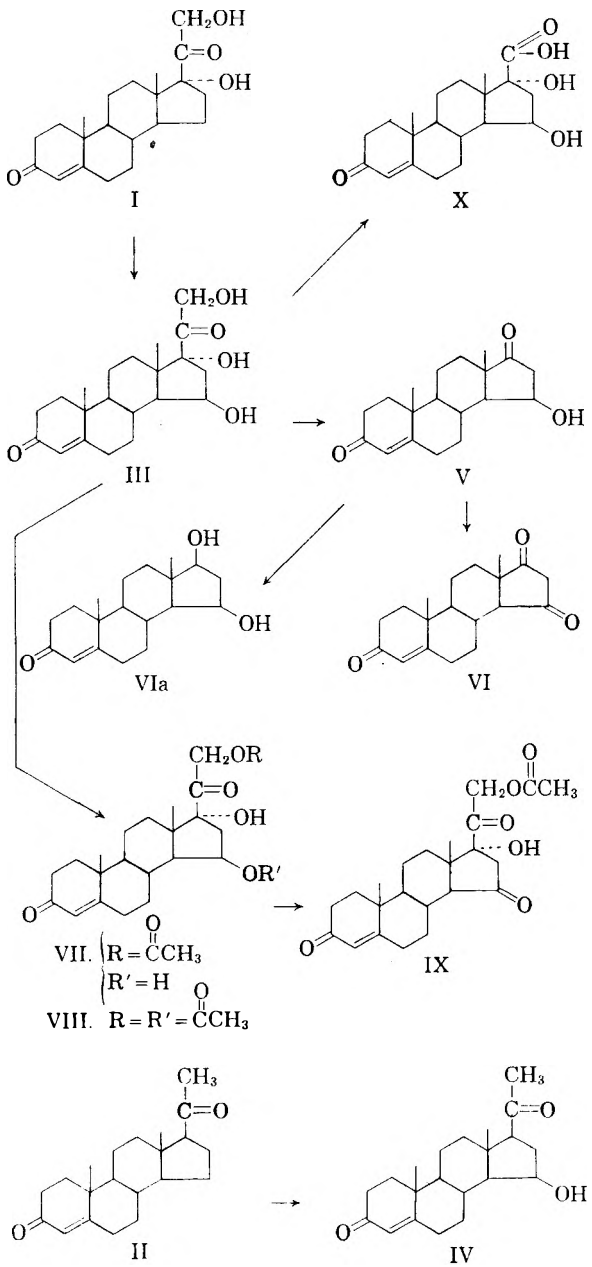
(5) For a number of examples, see the review of O. Hanc and E. Reidl-Tumova, *Die Pharmazie*, **11**, 877 (1954).

(6) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 297 (1956).

(7) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler, and T. Reichstein, *Helv. chim. Acta*, **37**, 1200 (1954).

Hydroxylation of II with *B. megaterium* (Schering 41) in the way described previously afforded a low yield of IV, whose constants were in reasonable agreement with those given by Fried.[1] At least nine other substances (ultraviolet-absorbing) were indicated as reaction products in a paper chromatogram.

On the other hand, 1-dehydrocortisol and 1-dehydrocortisone did not afford 15β-hydroxylated derivatives and were reduced in part to cortisol and cortisone respectively. The yields in these experiments were low and we were unable to isolate other crystalline products. We are not aware of any prior report of microbiological reduction of a 1,2-double bond in steroids.



EXPERIMENTAL[8]

4-Pregnene-15β,17α,21-triol-3,20-dione (III). A medium was prepared from 10 g. of yeast extract (Difco) and 10 g. of Cerelose made up to 1 l. with tap water and distributed equally among ten 300-ml. Erlenmeyer flasks. The contents of the flasks were sterilized and inoculated with a loopful of *Bacillus megaterium* (Schering 41) culture which had been maintained on nutrient agar. The culture was then incubated at 28°C. and shaken at 220 revolutions/minute for 16 hr. Thereupon, 25 mg. of I in 0.5 ml. of 80% aqueous ethanol was added to each flask, and incubation with shaking was continued for 24 hr. At the end of this time paper chromatography[9] by Shull's method of the chloroform extract of an aliquot indicated disappearance of the starting material and the formation of a single, new, ultraviolet-absorbing product which stained with red tetrazolium.[10] The reaction mixture was extracted thoroughly with chloroform, the extracts were washed with water, dried, concentrated, and the residue was crystallized from acetone-hexane and from acetone in turn. There resulted 0.128 g. of III, m.p. 240–241° dec., $[\alpha]_D^{25}$ + 103° (ethanol), $\lambda_{max}^{methanol}$ 242 mμ (ε = 16,600), λ_{max}^{Nujol} 2.91 μ (OH), 5.83 μ (20-carbonyl), 6.01 and 6.18 μ (Δ^4-3-one).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.51; H, 8.46.

The melting points of III varied from 216–220° dec. to 253–255° dec. At least two additional polymorphic varieties were observed. Bernstein[3] gives m.p. 240–242°, $[\alpha]_D^{24}$ + 96° (methanol).

4-Pregnene-15β,17α,21-triol-3,20-dione 21-acetate (VII). To a solution of 130 mg. of III in 4 ml. of pyridine was added 44 mg. of acetic anhydride. After 2.5 hr. the reaction mixture was poured into water and 100 mg. of precipitate, m.p. 226–231° was recovered by filtration. Recrystallization from acetone-hexane afforded 80 mg. of fine needles, m.p. 244–246° dec., $[\alpha]_D^{25}$ +92° (ethanol), $\lambda_{max}^{ethanol}$ 242 mμ (ε = 17,700), λ_{max}^{Nujol} 2.86 and 2.96 μ (OH), 5.72, 5.77 and 5.82 μ (combined 20-carbonyl 21-acetate), 6.06 and 6.20 μ (Δ^4-3-ketone) and 8.10 μ (C—O—C of acetate). Bernstein[3] reports VII, m.p. 245.5–247°, $[\alpha]_D^{24}$ + 98° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.38; H, 8.08.

4-Pregnene-15β,17α,21-triol-3,20-dione 15,21-diacetate (VIII). A solution of 260 mg. of III in 6 ml. of pyridine was treated with 3 ml. of acetic anhydride and allowed to stand overnight at room temperature. Dilution of the reaction mixture with water afforded a precipitate which was removed by filtration and recrystallized from acetone-hexane. If concentration of the acetone-hexane mixture was carried out slowly, in two of three experiments, it was possible to cause the crystallization from dilute solution of about 20 mg. of VII, m.p. 239–242°, as prisms, with an infrared spectrum identical with that from authentic VII. Further concentration of the filtrate afforded 180 mg. of soft needles of VIII, m.p. 193–197°. Chromatography on Florisil and recrystallization from acetone-hexane gave VIII, m.p. 211–214°, $[\alpha]_D^{25}$ + 56.8° (ethanol), $\lambda_{max}^{ethanol}$ 239 mμ (ε = 16,800), λ_{max}^{Nujol} 3.15 μ (OH), 5.78, 5.80, and 5.84 μ (20-carbonyl and acetate carbonyls), 6.06 μ and 6.20 μ (Δ^4-3-ketone), 8.20 μ (C—O—C of acetate). Bernstein[3] gives m.p. 252–254°, $[\alpha]_D^{25}$ + 109° ($CHCl_3$). Our sample was homogeneous (by paper chromatography), free of 21-monoacetate, and non-identical with Dr. Bernstein's (infrared).

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(8) All m.p.'s are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of these laboratories and by Galbraith Laboratories, Knoxville, Tenn.

(9) G. M. Shull, Abstracts of Papers, 126th meeting of the American Chemical Society, Sept. 12–17, 1954, New York, p. 9A.

(10) W. J. Mader and R. R. Buck, *Anal. Chem.*, 24, 666 (1952).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 66.93; 66.99; H, 7.46; 7.40.

4-Pregnene-17α,21-diol-3,15,20-trione 21-acetate (IX). A solution of 150 mg. of VII in 2 ml. of pyridine was added to slurry of 75 mg. of chromic acid in 5 ml. of pyridine[11] at 0° with mechanical stirring, and the mixture was allowed to warm slowly to room temperature. Stirring was continued overnight, and then a solution of 0.5 g. of sodium sulfite in 10 ml. of water was added. After stirring for an hour, the reaction mixture was poured into 200 ml. of water, and the resulting precipitate (120 mg., m.p. 240–247°) was removed by filtration. Recrystallization from acetone-hexane afforded IX, m.p. 258–260° dec., $[\alpha]_D^{25}$ + 129° (acetone), $\lambda_{max}^{ethanol}$ 240 mμ (ε = 17,300), λ_{max}^{Nujol} 3.05 μ (OH), 5.75 μ (acetate and 15-carbonyl), 5.83 μ (20-carbonyl), 6.10 and 6.20 μ (Δ⁴-3-one) and 8.15 μ (C—O—C of acetate). Bernstein[3] reports IX, m.p. 254–255.5°, $[\alpha]_D^{24}$ + 143° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.60; H, 7.78.

4-Androstene-15β-ol-3,17-dione (V). A solution of 250 mg. of III in 40 ml. of glacial acetic acid was diluted with 40 ml. of water and 5 g. of sodium bismuthate was added. The resulting mixture was stirred overnight at room temperature, whereupon the solids were removed by filtration. Both the filtrate and the solids were extracted with methylene chloride; then the extracts were combined, and washed free of acetic acid with water. Concentration of the resulting solution and chromatography of the residue over Florisil afforded a series of fractions, eluted with ether, m.p. 203–205°. After recrystallization from methylene chloride-hexane, there was isolated 60 mg. of V, m.p. 203–205°, $\lambda_{max}^{methanol}$ 240 mμ (ε = 16,900), $[\alpha]_D^{25}$ + 120° (ethanol), λ_{max}^{Nujol} 2.99 μ (OH), 5.77 μ (17-carbonyl), 6.01 and 6.20 μ (Δ⁴-3-one). Bernstein[3] reports m.p. 199.5–201°, $[\alpha]_D^{25}$ + 147° (methanol).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.31; H, 8.58.

A solution of 200 mg. of V in 4 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was then diluted with water and extracted with methylene chloride. The extracts were washed with 10% sulfuric acid and with water, and then dried. After concentration of the solution and crystallization of the residue from ether-hexane there resulted 60 mg. of V, m.p. 195–205°, with an infrared spectrum identical with that of starting material. The mother liquors from the crystallization were not examined further. While some 15-acetate may have been present, it is clear that conditions which are adequate for complete acetylation of most secondary hydroxyl groups do not suffice here.

4-Androstene-3,15,17-trione (VI). To a solution of 540 mg. of V in 40 ml. of glacial acetic acid was added 170 mg. of chromic acid dissolved in 4 ml. of water and 16 ml. of glacial acetic acid. After the reaction had proceeded for 3 hr. at room temperature, water was added, and the mixture was extracted with methylene chloride. The extracts were washed with water, dried, concentrated, and chromatographed over Florisil. Elution with 50% ether-in-hexane afforded 70 mg. of VI, m.p. 192–197°. Recrystallization from acetone-hexane raised the m.p. to 194–197°, $[\alpha]_D^{25}$ + 117.5° (methanol), $\lambda_{max}^{methanol}$ 241 mμ (ε = 17,300), 275 mμ (ε = 7,700), $\lambda_{minimum}^{methanol}$ 268 mμ (ε = 7,600), λ_{max}^{Nujol} 5.67 and 5.78 μ (D-ring carbonyl), 5.98 and 6.22 μ (Δ⁴-3-ketone).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.53, H, 8.56.

The equivalent weight of VI was determined by titrating potentiometrically with sodium hydroxide. The automatic recording titration assembly consisted of a motor-driven Gilmont microburet, capacity 0.1 ml., Beckman glass and calomel electrodes, a Leeds and Northrup Model 7664 line operated *p*H Indicator with recording attachment and a Brown recording potentiometer. A solution of 3.062 mg. of VI in 6.0 ml. of 50% by volume dimethylsulfoxide and water required 0.03954 ml. of 0.2558*N* sodium hydroxide for neutralization yielding an equivalent weight of 303 (MW of VI is 300). The apparent pK_a is 6.17.

4-Androstene-15β,17β-diol-3-one (VIa). To a sterile medium composed of 600 g. of cerelose and 100 g. of yeast extract (Difco) made up to 1 l. with tap water and buffered at *p*H 6.8 with phosphate buffer was added 300 ml. of an inoculum of *Saccharomyces cerevisiae*, prepared in shake flasks with the same medium, and the mixture was incubated at 28°, with aeration at one-half volume of air/volume of medium/minute for 42 hr. At the end of this time 0.5 g. of V in 10 ml. of methanol was added, the air rate was increased to 1.5 vol. of air/vol. of medium/minute and incubation was continued for 3 days. At the end of that period paper chromatography of the chloroform extract of an aliquot indicated that the reaction was essentially complete. The mixture was extracted with chloroform, the extracts were washed with water, dried, and concentrated. Crystallization of the residue from methylene chloride-hexane afforded 0.2 g. of VIa, m.p. 208–210°. Recrystallization raised the m.p. to 220–222°, $[\alpha]_D^{25}$ + 57° (ethanol), $\lambda_{max}^{methanol}$ 242 mμ (ε = 15,000), λ_{max}^{Nujol} 2.94 and 3.12 μ (OH), 6.05 and 6.21 μ (Δ⁴-3-one).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 74.96; H, 9.27. Found: C, 74.92; H, 9.72.

3-Keto-15β,17α-dihydroxy-4-etienic acid. To a solution of 40 mg. of III in 4 ml. of methanol was added 14.5 mg. of a solution of potassium periodate in water (1.18 g. per 200 ml. of water). The reaction mixture was allowed to stand overnight in the dark. The solution was then made acid with a few drops of 10% sulfuric acid. After 0.5 hour at room temperature the *p*H of the solution was adjusted to 5.0–6.0 (*p*H paper) with methanolic sodium hydroxide, 1 drop of glycerine was added, and the solution was concentrated in a stream of air. There followed crystallization of 26 mg. of the acid as needles, m.p. 265–270° dec., $\lambda_{max}^{methanol}$ 241 mμ (ε = 16,400), λ_{max}^{Nujol} 2.89, 3.01 and 3.14 μ (OH), 5.75 μ (?) 5.89 μ (carboxyl carbonyl), 6.14 and 6.22 μ (Δ⁴-3-ketone). The band at 5.75 μ was anomalous as was the absence of a band at 3.75 μ.

Anal. Calcd. for $C_{20}H_{28}O_5 \cdot H_2O$: C, 65.55; H, 8.25. Found: C, 65.55, 65.72; H, 8.47, 8.59.

The apparent *p*H of the acid was 4.4 in dimethylsulfoxide-water (apparent *p*H 7.3).

The water of crystallization could not be driven off by heating at 140° over phosphorus pentoxide *in vacuo*. Recrystallization from acetone-hexane afforded another crystalline variety of the acid, m.p. 261–263°, with variations in the infrared spectrum.

Methyl 3-keto-15β,17α,-dihydroxy-4-etienate. The carboxylic acid (50 mg.) from the preceding experiment was esterified in methanol solution by the addition of ethereal diazomethane in excess. The mixture was allowed to stand overnight at room temperature and was then concentrated and crystallized from methanol-water. Recrystallization from the same solvents afforded the methyl ester (22.5 mg.), m.p. 199–201°, $[\alpha]_D^{25}$ + 50° (dioxane), $\lambda_{max}^{methanol}$ 242 mμ (ε = 15,500) λ_{max}^{Nujol} 2.96 μ (OH), 5.79 μ (ester carbonyl), 6.01 and 6.21 μ (Δ⁴-3-one) and 8.33 μ (C—O—C of ester).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.30; H, 8.34.

4-Pregnene-15β-ol-3,20-dione (IV) *from progesterone* (II). A gram of II was transformed in 48 hr. according to the procedure described earlier, with *B. megaterium*. Paper chromatography indicated that at least ten substances absorbing in the ultraviolet were present. Chromatography of the residue from chloroform extraction over Florisil afforded a series of crystalline fractions (total weight 140 mg.) eluted with ether, which were pooled and crystallized from acetone–hexane. There resulted 90 mg. of needles of IV, m.p. 195–199°, $[\alpha]_D^{25}$ + 158° ($CHCl_3$), λ_{max}^{Nujol} 2.92 μ (OH), 5.88 μ (20-carbonyl), 6.02 and 6.19 μ (Δ⁴-3-one).

(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49; H, 9.34.

Fried[1] gives IV, m.p. 204–205°, $[\alpha]_D$ + 151°.

Cortisone from 1-dehydrocortisone. Incubation of 2.0 g. of 1-dehydrocortisone with *B. megaterium* for 48 hr. followed by isolation of the steroidal products in the usual way afforded 1.6 g. of crude solids. Paper chromatography[10] indicated that a substance with the same mobility as cortisone was present. Chromatography on 15 g. of Florisil and elution with 50% ether-in-hexane afforded small amounts of crystalline solids, which were pooled and recrystallized from acetone-hexane. There resulted 15 mg. of cortisone, m.p. 215–220° dec., whose infrared spectrum was identical with that of an authentic sample. No additional crystalline products other than some starting material were obtained on completing the chromatogram.

Cortisol from 1-dehydrocortisol. From 2 g. of 1-dehydrocortisol by incubation with *B. megaterium*, a crude mixture of 1.5 g. of oily steroids was obtained. Initial chromatography on 15 g. of Florisil and elution with 5% methanol in methylene chloride afforded a series of crystalline fractions of m.p. > 200°, which were pooled (420 mg.) and rechromatographed on 15 g. of Florisil. Elution with 1% methanol in methylene chloride afforded a series of fractions which had the same mobility as cortisol in a paper chromatogram. Recrystallization from acetone-hexane gave 45 mg. of cortisol, m.p. 210–215°, whose infrared spectrum was identical with an authentic sample.

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Microbiological Transformation of Steroids. VI. Stereospecific Reductions of the 20-Carbonyl Group

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Reduction of the 20-carbonyl to 20β-hydroxyl by microbiological means was first noted by Fried, Thoma, and Klingsberg[1] from the action of *Streptomyces lavendulae* on progesterone. Szpilfogel, Van Hemert, and DeWinter[2] have described the simultaneous reduction at 20- and 1,2-dehydrogenation of cortisone with *Fusarium* and *Calonectria* strains to give 1-dehydro Reichstein's U. None of these organisms is suitable for the generalized reduction of 4-pregnene-3,20-diketosteroids to the corresponding 4-pregnene-3-keto-20β-hydroxysteroids because of the other chemical transformations promoted simultaneously by these organisms.

We have found that various species of *Streptomyces*, in particular *Streptomyces griseus* (Schering FC No. 103), *Streptomyces sp.* (FC No. B222), and *Streptomyces sp.* (QM No. 1086), and an unidentified bacterium (FC No. C78) are capable of reducing the 20-carbonyl to 20β-hydroxyl in a variety of corticosteroids in good yield without producing other chemical alterations in the molecule. In this way we have transformed 4-pregnene-17α,21-diol-3,20-dione (I) (Reichstein's Compound S) into 4-pregnene-17α,20β,21-triol-3-one (II),[3a,3b] cortisone (III) into 4-pregnene-17α,20β,-21-triol-3,11-dione (IV),[4] cortisol (V) into 4-pregnene-11β,17α,20β,21-tetrol-3-one (VI),[5] 1-dehydrocortisone (VII)[6] into 1,4-pregnadiene-17α,-20β,21-triol-3,11-dione (VIII),[7] and 1-dehydrocortisol (IX)[6] into 1,4-pregnadiene-11β,17α,20β,21-tetrol-3-one (X).

Formation of the 20β-carbinols was carried out by aerobic incubation of the appropriate steroid with the *Streptomyces* strain in a yeast extract–dextrose–corn steep liquor medium. Progress of the reaction was measured by the disappearance of the substrate as estimated by paper chromatography according to Shull,[8] and by appearance of a more polar spot which did not stain with "red tetrazolium".[9] When the starting material had been consumed (usually 1–3 days), the reaction mixture was extracted with chloroform, and the product was isolated by concentration of the extract and crystallization from a suitable solvent (usually acetone-hexane). Yields of the reduced product varied between 20% and 75%. The poorest results occurred in the 11 β-hydroxyl series.

The structure of II was assigned on the basis of the absence of the 20-carbonyl band in the infrared spectrum (and the presence of the other appropriate bands), the correspondence of physical constants with those reported by Julian,[3b] and the preparation of the known diacetate.[3b] The structure of IV was confirmed by comparison of its melting point with that given by Reichstein and von Euw,[4] and by preparation of the diacetate.[4] The structure of VI was assigned by similar techniques. Compound VIII was characterized by preparation of the previously described diacetate[6] and by the changes in the molecular rotation accompanying this reaction[10] (see Table I). Compound

(1) J. Fried, R. W. Thoma, and A. Klingsberg, *J. Am. Chem. Soc.*, 75, 5764 (1953).

(2) S. A. Szpilfogel, P. A Van Hemert, and M S. DeWinter, *Rec. trav. chim.*, 75, 1227 (1956).

(3a) L. Ruzicka and P. Muller, *Helv. Chim. Acta*, 22, 755 (1939).

(3b) P. L. Julian, E. W. Mayer, W. J. Karpel, and W. Cole, *J. Am. Chem. Soc.*, 75, 1982 (1951).

(4) T. Reichstein and J. von Euw, *Helv. Chim. Acta*, 24, 247E (1941).

(5) T. Reichstein, *Helv. Chim. Acta*, 19, 29 (1936); 20, 953 (1937).

(6) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto, and E. B. Hershberg, *J. Am. Chem. Soc.*, 77, 4781 (1955).

(7) H. L. Herzog, Gordon Conference on Steroids and Natural Products, August, 1955.

(8) G. M. Shull, Abstracts of Papers, 126th Meeting of the American Chemical Society, September 1954, New York, p. 9A.

(9) W. J. Mader and R. R. Buck, *Anal. Chem.*, 24, 666 (1952).

(10) *Cf.* L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrane*, Rheinhold Publishing Corp., New York, N. Y., 1949, 3rd ed., p. 434.

X, isolated only as its 20,21-diacetate, has not been prepared previously and the structure has been assigned by analogy with the other transformations in this series.

Although reduction of the 20-carbonyl group to 20α-hydroxyl has been demonstrated with mammalian enzyme systems,[11] so far as we are aware no microbiological reductions of this kind have been reported.[11a] The chemical reduction has been solved in certain special cases,[3b,12] but the methods employed are not suitable for the direct, one-step reduction of the 20-carbonyl in the cortical steroid series. We now find that a strain of the yeast *Rhodotorula longissima* (Schering OFV No. 2[12a]) can transform I into 4-pregnene-17α,20α,21-triol-3-one (XI), III into 4-pregnene-17α,20α,21-triol-3,11-dione (XII), and VII into 1,4-pregnadiene-17α,20α,21-triol-3,11-dione (XIII). The reactions were carried out in an Edamin-dextrose–corn steep liquor medium in essentially the way described earlier in this article. As a rule, the reaction was slower than in the reductions leading into the 20β-series (usually 1–7 days) and the yields were somewhat lower (ca. 10–25%).

The structure of XI was determined by comparison of physical constants with literature values,[3b] by preparation of the known diacetate,[3b] and by degradation to 4-androstene-3,17-dione with sodium bismuthate.[13] A side reaction occurring during this microbiological transformation involves reduction of the 3-carbonyl group. A small amount of an unidentified steroid, possessing no important carbonyl absorption bands in the infrared, was isolated from the reaction mother liquors. The structure of XII was derived by analogy with that of XI, and confirmed by the anticipated changes in rotation on acetylation[10] (see Table I). The structure of XIII was assigned in the same way.

In the eosinophil test[14] IV displayed an activity equal to cortisone while XIII was about one third as active. Biological and clinical studies with these and related compounds will be described by Drs. S. Tolksdorf and P. L. Perlman of these laboratories, to whom we are indebted for these data, and by Dr. Maurice Pechet of Harvard University.

TABLE I

CHANGES IN MOLECULAR ROTATION OF 20-HYDROXYSTEROIDS UPON ACETYLATION

Compound	M_D[a]	M_D of 20,21-diacetate[a]	Δ^{Ac}
4-Pregnene-17α,20β,21-triol-3-one	226	554	+328
4-Pregnene-17α,20α,21-triol-3-one	+192	82	−110
4-Pregnene-17α,20α,21-triol-3,11-dione	571	478	−93
1,4-Pregnadiene-17α,20β,21-triol-3,11-dione	425	710	+285
1,4-Pregnadiene-17α,20α,21-triol-3,11-dione	421	333	−88
Average of 17α,20β,21-triols[10]			+240 to +410°

[a] All rotations in dioxane.

(11) R. I. Dorfman and F. Ungar, *Metabolism of Steroid Hormones*, Burgess Publishing Co., Minneapolis, Minn., 1953, p. 45.

(11a) NOTE ADDED IN PROOF: Our attention has since been drawn to the reductions of some 16,17-oxido-20-ketosteroids to 20α-hydroxy-steroids by an unidentified yeast, which were accompanied by Wagner-Meerwein rearrangement in all instances; B. Camerino *et al.*, *Gazz. Chim. ital.*, **86**, 260 and 1219 (1956).

(12) E. L. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 2912 (1955); D. K. Fukushima and E. D. Meyer, *J. Org. Chem.*, **23**, 174 (1958).

(12a) This culture was deposited at the Culture Collection of the Northern Regional Research Laboratories (USDA) at Peoria, Ill., where it was entered as *Rhodotorula longissima* NRRL No-Y 2343.

(13) C. J. W. Books and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(14) R. S. Speirs and R. K. Meyer, *Endocrinology*, **48**, 316 (1951); E. Rosemberg, *et al.*, *Endocrinology*, **54**, 363 (1954).

(15) All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of Schering Corporation and by the Galbraith Laboratories, Knoxville, Tenn., Dr. Jo-Yun Chen and Mr. Edward Townley interpreted the infrared spectra.

EXPERIMENTAL[15]

Representative procedure for reduction of 20-carbonyl to 20β-hydroxyl. The appropriate microorganism (for ex. *S. griseus*, Schering FC No. 103) was propagated on nutrient agar medium at 28° for 7 days. A medium, prepared from 3 g. of yeast extract (Difco), 10 g. of dextrose, and 1 g. of corn steep liquor made up to 1 l. with tap water, was adjusted to *p*H 7 and distributed among ten 300-ml. Erlenmeyer flasks (100 ml. of medium per flask). The flasks and contents were sterilized and then inoculated with spores (from the agar slants) which were suspended in distilled sterile water. Incubation on a rotary shaker (28°, 220 r.p.m.) was continued for 1–2 days, and then there was added to each flask a solution of 25–100 mg. of steroid in 1–6 ml. of 95% ethanol (methanol or acetone may also be used). After 1–3 days of incubation with shaking, paper chromatography[8] of the chloroform extract of an aliquot revealed complete consumption of the starting material and the appearance of a more polar ultraviolet absorbing spot which did not stain with "red tetrazolium." The reaction mixture was then extracted thoroughly with chloroform and the extracts were washed with water, dried, and concentrated to a residue. Recrystallization of the residue from the appropriate solvent (usually acetone) afforded crystalline steroid in yields averaging between 20% and 75%.

In general, transformation was less rapid and yields were poorer with 11β-hydroxylated steroids than with 11-unsubstituted or 11-ketosteroids.

Procedure for reduction of 20-carbonyl to 20α-hydroxyl. Rhodotorula longissima (Schering OFV No. 2) was propagated on nutrient agar at 28° for 7 days. A medium, prepared from 20 g. of Edamin, 3 g. of corn steep liquor, and 50 g. of dextrose made up to 1 l. with tap water, was adjusted to *p*H 5.3. The growth of the culture and the transformation of the steroids were carried out as described in the first example. Transformation time tended to be longer in this reduction than in that of the first example, occasionally extending to as much as 7 days. The methods of control and isolation were

the same, and the products could usually be purified by crystallization, although those experiments with I as substrate did not proceed to completion and required chromatographic purification.

4-Pregnene-17α,20β,21-triol-3-one (II) *from Reichstein's Compound S.* From the action of *Streptomyces sp.* FC No. B222 on I (0.9 g.) (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. ethanol; complete transformation in 48 hr.) there was isolated a nicely crystalline crude product which, after recrystallization from acetone-hexane, afforded 0.43 g. of II, m.p. 175°, resolidification 178°, remelt 190°, λ_{max}^{EtOH} 242 mμ (ε = 16,300), $[\alpha]_D^{25}$ +65° (dioxane), λ_{max}^{Nujol} 2.92 mμ (OH), 6.05 and 6.17 μ (Δ⁴-3-one). Julian[3b] gives m.p. 188–190°, $[\alpha]_D^{25}$ +65° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.21; H, 9.35.

4-Pregnene-17α,20β,21-triol-3-one 20,21-diacetate. A solution of 240 mg. of II in 5 ml. of pyridine and 5 ml. of acetic anhydride was allowed to stand overnight at room temperature. Dilution of the reaction mixture with water caused the precipitation of needles which were removed by filtration and recrystallized from acetone-hexane. There resulted 240 mg. of 20,21-diacetate, m.p. 191–193°, $[\alpha]_D^{25}$ + 128° (dioxane); λ_{max}^{EtOH} 241 mμ (ε = 16,600), λ_{max}^{Nujol} 2.93 μ (OH), 5.71 and 5.75 μ (split acetate carbonyl bands), 6.02 and 6.18 μ (Δ⁴-3-one) and 8.12 μ (C—O—C of acetate). Julian[3b] reports m.p. 189–191°, $[\alpha]_D^{25}$ + 150° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; N, 8.39. Found: C, 69.28; H, 8.50.

4-Pregnene-17α,20β,21-triol-3,11-dione (IV) *from cortisone.* From the action of *Streptomyces griseus* (FC No. 103) on 925 mg. of III (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 24 hr.) there was isolated an oily crude product which afforded 0.46 g. of IV, m.p. 203–205° dec. on crystallization from acetone-hexane. Further recrystallization raised the m.p. to 206–207° dec. Fieser[16] cites Reichstein and von Euw[4] as reporting m.p. 208°.

4-Pregnene-17α,20β,21-triol-3,11-dione 20,21-diacetate. Acetylation of IV by the aforedescribed procedure gave a diacetate which, after recrystallization from acetone-hexane, melted at 255.5–257°, $[\alpha]_D^{25}$ + 186° (dioxane). Reichstein and von Euw[4] give m.p. 252–253°, $[\alpha]_D^{21}$ + 178.5° (acetone).

4-Pregnene-11β,17α,20β,21-tetrol-3-one (VI) *from cortisol.* From the action of *Streptomyces griseus* (FC No. 103) on 915 mg. of V (final concentration of steroid in medium 0.5 g./l. added in 40 ml. of ethanol; transformation in 4 days) there was isolated 150 mg. of VI, m.p. 105–110° after crystallization from acetone-hexane. Recrystallization from ethanol water raised the m.p. to 133–135°, $[\alpha]_D^{25}$ + 85° (dioxane), λ_{max}^{Nujol} 2.94 and 3.07 μ (OH), 6.07 and 6.21 μ (Δ⁴-3-one). Reichstein and von Euw[4] report m.p. 124–129°, $[\alpha]_D^{25}$ + 87° (ethanol).

1,4-Pregnadiene-17α,20β,21-triol-3,11-dione (VIII) *from 1-dehydrocortisone.* The product from the action of *Streptomyces griseus* (FC No. 103) on VII (2 g.) (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 48 hr.) was crystallized from methylene chloride–hexane to give 1.5 g. of crystalline VIII, m.p. 115–125°, resolidifying and remelting at 182–183°. Recrystallization from acetone-hexane raised the m.p. to 184–185° without intermediate phase change, $[\alpha]_D^{25}$ + 118° (dioxane), $\lambda_{max}^{methanol}$ 238 mμ (ε = 15,300), λ_{max}^{Nujol} 2.94 and 3.06 μ (OH), 5.87 μ (11-carbonyl and solvent carbonyl), 6.01, 6.19, and 6.24 μ (Δ¹·⁴-3-one).

Anal. Calcd. for $C_{21}H_{28}O_5.C_3H_6O$: C, 68.87; H, 8.19. Found: C, 69.12; H, 7.91.

1,4-Pregnadiene-17α,20β,21-triol-3,11-dione 20,21-diacetate. Acetylation of VIII in the usual way yielded a 20,21-diacetate which, after recrystallization from acetone-hexane, melted at 239–242°, $[\alpha]_D^{25}$ + 160° (dioxane), λ_{max}^{Nujol} 2.91 μ (OH), 5.74 and 5.77 μ (split acetate carbonyls), 5.90 μ (11-carbonyl), 6.01, 6.14, and 6.22 μ (Δ¹·⁴-diene-3-one) and 8.20 μ (C—O—C of acetate). This sample was identical with that obtained from the action of *Corynebacterium simplex*[1] on cortisone, followed by acetylation.

1,4-Pregnadiene-11β,17α,20β,21-tetrol-3-one 20,21-diacetate from 1-dehydrocortisol. From the action of *Streptomyces griseus* (FC No. 103) on 925 mg. of IX (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 4 days) a glassy product was obtained. Acetylation of this product in the usual way afforded 175 mg. of 20,21-diacetate of X, m.p. 228–230°. Several recrystallizations from acetone-hexane raised the m.p. to 243–244°.

Anal. Calcd. for $C_{25}H_{34}O_7.C_3H_6O$: C, 66.64; H, 7.99. Found: C, 66.53; H, 7.57.

4-Pregnene-17α,20α,21-triol-3-one (XI) *from Reichstein's Compound S.* From the action of *Rhodotorula longissima* (Schering OFV No. 2) on 2.0 g. of I (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 5 days) the chloroform concentrate was chromatographed on Florisil (40 g.). From methylene chloride elution 920 mg. of I was recovered and elution with 1–5% methanol in methylene chloride gave a total of 840 mg. of crude solid, m.p. 168–190°. The latter was recrystallized from acetone-hexane affording 540 mg., m.p. 199–209°. The m.p. of this mixture could not be raised significantly by further recrystallization, so it was acetylated with 5 ml. of acetic anhydride and 5 ml. of pyridine. Upon dilution of the reaction mixture with water, a precipitate formed which was removed by filtration and melted 225–240°. Chromatography on 30 g. of Florisil and elution with ether gave 360 mg. of crude solid, m.p. 242–252°. Recrystallization from acetone-hexane yielded 230 mg. of shiny needles of 20,21-diacetate of XI, m.p. 251–253°, $\lambda_{max}^{methanol}$ 242 mμ (ε = 16,100), $[\alpha]_D^{25}$ + 35° ($CHCl_3$), + 19° (dioxane), λ_{max}^{Nujol} 2.90 μ (OH), 5.78 μ (acetate), 5.93 and 6.14 μ (Δ⁴-3-one), 7.94 and 8.09 μ (C—O—C of acetate). Julian[3b] gives m.p. 251–253°, $[\alpha]_D^{32}$ + 31.5° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.05; H, 8.43.

From another run (3 g. of I) the crude, extracted steroids were washed with cold hexane and crystallized from acetone-hexane. There resulted 1.6 g. of solid, which was then acetylated. There was isolated 2.29 g. of crude acetate, m.p. < 190°, which was chromatographed on 125 g. of Florisil. From 25% ether-hexane eluates there was obtained 20 mg. of needles, m.p. 187–189°, λ_{max}^{Nujol} 2.89 μ (OH), 5.69, 5.73, and 5.80 μ (acetate carbonyl), 7.98 and 8.23 μ (C—O—C of acetate). (Hydrolysis of this product afforded a compound, m.p. 230–232° which had no carbonyl bands in its infrared spectrum.) From 100% ether and from 25% methylene chloride–ether there resulted a total of 740 mg. of XI diacetate, m.p. 245–250° dec.

Hydrolysis of 150 mg. of purified 20,21-diacetate was accomplished by solution in 10 ml. of 0.5*N* methanolic sodium hydroxide and standing at room temperature overnight. The solution was concentrated *in vacuo*, and the residue was made acid and extracted with methylene chloride. Chromatography of the extracts on Florisil and elution with 5% methanol in methylene chloride afforded, after crystallization from acetone-hexane, 40 mg. of XI, m.p. 221–225°, $[\alpha]_D^{25}$ + 55° (dioxane), λ_{max}^{Nujol} 2.88, 2.93, and 3.01 μ (OH), 6.04 and 6.19 μ (Δ⁴-3-one). Julian[3b] gives m.p. 225–227.5°, $[\alpha]_D^{25}$ + 76° (chloroform), ΔM^{Ac-H} −129.

4-Androstene-3,17-dione from XI. A solution of 65 mg. of XI was dissolved in 8 ml. of acetic acid and diluted to 16 ml. with water. One gram of sodium bismuthate was added, and the mixture was stirred overnight at room temperature, whereupon the solids were removed by filtration and leached with methylene chloride. The filtrate was diluted with water and extracted with methylene chloride. The combined extracts were washed with water, dried, and

(16) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., p. 426.

concentrated to a crystalline residue. Recrystallization from ether-hexane gave 18 mg. of 4-androstene-3,17-dione, m.p. 157–165°, with an infrared spectrum identical with that of an authentic sample.

4-Pregnene-17α,20α,21-triol-3,11-dione (XII) *from cortisone.* From the action of *R. longissima* (OFV No. 2) on 2 g. of cortisone (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 5 days) there was obtained, after crystallization from acetone-hexane, 0.65 g. of XII, m.p. 229–231° dec. Several recrystallizations from the same solvent mixture raised the m.p. to 240–242° (dec.), $[\alpha]_D^{25}$ + 158° (dioxane), λ_{max}^{Nujol} 2.89, 2.96, and 3.03 μ (OH), 5.87 μ (11-carbonyl), 6.02 and 6.19 μ (Δ^4-3-one).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.97; H, 7.83. Found: C, 69.69; H, 8.01.

4-Pregnene-17α,20α,21-triol-3,11-dione 20,21-diacetate. Acetylation in the usual way afforded a 20,21-diacetate m.p. 273–275° (dec.) after recrystallization from acetone, $[\alpha]_D^{25}$ + 107°, $\lambda_{max}^{methanol}$ 238 mμ (ε = 15,500), λ_{max}^{Nujol} 2.91 μ (OH), 5.76 and 5.80 μ (acetate carbonyls), 5.85 μ (11-carbonyl), 5.94 and 6.16 μ (Δ^4-3-one), 8.00 and 8.11 μ (C—O—C of acetate).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.09; H, 7.87.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione (XIII) *from 1-dehydrocortisone.* From the action of *R. longissima* (OFV No. 2) on 1.875 g. of VII (final concentration of steroid in medium 0.25 g./l. added in 40 ml. of methanol; transformation in 6 days) there was isolated after recrystallization from acetone-hexane 0.41 g. of XIII, m.p. 233–235° dec. Additional recrystallization raised the m.p. to 238–240° dec. with a phase change at 225° (polymorphic samples of XIII which melted at 225–228° have also been obtained), $[\alpha]_D^{25}$ + 117° (dioxane), $\lambda_{max}^{methanol}$ 239 mμ (ε = 15,400), λ_{max}^{Nujol} 2.95 μ (OH), 5.85 μ (11-carbonyl), 6.01, 6.19, and 6.23 μ ($\Delta^{1,4}$-diene-3-one).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.06; H, 7.71.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione 20,21-diacetate. Preparation of the 20,21-diacetate in the usual way gave a compound, m.p. 250–251° dec. (samples have also been obtained m.p. 267–270° dec.) $[\alpha]_D^{25}$ + 75° (dioxane), $\lambda_{max}^{methanol}$ 239 mμ (ε = 15,100), λ_{max}^{Nujol} 2.92 μ (OH), 5.74 and 5.81 μ (split acetate carbonyls), 5.86 μ (11-carbonyl), 5.97, 6.11, and 6.21 μ ($\Delta^{1,4}$-diene-3-one) and 8.05 μ (C—O—C of acetate).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.67; H, 7.13.

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The Pyrolysis of Perfluoroethyl Ether[1]

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In this work perfluoroethyl ether, $C_2F_5OC_2F_5$, was pyrolyzed by passing it slowly over a bed of sodium fluoride pellets in a nickel reactor heated to 800°. The isolable and identified products were C_2F_6, COF_2, C_3F_8, $CF_3CF{=}CF_2$, $(CF_3)_2C{=}CF_2$ and carbon. In the main this ether shows a pyrolytic stability comparable to most fluorocarbons. Except for the COF_2 evolved the ether yields products similar to many of the fluorocarbons pyrolyzed by the hot filament technique.[3] At least one report[4] shows that under pyrolytic conditions in a static system at pressures less than an atmosphere $CF_2{=}CF_2$ corrodes nickel less than it does stainless steel at temperatures between 600–700°.

In general past work tends to show that nature of the pyrolysis reaction of a simple molecule such as $CF_2{=}CF_2$ depends at least upon the variables of temperature, pressure, the contact time, and the geometry and composition of the reaction vessel.[4–7] A correlation of the results is further complicated by whether the pyrolysis is performed by a static or flow method.

EXPERIMENTAL

The perfluoroethyl ether was prepared by the electrochemical (Simons) process[8] in a nominally 50-ampere cell not unlike that described by Hoffmann, Simmons, *et al.*[9] Seven hundred and four g. of ether (11 moles) produced 690 g. of product condensable at −80° of which 450 g. (1.77 moles) was the fluorocarbon ether, b.p. 2.5°, mol. wt. 254.

The pyrolysis equipment was simple. The ether was allowed to escape from a cylinder through a needle valve, its flow being observed with a flow meter. It was then passed through a 1/2-in. i.d. nickel tube, packed with 1/8-in. sodium fluoride pellets, which was heated in a Hoskins furnace. Products were collected in cold traps. A pressure of about 1 atm. in the system was controlled by a valve before the traps and was observed on a manometer. Air was never in contact with the system. Temperatures were measured with a thermocouple placed in a well welded to the top the reactor.

Several small trial pyrolyses established that at contact times as high as 3.5 min. there was no reaction at 650°, 3% conversion to products at 700° and 30–50% conversion to products at 800°. It was also established that the number of equivalents of COF_2 formed was always equal to the number of equivalents of fluorocarbon ether used.

Finally, in order to effect a more complete study of the reaction 102 g. (0.402 mole) of $C_2F_5OC_2F_5$ were pyrolyzed at a flow rate of 0.03 g./min., equivalent to a theoretical contact time of not less than 6.3 min. The reaction products were collected in a liquid air–cooled trap, transferred to the pot of a low temperature microcolumn and allowed to reflux from the head cooled with a mixture of Dry Ice and acetone. A liquid air–cooled trap was attached to the head outlet in which the uncondensed gases that escaped overhead were collected. The column equilibrated at a head

(1) This work was supported by the Chemistry Branch, Office of Naval Research. Reproduction of all or any part of this paper is permitted for purposes of the United States Government.

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temperature of −56°. Fifty-two g. of material were carried overhead. It was passed through conc. NaOH solution to remove the COF_2 which was formed, amounting to 18.0 g., while the residual C_2F_6 amounted to 34.0 g. Aliquots of the basic solution was acidified with conc. H_2SO_4 and the evolved gas dried. The amounts of CO_2 (mol. wt. 44) evolved agreed within 1% with the amount of COF_2 trapped out. It had been shown previously that the base-soluble gas was COF_2 rather than CF_3COF. Pure COF_2 from an independent source was found to form an insoluble derivative, bis(*p*-chlorophenyl)carbonate (m.p. 144–146°) when reacted with sodium *p*-chlorophenolate in dry isopropyl ether. The COF_2 in a gas mixture prepared by pyrolysis of the fluorocarbon ether formed the same derivative under the same conditions. Furthermore, the sodium fluoride formed on hydrolysis gave a fluorine analysis in good (within 2%) agreement for the amount of COF_2 involved. The residual 34 g. of C_2F_6 were identified by mol. wt. (137–138) and a comparison infrared spectrum. No vestigial unsaturation was detected.

The following fractions were found in the fractionation:

(1) Boiling range −56° to −40°, 58 g. This was scrubbed through NaOH solution to remove any trace of COF_2. An infrared spectrum from the top of this material showed about equal amounts of C_2F_6 and C_3F_8 to be present and nothing else. The mol. wt. range of the fraction varied between 157 and 167.

(2) Boiling range −39° to −35°, mol. wt. 183 to 176, 6.0 g. An infrared spectrum showed a mixture of C_2F_6 and C_3F_8 with a preponderance of the former. There was C=C evidence at 5.55 microns. Several parts of this fraction were checked by gas chromatography and averaged about 90% C_3F_8 by wt. The whole fraction was reacted with excess bromine in a sealed ampoule, after which the mol. wt. of the bromine-free volatile portion was exactly 188 and the infrared spectrum was that of C_3F_8. The bromine-free less volatile portion amounted to 1.6 g. and boiled at 71° but the n_D^{25} was somewhat higher than that of pure $CF_3CFBrCF_2Br$.

(3) Boiling range −35° to −25°, mol. wt. 165 to 155, 3.0 g. Its infrared showed a much stronger C=C assignment at 5.55 microns than Fraction 2 did at the same experimental pressure. When this portion was similarly treated with bromine, a recovery of $CF_3CFBrCF_2Br$ amounting to 3.0 g. was obtained.

(4) At this point the head temperature rose abruptly to −3.0° and no attempt was made to fractionate further. This residue amounted to 34.3 g. It showed weak infrared evidence for C=C at 5.70 microns which is the correct value for $(CF_3)_2C{=}CF_2$.[10] The mol. wt. range of the material was 246–254. Chromatographically it showed several very minor impurities and one large impurity which was in the order of 5% by wt., besides the main peak of the ether, which were not present in the starting material. As the amount of suspected iso C_4F_8 was not present in sufficient quantity to remove successfully by chemical means, the 5% impurity was recovered in a large scale chromatographic separation unit[11] described in detail elsewhere. In the main it consisted of 2 meters of 1-in. tubing packed with the ethyl ester of Kel-F and 8114 supported on Celite. The material under pressure was charged into the column in 2-cc. quantities and developed with nitrogen. The separated fractions were collected in separate traps as they eluted from the column. Over 1.5 g. of the portion corresponding to the impurity under consideration was recovered. It had a mol. wt. of 196 and its infrared spectrum was that reported for iso C_4F_8.[10]

When the reaction vessel was emptied of its contents, the sodium fluoride pellets in the reaction zone were black. The discoloration was suspected of being free carbon and was observed to permeate the pellets completely. The number of pellets so affected indicated that a 9-in. length of the tube was effectively involved as the reaction zone. The blackened pellets were returned to the tube and treated with oxygen at 500° to 700°. One and three quarters g. of carbon dioxide equivalent to 0.48 g. carbon were recovered. The decarbonized pellets now appeared opalescent and had shrunk somewhat but were essentially white and free of carbon.

The product material balance of the pyrolysis of 102 g. of $C_2F_5OC_2F_5$ is given in the following table. Only 69.3 g. were converted to products.

Substance	Wt., G.	Mole	Carbon, Moles
COF_2	18.0	0.273	0.273
C_2F_6	36.6	0.265	0.530
C_3F_8	9.5	0.050	0.15
C_3F_6	2.7	0.018	0.054
iso C_4F_8	1.7	0.0085	0.026
C	0.45	0.037	0.037
	68.9		1.07
Ether	69.3	0.273	1.09

The conversion of ether to products was in the order of 68%.

Discussion of the results. While evidence regarding a detailed reaction mechanism cannot be in any way conclusive as kinetic data are lacking, a few comments based on product data and other evidence may be appropriate.

Unpublished work from this laboratory has shown that COF_2 is always a product of the ultimate pyrolysis of oxygen-containing perfluoro materials. In at least one other case an ether linkage was involved. The failure to detect any evidence of $CF_3OC_2F_5$ in this pyrolysis of $C_2F_5OC_2F_5$ suggests that the first bond cleavage occurs at a C—O bond. Similarly the lack of any n—C_4F_{10} suggests that no significant amount of C_2F_5 and OC_2F_5 radicals was formed but rather that the first step in the reaction may be regarded as a concerted disproportionation of the ether to form C_3F_8 and COF_2, involving a shift in a CF_3 group. As COF_2 is formed in quantitative amounts, the other observed products must form as a consequence of further decomposition of the C_3F_8. It would not be amiss to assume that C_3F_8 would crack to C_2F_6 and CF_2 radicals as suggested by Steunenberg and Cady[3b] at a lower temperature in a hot tube than by the heated filament technique they used. They observed the products C_2F_6, C_3F_6, iso C_4F_8, C and $(—CF_2—)_n$ polymer, which deposited on the cool walls of the reaction vessel, as a consequence of the pyrolysis of C_3F_8 with a wire temperature as low as 1050°. Lewis and Naylor[5] have shown that Teflon polymers would not exist at 800° in a hot tube. If the CF_2 radicals formed from the pyrolysis of C_3F_8 combine to form $CF_2{=}CF_2$, the work of Atkinson and Atkinson[4] shows the steps whereby C_3F_6 and iso C_4F_8 are formed. They also show that iso C_4F_8 can be cracked to C_2F_6 and other products and that for contact times of 6 min. the amounts of C_2F_4 and perfluorocyclobutane involved are vanishingly small. If it can be stipulated that over sodium

(10) T. J. Brice, J. D. Lazerte, L. J. Hals, W. H. Pearlson, *J. Am. Chem. Soc.*, **75**, 2698 (1953).

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fluoride iso C_4F_8 cracks to C_2F_6, CF_2 and C, the amount of carbon and C_2F_6 formed in the pyrolysis of $C_2F_5OC_2F_5$ can be readily explained and is compatible with the stoichiometry of the following set of reactions:

$$C_2F_5OC_2F_5 \longrightarrow COF_2 + C_3F_8 \quad (1)$$

$$C_3F_8 \longrightarrow C_2F_6 + CF_2: \quad (2)$$

$$2CF_2 \rightleftharpoons C_2F_4 \quad (3)$$

$$C_2F_4 + CF_2 \longrightarrow C_3F_6 \quad (4)$$

$$C_3F_6 + CF_2 \longrightarrow \text{iso } C_4F_8 \quad (5)$$

$$\text{iso } C_4F_8 \longrightarrow C_2F_6 + CF_2: + C \quad (6)$$

Equation 2 is suggested by the work of Steunenberg and Cady, Equations 4 and 5 are proposed by Atkinson and Atkinson, and Equation 6 is suggested by their work.

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6-Methoxy-8-(5-propylaminopentylamino)-quinoline Phosphate

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The marked toxicity of 8-aminoquinoline derivatives is clinically hazardous, and their use as gametocides in the treatment of malaria must be accompanied by laboratory studies. This is true for for the newer drugs (*cf.* refs. 2–5) as well as pamaquin,[2,3,6,7] all of which should be administered with attention to possible blood dyscrasia. Our work has led to the synthesis of 6-methoxy-8-(5-propylaminopentylamino)quinoline phosphate, an 8-aminoquinoline drug, which has a high chemotherapeutic index, and produces an unusually low incidence of blood dyscrasia. This isomer of pentaquine (the related isopropylamino type[2-4,8,9]) had a definitely superior profile of activity[10] over both pentaquine[3,4] and primaquine.[5] The synthesis of the new antimalarial agent was achieved by conversion of dihydropyran to 5-propylaminopentyl chloride hydrochloride and the reaction of the latter with 8-amino-6-methoxyquinoline, all described below.

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(3) G. M. Findlay, *Recent Advances in Chemotherapy*, J. and A. Churchill, Ltd., London, 1951, Vol. 2, p. 256.

EXPERIMENTAL[11]

5-Propylaminopentanol hydrochloride (*cf.* ref. 8). Dihydropyran (112 g., 1.33 mole) was added to a mixture of 28 ml. of conc. hydrochloric acid and 333 ml. of water at 5°. The entire mixture was stirred for 0.5 hr. without cooling, then was chilled to 10° and 22 g. (0.372 mole) of propylamine added to give *p*H 8. To this was added more of the amine (79.0 g., 1.33 mole) at 5°, and the resulting mixture reduced at 25° under 2525 p.s.i. of hydrogen pressure, using 1 g. of Adams' catalyst. Reduction ceased after 4 hr., when 83% of the theoretical maximum had been absorbed. The filtered liquors were basified to *p*H 9 and concentrated until the still-head temperature was 95°. Two layers had formed. The aqueous phase was extracted with hexane and the united organic layers were dried by refluxing under a Dean-Stark water separator. 5-Propylaminopentanol hydrochloride was precipitated by the addition of dry hydrogen chloride to the hexane solution of the base. The crude, pinkish salt (121 g., 50% yield) was crystallized from propanol-2 and ether with use of charcoal, m.p. 97–98°.

Anal. Calcd. for $C_8H_{19}NO\cdot HCl$: N, 7.71; Cl^-, 19.51. Found: N, 7.78; Cl^-, 19.48.

5-Propylaminopentyl chloride hydrochloride. The above hydrochloride (80.4 g., 0.445 mole) was suspended in hexane (450 ml.) and kept at 0° to +5° during the addition of thionyl chloride (58.5 g., 0.49 mole) in 2 hr. The reaction mixture was then heated at 50° for 1 hr., and refluxed for 6 hr. Excess of thionyl chloride was removed by distillation, and the greyish hydrochloride (87 g.) collected. It crystallized from acetone and absolute ether as needles, m.p. 201–202°. The yield was 70.5 g. (79%).

Anal. Calcd. for $C_8H_{18}ClN\cdot HCl$: N, 7.00; Cl^-, 17.72. Found: N, 6.97; Cl^-, 17.60.

6-Methoxy-8-(5-propylaminopentylamino)quinoline phosphate. A mixture of 40.0 g. (0.2 mole) of 5-propylaminopentyl chloride hydrochloride and 69.6 g. (0.4 mole) of commercial 8-amino-6-methoxyquinoline in 50 ml. of water was stirred at 80° for 20 hr., and at 100° for 4 hr. It was diluted with 200 ml. of water and adjusted carefully to *p*H 4.5 with aqueous sodium hydroxide, and then aqueous sodium acetate added to *p*H 5.1. The excess 8-amino-6-methoxyquinoline was removed by extraction with benzene (200 ml. each, 4 times) at 65°. When chilled, the aqueous layer gave a brownish solid; this was taken up in 200 ml. of water at 50° and basified. The crude base was extracted well with ether, washed well with saturated brine, dried, and the solvent removed. 6-Methoxy-8-(5-propylaminopentylamino)quinoline (38.2 g., 63.5% yield) was obtained as a brownish oil.

The base (14.8 g.) was dissolved in ether (150 ml.) and treated with ethanolic phosphoric acid (5.52 g. of 85% acid

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(10) Testing was done in this institute, under the direction of Dr. E. W. Dennis and Dr. D. A. Berberian.

(11) The analyses were carried out under supervision of Messrs. M. E. Auerbach and K. D. Fleischer in these laboratories. Melting points were corrected for stem exposure.

in 50 ml. of ethanol). Trituration of the resultant gummy, red mass with ethanol and with acetone produced a tan solid (18.0 g.) which melted 75–94°. It was crystallized twice from absolute ethanol to give light tan platelets (17.0 g., 51% yield), m.p. 82–89°. The salt retained moisture and solvent of crystallization very firmly, and these could be removed only at 100° *in vacuo*, accompanied with some decomposition.

Anal. Calcd. for $C_{18}H_{27}N_3O.H_3PO_4$: N, 10.52; H_3PO_4, 24.54. Found:[12] N, 10.68; H_3PO_4, 24.58.

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(12) Corrected for 3.50% loss at 100°, *in vacuo*. Of this total, 1.04% was moisture, as determined by the Karl Fischer method.

7-Chloro-4-(4-dibutylaminobutylamino)-3-methylquinoline

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4-Aminoquinolines are well known for a considerable range of used as chemotherapeutic agents. Representatives of the group have antibacterial,[2] antimalarial,[3] and antitrypanosomal[4] activities, and also worth against extra-intestinal forms of amebiasis.[5–7] 7-Chloro-4-(4-dibutylaminobutylamino)-3-methylaminoline triphosphate has now been shown[8] to be effective against both intestinal and extra-intestinal forms of *Endameba muris*, the protozoan responsible for amebiasis in the hamster. The preparation of the drug was achieved by reaction of 4,7-dichloro-3-methylquinoline with 4-dibutylaminobutylamine, followed by conversion of the resultant base to the phosphate.

EXPERIMENTAL[9]

The reaction of 4,7-dichloro-3-methylquinoline[10,11] (21.2 g., 0.1 mole) with 4-dibutylaminobutylamine[12] (44 g., 0.22 mole) was run in phenol (60 g.) at 160–165° in the presence of a trace of potassium iodide. After 13 hr., the viscous mixture was cooled and quenched in an excess of cold aqueous sodium hydroxide, and the bases taken into methylene chloride. The mixture was extracted with a 2*N* hydrochloric acid, the bases then liberated, extracted with methylene chloride, dried, and fractionated. A 70% yield (25.6 g.) of the desired base was obtained as a viscous, golden oil; b.p. 190–193° (0.08 mm.); n_D^{25} 1.5741.

Anal. Calcd. for $C_{22}H_{34}ClN_3$: C, 70.28; H, 9.11; N, 11.18. Found: C, 69.98; H, 8.74; N, 11.18.

The base (25.5 g.) was dissolved in 150 ml. of propanol-2, chilled to 5°, and treated with a cold solution of 85% phosphoric acid (25.4 g.) in ethanol (100 ml.). A creamy-white phosphate resulted in crystalline form after scratching the vessel, and the solid was collected, washed (ether) and dried superficially. It was suspended in 500 ml. of boiling ethanol, boiling water added to effect solution, and then treated with charcoal. The pure 7-chloro-4-(4-dibutylaminobutylamino)-3-methylquinoline triphosphate (20.5 g., m.p. 186–186.6°) was obtained by two further crystallizations of the slightly impure salt (32.0 g.).

Anal. Calcd. for $C_{22}H_{34}ClN_3.3H_3PO_4$: N, 6.27; H_3PO_4, 43.90. Found: N, 6.17; H_3PO_4, 44.20.

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(2) W. C. Austin, M. D. Potter, and E. P. Taylor, *J. Chem. Soc.*, 1489 (1958).

(3) F. Y. Wiselogle (ed.), *Survey of Antimalarial Drugs, 1941–1945*. Edward Brothers, Ann Arbor, Mich., 1946. Vol. II, pt. 2, pp. 1146, 1149.

(4) E. A. Steck in R. E. Kirk and D. F. Othmer (eds.). *Encyclopedia of Chemical Technology*, Interscience Publishers, Inc., New York, N. Y., 1955, Vol. 14, p. 330.

(5) N. J. Conan, Jr., *Am. J. Trop. Med.*, **28**, 107 (1948); **31**, 18 (1951).

(6) M. T. Hoekenga and Q. Gonzalo-M., *Am. J Trop. Med.*, **30**, 625 (1950).

(7) N. J. Conan, Jr., J. A. Head, and A. E. Brewer, *Trans. Roy. Soc. Trop. Med. Hyg.*, **43**, 659 (1950).

(8) The chemotherapeutic testing of the quinoline derivative was done under the direction of Dr. D. A. Berberian at this Institute.

(9) Analyses were run in these laboratories, and under guidance of Mr. M. E. Auerbach and Mr. K. D. Fleischer. Melting points given are corrected values, whereas boiling points are uncorrected.

(10) E. A. Steck, L. L. Hallock, and A. J. Holland, *J. Am. Chem. Soc.*, **68**, 380 (1946).

(11) H. Andersag, *Chem. Ber.*, **81**, 506 (1948).

(12) S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4305 (1952).

Preparation of Aliphatic Ketones from Lithium Alkyls and Dimethylamides

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The condensation of lithium alkenyls, alkyls, and aryls with dimethylamides to give aldehydes and methyl ketones as a preparative method has been studied by Evans and co-workers.[1,2] In the ketone series, Evans[2] prepared several methyl ketones in practical yields by reacting lithium alkyls with *N,N*-dimethylacetamide. The present paper describes an extended application of this reaction to the synthesis of other aliphatic low molecular weight ketones. This extension includes the use of longer chain *N,N*-dimethylamides and the comparison of yields by interchanging the alkyl chains associated with the carboxamide and lithium groups. For example, ethylisopentyl ketone was formed in 75% yield from the condensation of isopentyllithium and *N,N*-dimethylpropionamide and in 78% yield from ethyllithium and *N,N*,4-trimethylvaleramide. Incidental to this work, this method of ketone synthesis was compared with those involving the well known nitrile-Grignard, and acid halide–

(1) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3334 (1955).

(2) E. A. Evans, *J. Chem. Soc.*, 4691 (1956); *Chem. and Ind. (London)*, 1596 (1957).

TABLE I

PREPARATION OF KETONES FROM LITHIUM ALKYLS

Alkyl Halide	Amide[a]	Ethyl Ketone	Yield, %	B.P., °C. (mm.)	n_D	Analyses, % Calcd. C	Calcd. H	Found C	Found H	2,4-Dinitrophenylhydrazone, M.P., °C. (Uncorr.)
Isopentyl bromide	*N,N*-Dimethylpropionamide	6-Methyl-3-heptanone[b]	75	65–66 (25)	1.4118[26]	74.94	12.58	75.06	12.63	73–75[c]
Ethyl bromide	*N,N*,4-Trimethylvaleramide[d]	6-Methyl-3-heptanone[b]	78	71 (28)						72–73[c]
Ethyl bromide	*N,N*,2-Trimethylvaleramide[e]	4-Methyl-3-heptanone	80	70–76 (38)	1.4109[25]	74.94	12.58	74.77	12.68	[f]
Ethyl bromide	*N,N*,2-Trimethylpropionamide[g]	2-Methyl-3-pentanone	56[h]	114–115[i] (760)						111–112
Ethyl bromide	*N,N*-Dimethylcyclohexanecarboxamide[j]	Ethylcyclohexyl ketone	70	73–77[k] (8)	1.4508[28]	77.09	11.50	77.09	11.80	150–151

[a] Prepared by the slow addition of an ethereal solution of 1 molar equivalent of the required acid chloride to an ethereal solution containing 2.2 molar equivalents of dimethylamine at 0°. [b] G. Ponzio and A. de Gaspari, *Chem. Zentr.*, 189 (1899I), and H. Thoms and H. Kahre, *Chem. Zentr.*, 547 (1925II), reported the synthesis of this ketone by other methods. The first workers reported a b.p. of 163–163.5°/734.2 mm. The latter reported a b.p. of 160–163°/760 mm., n_D 1.42087, and a semicarbazone melting at 131–132°. A semicarbazone, m.p. 132–133°, was also reported by L. Bouveault and R. Locquin, *Bull. soc. chim. France*, **31**, 1153 (1904). [c] Despite the fact that the ketone obtained by either of the methods given in the table was shown to be homogeneous by vapor phase chromatography, we were unable to duplicate the m.p.'s of the semicarbazones reported by the aforementioned workers. In our hands the semicarbazones gave indefinite and erratic m.p.'s, although they gave satisfactory elemental analyses. The 2,4-dinitrophenylhydrazone proved to be a more reliable and easily purified derivative giving constant m.p.'s regardless of the method of preparation used. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.70; N, 18.35. [d] B.p. 94–95°/10 mm.; n_D^{25} 1.4444. [e] B.p. 88–90°/10 mm.; n_D^{25} 1.4405. [f] No crystalline carbonyl derivative could be obtained. This confirmed the experience of J. Dubois and R. Luft, *Bull. soc. chim. France*, 1153 (1954), who prepared this ketone by another method. Their physical constants were: b.p. 53–54°/10 mm., n_D^{25} 1.4137, MR 39.05. Calcd. MR: 39.16. Found: 39.16. Vapor phase chromatography revea'ed a small impurity closely associated with the product. [g] B.p. 29°/13 mm.; n_D^{30} 1.4341. H. Rapoport and R. Bonner, *J. Am. Chem. Soc.* **72**, 2783 (1950) reported a b.p. of 178–179°, and n_D^{25} 1.4388. [h] This yield was obtained in the one run which was made. [i] G. Wagner, *J. prakt. Chem.*, **44**, 257 (1891), reported b.p. 113.8–114°/745 mm. [j] B.p. 118–121°/12 mm., n_D^{24} 1.4765. M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. soc. chim. France*, 1042 (1952), reported b.p. 135–140°/20 mm. [k] W. Scharvin, *Ber.*, **30**, 2864 (1897), reported b.p. 195°.

Grignard condensations and was found to be greatly superior in yield and ease of purification of the products. For example, ethylisopentyl ketone was formed in only 20–38% yield from either the condensation of 4-methylvaleronitrile with ethylmagnesium bromide or the condensation of propionitrile with isopentylmagnesium bromide.[3] It was found, however, that the scope of the reaction was limited to primary lithium alkyls, as attempts to prepare 4-methyl-3-heptanone and ethylcyclohexyl ketone from *N,N*-dimethylpropionamide, lithium, and 2-bromopentane and cyclohexyl bromide, respectively, gave only negligible amounts of ketonic products.[4] These two ketones were, however, prepared smoothly and in good yields from *N,N*,2-trimethylvaleramide and *N,N*-dimethylcyclohexylcarboxamide and ethyllithium.

Table I summarizes the results obtained in the preparation of some known representative ethyl ketones.

EXPERIMENTAL[5,6]

The following is a general procedure by which the ketones listed in Table I were prepared.

The lithium alkyls were prepared by the procedure of Gilman and co-workers.[7]

A suspension of 1.6 gram-atoms of lithium ribbon, cut into small pieces, in 800 ml. of anhydrous ether was prepared in a flask fitted with reflux condenser, nitrogen inlet tube, thermometer, and addition funnel. The suspension was cooled to −10°, and, while the system was being swept with nitrogen, a solution of 0.83 mole of the required alkyl bromide in 200 ml. of anhydrous ether was added over a period of 2 hr. The mixture was stirred for 1 hr. longer at −10°. Then the temperature was lowered to −20° and a solution of 0.8 mole of the required *N,N*-dimethylamide in 200 ml. of anhydrous ether was added dropwise over a period of 1.5 hr. The temperature was then allowed to rise gradually to 25° over a period of 3 hr. with continued stirring under nitrogen atmosphere. At the end of this time, the solution was cooled to −10° and 500 ml. of a cold, saturated ammonium chloride solution was slowly added. The mixture was stirred for 30 min., and the ether layer was separated, washed with 1*N* hydrochloric acid and with water and dried.

(3) For a discussion of the reactions of nitriles having α-hydrogens with Grignard reagents see C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, 15, 359 (1950).

(4) Evans, ref. 2, noted a similar limitation with other examples.

(5) All melting points and boiling points are uncorrected.

(6) The authors are indebted to Mr. Louis Brancone and staff for the microanalyses.

(7) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

Evaporation of the solvent at reduced pressure left a colorless liquid residue which was distilled through a 10-in. Vigreux column.

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The Question of Active Cobalt in the Decomposition of Grignard Reagents in the Presence of Cobaltous Halides

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Kharasch, Lewis, and Reynolds[1] have proposed the following reaction scheme to account for the products formed when phenylmagnesium bromide is allowed to react with an alkyl halide in the presence of a cobaltous halide.

$$C_6H_5MgBr + CoX_2 \longrightarrow C_6H_5CoX + MgBrX$$

$$2C_6H_5CoX \longrightarrow C_6H_5C_6H_5 + 2\cdot CoX$$

$$RX + \cdot CoX \longrightarrow R\cdot + CoX_2$$

Wilds and McCormack[2] have pointed out several weaknesses of the above scheme, such as the fact that organocobalt compounds of this type have not been prepared before, nor is there any evidence for the existence of the cobalt subhalide radical. Furthermore, they found that the reactivity of the mixture was only somewhat diminished if the Grignard reagent and the cobaltous halide were brought together several hours before the introduction of the alkyl halide; a fact which argues against the presence of a thermally unstable intermediate. As an alternative path they have proposed finely divided, active cobalt as the reactive intermediate.

$$2RMgX + CoX_2 \longrightarrow 2MgX_2 + CoR_2$$

$$CoR_2 \longrightarrow Co + 2R\cdot$$

$$Co + 2R'X \longrightarrow CoX_2 + 2R'\cdot$$

Walling[3] has stated a preference for this latter proposal and has cited as additional evidence the work of Chu and Friel[4] who found that the sodium-naphthalene radical ion in tetrahydrofuran solution instantly reduced cobaltous chloride to metallic cobalt in a highly reactive colloidal form which reacted with air and reduced cupric chloride to the cuprous state.

In order to test the hypothesis of active cobalt as the reactive intermediate in the reactions of Grignard reagents with alkyl halides in the presence of cobaltous halides, a tetrahydrofuran solution of active cobalt was prepared by the method of Chu and Friel. Treatment of this solution with ethyl bromide failed to produce any gaseous reaction products. A further test of this hypothesis was conducted by adding a suspension of cobaltous chloride and ethyl bromide in tetrahydrofuran to a solution of the sodium-naphthalene radical ion. Again no gaseous products were produded.

In order to rule out the possibility that the solvent or the naphthalene was entering into the above reactions a solution of phenylmagnesium bromide in tetrahydrofuran was prepared. A portion of naphthalene was also added to this solution. Addition of ethyl bromide and cobaltous bromide in tetrahydrofuran now produced an immediate evolution of gas which amounted to 48% of the theoretical amount. Analysis of this gas showed that it was 28% ethane and 72% ethylene. These findings are in good agreement with the observations of Kharasch, Lewis, and Reynolds[1] who reported a similar yield for the reaction of phenylmagnesium bromide, ethyl bromide, and cobaltous chloride in ethyl ether.

While the above results do not allow one to draw any further conclusions regarding the mechanism proposed by Kharasch *et al.*, it seems reasonable that the postulation of reactive colloidal cobalt may now be abandoned. It is not likely that the state of the cobalt produced by the Grignard reagent is sufficiently different from that produced by the reaction with the sodium-naphthalene radical ion to account for the complete inactivity toward ethyl bromide in the latter case.

EXPERIMENTAL

All reactions were carried out in a 500 ml., two necked flask equipped with a dropping funnel and a condenser. The apparatus was flushed with nitrogen before each reaction. Stirring was provided by a magnetic stirrer. All gases were collected over a saturated brine solution. Gas analysis was carried out by chromatography over a charcoal filled column at 32° with helium as the eluting gas.

Reaction of ethyl bromide with active cobalt. A solution of the sodium-naphthalene radical ion was prepared by reacting 2.4 g. of finely dispersed sodium with 14 g. of naphthalene in 150 ml. of anhydrous tetrahydrofuran. To the dark green solution was added a mixture of 6.5 g. of anhydrous cobaltous chloride and 7.85 g. of ethyl bromide in 100 ml. of tetrahydrofuran. The reaction immediately turned to dark black, and heat was evolved. However, no gas was given off.

In another experiment the cobaltous chloride was added to the solution of the radical ion before the addition of the ethyl bromide in the tetrahydrofuran. Again the solution turned dark black, and no gas was evolved.

Reaction of phenylmagnesium bromide, ethyl bromide, and cobaltous bromide. A solution of phenylmagnesium bromide in tetrahydrofuran was prepared from 7.85 g. (0.05 mole) of bromobenzene, 1.30 g. of magnesium, and 50 ml. of tetrahydrofuran. The mixture was heated for 0.5 hr. after the initial vigorous reaction had subsided. The mixture was

(1) M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *J. Am. Chem. Soc.*, 65, 495 (1943).

(2) A. L. Wilds and W. B. McCormack, *J. Org. Chem.*, 14, 45 (1949).

(3) Cheves Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, 1957, p. 589.

(4) T. L. Chu and J. V. Friel, *J. Am. Chem. Soc.*, 77, 5838 (1957).

cooled to room temperature, and 5 g. of naphthalene was added. To this stirred mixture was slowly added a solution of 1.0 g. of cobaltous chloride and 5.45 g. (0.05 mole) of ethyl bromide in 40 ml. of tetrahydrofuran. Gas was evolved continuously throughout the addition (535 ml. at S.T.P., 48% of the theoretical yield). Analysis of this gas indicated that it was 28% ethane and 72% ethylene.

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Crystalline Complexes of the Phosphoryl Group with Polyphenols[1]

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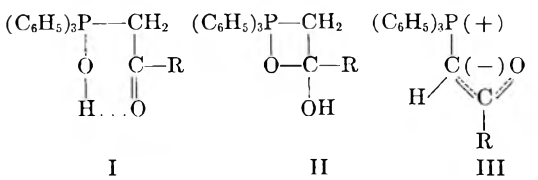
The "quasi-phosphonium" compounds,[3] for instance $[R_3P(OR')X]$, constitute an interesting variation of the phosphonium structure, $[R_4PX]$, in which one or more R groups are replaced by OR groups. This structural change might conceivably alter significantly the bonding characteristics of the phosphorus atom. A substance of composition $[R_3PO, HX]$ could be formulated as a hydrogen-bonded complex, $[R_3PO\ldots HX]$, a phosphonium hydroxide, $[R_3P(OH)]^+X^-$, or as a structure with pentacovalent phosphorus, $[R_3P(OH)X]$. Halmann and Pinchas[4] have discussed recently the structure of triphenylphosphine oxide hydrate, which they formulate as $[(Ph_3PO)_2, H_2O]$. It was concluded that the hydrate is a molecular complex between the phosphine oxide and the water molecule, and that it does not have the dihydroxy structure, $[Ph_3P(OH)_2]$.

We have recently shown[5] that the "acylphosphine-methylene hydrates" which had been previously formulated[6] with pentacovalent phosphorus, such as in I[6a] or II,[6b] are actually *ylides* of type III. These ylides have a strong tendency to retain water.



I II III

In another investigation,[7] it was shown that the crystalline, sharp-melting adducts formed from triphenylphosphine oxide and tetrachlorohydroquinone do not have the quasi-phosphonium structure $[(C_6H_5)_3P(OAr)(OH)]$. These adducts are formed: (a) when the oxide and the polyphenol are fused together in a 2:1 molar ratio or (b) when an alcoholic solution containing the oxide and the polyphenol is evaporated to dryness or is diluted with water. The adducts were formulated as hydrogen-bonded complexes, such as IV. Related compounds[8] are probably of the same type.

We have now extended these observations to include other polyphenols, as shown in Table I. Furthermore, it was found that certain *phosphate esters* also form crystalline, sharp-melting complexes with tetrachlorohydroquinone. The infrared spectra of these complexes, the ease with which they are formed and the ease with which they are split into their components by cold, dilute alkali, are consistent with the hydrogen-bonded formulations VIII, IX, X, and XI. The substances listed in Table I were obtained by addition of water to an alcoholic solution containing the phosphoryl derivative and the polyphenol in the proper molar ratio. The melting point of the original precipitate does not change significantly by recrystallization. It should be noted that the solubility of the polyphenol itself in a nonpolar solvent like benzene is quite small; the adducts, however, are appreciably soluble in benzene. The adducts derived from phosphate esters are quite soluble even in cyclohexane.

TABLE I

CRYSTALLINE COMPLEXES OF THE PHOSPHORYL GROUP (>PO) WITH POLYPHENOLS[a]

Formula	Molar Ratio[b]	M.P.,[c] °C.	Analyses[d] Calcd. C	Calcd. H	Found C	Found H
IV	2:1	180–182	62.7	4.0	62.3	4.3[e]
V	2:1	164–165	68.6	4.7	68.5	4.9[f]
VI	2:1	144–146	75.7	5.5	75.9	5.9[f]
VII	1:1	120–121	54.8	3.3	54.9	3.4[f]
VIII	2:1	106–108	29.2	2.0	29.3	2.2[h]
IX	2:1	74–75	33.9	3.0	33.6	3.3[i]
X	1:1	193–194	27.0	2.0	27.4	2.2[j]
XI	1:1	140–141	31.3	2.9	31.8	3.1[h]

[a] A methanol solution containing the components in the molar ratio indicated, was diluted with water. The crystalline precipitate was dried and its m.p. determined; the m.p. did not change significantly upon repeated recrystallizations. For the preparation of the phosphoryl components see ref. 12. [b] Phosphoryl derivative: polyphenol. [c] Corrected capillary – m.p. [d] Micro-Tech Laboratories, Skokie, Ill. [e] Calcd.: P, 7.7; Cl, 17.6. Found: P, 7.6; Cl, 17.5. [f] Recrystallized from benzene–petroleum ether. [g] Calcd.: P, 8.4; Cl, 9.4. Found: P, 8.5; Cl, 9.5. [h] Recrystallized from cyclohexane. [i] Recrystallized from hexane. [j] Recrystallized from benzene.

(1) This work was supported by Grant CY-3250 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(3) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter II.

(4) M. Halmann and S. Pinchas, *J. Chem. Soc.*, 3264 (1958).

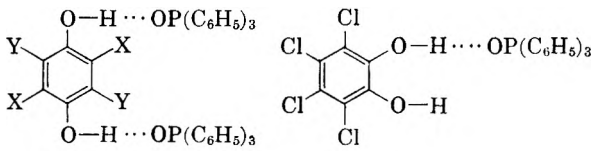
(5) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, 22, 41 (1957).

(6) (a) G. Wittig and U. Schollkopf, *Chem. Ber.*, 87, 1318 (1954); (b) A. Michaelis and E. Kohler, *Ber.*, 32, 1566 (1899).

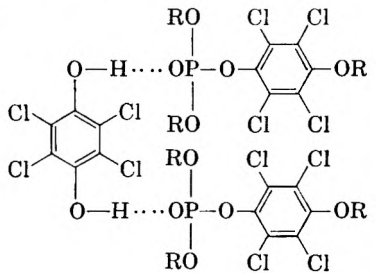
(7) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, 78, 5614 (1956).

(8) W. Lommel and H. Munzel, U. S. Patent 1,844,015 (1932); *Chem. Abstr.*, 26, 1941 (1932).

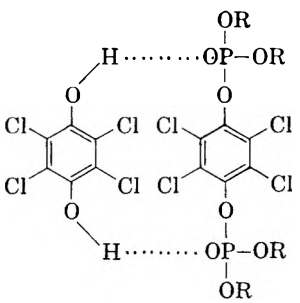
The composition of the complexes depend, as shown by X and XI, on the number of phosphoryl groups in the molecule or, as in the case of VII, on steric requirements in the polyphenol. The latter complex, m.p. 122°, has already been encountered by Horner[9] as a product of the hydrolysis of the tetrachloro-*o*-benzoquinone-triphenylphosphine adduct. It was formulated by him as a hydrate VIIA.



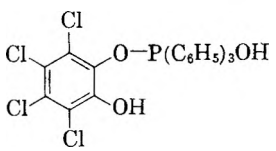
IV. X = Y = Cl
V. X = Cl; Y = H
VI. X = Y = H



VIII. R = CH_3
IX. R = C_2H_5



X. R = CH_3
XI. R = C_2H_5



VIIA

The structural problems involved in the formulation of some of the compounds of the general type $(RO)_xPZ_{5-x}$ have been clarified by recent investigations of Lipkin[10] and of Rydon.[11] For the particular instance in which one R group = H, a satisfactory representation seems to be that of loosely bonded complex, probably of the hydrogen-bonded type.

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(12) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, 81, 587 (1959).

(9) L. Horner and K. Klupfel, *Ann.*, 591, 69 (1955).

(10) J. P. Forsman and D. Lipkin, *J. Am. Chem. Soc.*, 75, 3145 (1953).

(11) (a) D. G. Coe, H. N. Rydon, and B. L. Tonge, *J. Chem. Soc.*, 323 (1957); (b) H. N. Rydon in *Phosphoric Esters and Related Compounds*, The Chemical Society, London (1957), Special Publication No. 8, p. 61.

Some Heterocyclic Compounds Containing Phosphorus

Henry Tolkmith and Edgar C. Britton

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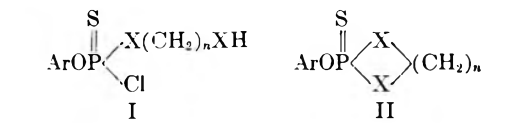
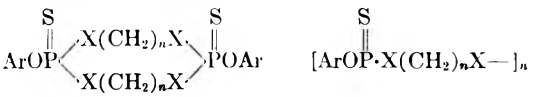
In the course of investigations involving *O*-halophenyl phosphorodichloridothioates, $ArOPSCl_2$,[1] it became desirable to study reactions of these acid dichlorides with difunctional nucleophiles of the structure $HX(CH_2)_yXH$ (X being oxygen or —NH—, y being zero or integer). At a constant mole ratio of 1:1, the formation of four types of compound appeared possible:



I II



III IV

In order to investigate the tendencies of formation[2] of the heterocyclic structures II and III, experiments were carried out with hydrazine, ethylenediamine, and ethylene glycol as representative dinucleophiles and with various substituted phenyl groups in place of Ar.

Reactions involving *hydrazine*[3–5] were reported to produce compounds of structure III, *viz.*, $C_6H_5OP(O)(NHNH)_2P(O)OC_6H_5$[5] and $C_6H_5OP(S)(NHNH)_2P(S)OC_6H_5$[4]. Repetition of the work involving $C_6H_5OPSCl_2$ gave a crystalline compound which melted at 184–185° and showed analytical data as required for structure III. The yield of this compound was found to be 16% of theory, when prepared in the presence of a water-glycerol mixture, as mentioned in the literature.[4] The other reaction products formed were not found to represent structures I, II, or IV, but to consist of hydrazine salts of *O*-phenyl phosphoro-

(1) H. Tolkmith, *J. Org. Chem.*, 23, 1685 (1958).

(2) *Cf.* F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth and Silicon," Interscience Publishers Inc., New York (1950).

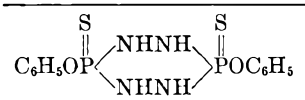
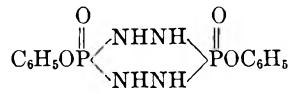
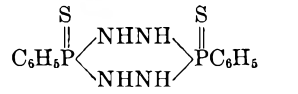
(3) W. Strecker and H. Heuser, *Ber.*, 57, 1372 (1924).

(4) W. Autenrieth and W. Meyer, *Ber.*, 58, 848 (1925).

(5) W. Autenrieth and E. Bolli, *Ber.*, 58, 2144 (1925).

TABLE I

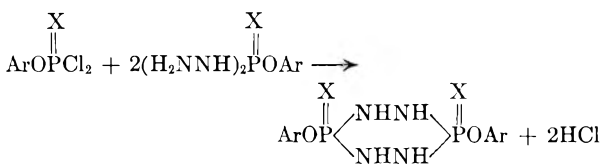
HETEROCYCLIC COMPOUNDS FROM HYDRAZINE

Compound	Yield, % Th.	M.P.	Mol. Wt. Calcd.	Mol. Wt. Found	% N Calcd.	% N Found	% P Calcd.	% P Found	% S Calcd.	% S Found
	53.5	184–185	372.35	404[a]	15.05	14.89	16.64	16.20	17.22	16.71
	8.0	210–211	340.21	330[b]	16.47	16.75	18.21	18.45		
	12.5	168–169	340.33	383[c]	16.46	16.48	18.2	17.86	18.8	18.27

[a] In tetrahydrofuran. [b] In dimethylformamide. [c] In methyl ethyl ketone.

thioic acid. Anhydrous reactants in benzene were found to produce compounds possessing structure III in varying yields depending upon the structure of the dichloride employed (*cf.* Table I). The melting point found for $C_6H_5OP(O)(NHNH)_2P(O)OC_6H_5$, when prepared under anhydrous conditions, varied considerably from the value given in the literature (m. p. 132°).[5]

The following reaction was investigated also (X being oxygen or sulfur):



This reaction required the presence of stoichiometric quantities of triethylamine and gave the compound, $C_6H_5OP(S)(NHNH)_2P(S)OC_6H_5$, in a yield of 89% of theory. Reactions involving negatively substituted phenyl groups in place of Ar were found to produce mixtures of reaction products from which no heterocyclic components could be isolated.

Autenrieth and Meyer[4] reported formation of an insoluble reaction product from *O*-phenyl phosphorodichloridothioate and *ethylenediamine* and assigned structure II to it, although analytical evidence was insufficient. It was found that *O*-aryl phosphorodichloridothioates and ethylenediamine, when reacting under anhydrous conditions, at a mole ratio of 1:2, produced heterocyclic derivatives for which structure II could be proved. The yields of these compounds increased with increasing negative substitution of their aryl group. The melting points also were found to increase in first approximation with increasing negative substitution of the phenyl group (*cf.* Table II) with the notable exception of the derivative of $C_6H_5OPSCl_2$ whose melting point was found to be almost as high as already reported (m.p. 189°).[4] Contrary to statements in the literature,[4] these compounds were found to be appreciably soluble in acetone, dimethylformamide, methanol, and tetrahydrofuran.

Reactions of *O*-aryl phosphorodichloridothioates with *glycols* were not described in the past. Conceivably, all four structures (I, II, III, and IV) could be formed from these reactants. The existence of a five-membered, heterocyclic ring as present in structure II (X being oxygen, *n* being two) with aliphatic groups in place of Ar, was proved by A. E. Arbuzov and V. M. Zoroastrova.[6]

The investigation reported in the following involved reactions in the absence of HCl–acceptors and catalysts at temperatures of 50–60° under a pressure of less than 200 mm. Under these conditions reaction occurred readily with evolution of HCl, although *O*-aryl phosphorodichloridothioates have been reported to possess remarkable resistance to attack by hydroxyl compounds.[7,8] Independent of the mole ratio of the reactants employed, the mixture of reaction products was always found to contain compounds representing structure II. The yield of this type of component increased with increasing negative substitution of the phenyl group in $ArOPSCl_2$. The yields were particularly good with two negative substituents in *ortho*-position (*cf.* Table III). The structure of side products formed could not be established with certainty but might have corresponded to structure III whose nonsulfurated, ten-membered ring probably exists.[9] Compounds of structure I were not isolated, even at a 1:1 mole ratio of reactants. The heterocyclic *O*-halophenyl *O,O*-ethylene glycol phosphorothioates obtained were found to be well crystallizing compounds, being soluble in acetone, aromatic hydrocarbons, and methanol.

It has been shown in this laboratory that reactions of O-halophenyl phosphorodichloridothioates with primary monohydric alcohols and primary monoamines, under reaction conditions almost

(6) A. E. Arbuzov and V. M. Zoroastrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 357 (1950).

(7) W. Autenrieth and O. Hildebrand, *Ber.*, **31**, 1094 (1898).

(8) W. Strecker and Ch. Grossmann, *Ber.*, **49**, 63 (1916).

(9) H. G. Cook, J. D. Ilett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Wilding, and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949).

TABLE II

HETEROCYCLIC COMPOUNDS FROM ETHYLENEDIAMINE

Compound	Yield, (% Th)	M.P.	Mol. Wt. Calcd.	Mol. Wt. Found	% N Calcd.	% N Found	% P Calcd.	% P Found	% S Calcd.	% S Found
$C_6H_5OP(S)(NHCH_2)(NHCH_2)$	25.5	185.5–186.5	214.23	203	13.08	13.01	14.46	14.35	14.97	14.57
$4F\text{-}C_6H_4OP(S)(NHCH_2)(NHCH_2)$	57.5	63–64	232.22	220	12.08	11.91	13.33	13.04	13.8	13.6
$3Cl\text{-}4NO_2\text{-}C_6H_3OP(S)(NHCH_2)(NHCH_2)$	55.0	108–109	293.67	271	14.3	13.8	10.58	10.6	10.9	10.8
$2,4,5\text{-}Cl_3\text{-}C_6H_2OP(S)(NHCH_2)(NHCH_2)$	83.0	156.5–158	317.57	298	8.84	8.81	9.76	9.82	10.10	10.01
$2,4,6\text{-}Cl_3\text{-}C_6H_2OP(S)(NHCH_2)(NHCH_2)$	83.0	207–208	317.57	285	8.84	8.37	9.76	9.61	10.10	9.91
$2,4,6\text{-}Br_3\text{-}C_6H_2OP(S)(NHCH_2)(NHCH_2)$	51.5	222–223	450.95	463	6.22	5.95	6.89	6.95	7.10	7.34

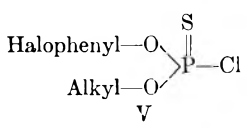
TABLE III

HETEROCYCLIC COMPOUNDS FROM ETHYLENE GLYCOL

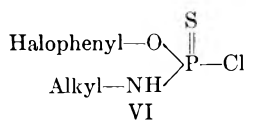
Compound	Ratio[a]	Yield, % Th.	M.P.	Mol. Wt. Calcd.	Mol. Wt. Found	% Halogen Calcd.	% Halogen Found	% P Calcd.	% P Found	% S Calcd.	% S Found
$2,4,5\text{-}Cl_3C_6H_2OP(S)(OCH_2)(OCH_2)$	1:0.5	32	123–124	319.54	268	33.4	33.1	9.7	9.9	10.0	10.3
	1:2	30	122–123								
$2,4,6\text{-}Cl_3C_6H_2OP(S)(OCH_2)(OCH_2)$	1:2	69	80–81	319.54	315	33.4	33.5	9.7	9.87	10.0	10.2
$2,4,6\text{-}Br_3C_6H_2OP(S)(OCH_2)(OCH_2)$	1:2	44	64–65	452.92	395	53.0	53.24	6.84	6.73	7.06	6.93
$2Cl\text{-}4NO_2\text{-}C_6H_3OP(S)(OCH_2)(OCH_3)$	1:1	35.5	93.5–94.5	295.64	273	12.02	12.3	10.48	9.8	10.83	10.7
$4NO_2\text{-}C_6H_4OP(S)(OCH_2)(OCH_2)$	1:2	16	48–49	261.19	238			11.57	11.3	11.92	12.01

[a] Mole ratio, $ArOPSCl_2$:HOC_2H_4OH.

identical to those employed with the analogous dinucleophiles of the present investigation, produce near-quantitative yields of the following types of compound.[10,11] Hersman and Audrieth[12] have found that the reaction of aryl phosphonodichloridates and dichloridothioates with alcohols gives compounds of a structure analogous to V.



V



VI

In view of these findings the following conclusions may be drawn:

Phosphorodichloridothioates, $ArOPSCl_2$, and dinucleophiles (as defined) may well react with initial formation of compounds representing structure I,

(10) H. Tolkmith, E. H. Blair, and K. C. Kauer, Can. Patent **555,938** (April 15, 1958).

(11) E. H. Blair and H. Tolkmith, paper presented before the Division of Organic Chemistry at the 134th meeting of the American Chemical Society, September 7–12, 1958, Chicago, Ill.

(12) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23**, 1889 (1958).

but at temperatures of at least 20°, these intermediates undergo dehydrochlorination of reaction rates evidently faster than the rates of formation of the intermediates themselves. Such dehydrochlorination reactions produce heterocyclic phosphorus compounds predominantly, with formation of five- and six-membered heterorings and, possibly, ten-membered rings (structures II and III). The formation organic, five-membered rings (structure II) evidently is favored by increased electron-attracting power of the halophenyl group as well as by increasing nucleophilicity of the dinucleophile participating. The formation of inorganic, six-membered P—N rings appears to be hindered by increasing electrophilicity of the Ar group. Electron withdrawal by this group from the hydrazine nitrogens may decrease the extent of hydrogen-hydrogen repulsion, which is considered to be the cause for fixation of the hydrazine molecule in *trans* position.[13] With acquisition of free rotation about the N—N axis, hydrazine becomes more likely to form nonheterocyclic polycondensation products instead of heterocyclics of structure III.

EXPERIMENTAL

The *O*-aryl phosphorodichloridothioates employed were of a quality as described previously,[1] while the dinucleophiles were anhydrous, commercial grade products.

Hydrazine derivatives. Anhydrous hydrazine (1.5 gram moles) was added dropwise over a period of 3 hr. at room temperature to an agitated solution prepared from 500 cc. of benzene and 0.5 gram mole of $C_6H_5OPSCl_2$, $C_6H_5OPOCl_2$, or $C_6H_5PSCl_2$, respectively. After completed reaction the reaction mixture was filtered and the solid thus isolated was dissolved in ethanol. Addition of water to this solution gave the crude main product which was recrystallized from methanol. The products obtained showed yields, melting points and analyses as given in Table I. The molecular weights were determined ebullioscopically as indicated in this table.

The compound, $C_6H_5OPS(NHNH)_2PS.OC_6H_5$, was also prepared by dropwise addition of triethylamine (0.225 gram mole) to an agitated solution of $C_6H_5OPSCl_2$ (0.1 gram mole) and $C_6H_5OPS(NHNH_2)_2$ (0.1 gram mole) in 400 cc. of toluene. After completed addition the mixture was slowly heated to reflux over a period of 5 hr., cooled to room temperature, and treated with 400 cc. of water. Separation of the solid phase from this mixture gave 36 grams of a white solid which was recrystallized from aqueous ethanol. Obtained was 33 grams of desired compound, melting at 184–185°. Its infrared analysis showed identity with the compound obtained from $C_6H_5OPSCl_2$ and anhydrous hydrazine.

Reactions involving ethylenediamine. One fourth of a gram mole of ethylenediamine was added dropwise to an agitated solution of one tenth of a gram mole of $ArOPSCl_2$ in 500 cc. of ethylene dichloride at such a rate that the reaction mixture maintained a temperature of +15 to +25° when cooled with ice water. After completed reaction the mixture was washed twice with 200 cc. of water in order to remove ethylenediamine hydrochloride formed. The ethylene dichloride layer was separated and evaporated. The evaporation residues were recrystallized from methanol and gave main products with yields, analyses, and melting points as given in Table II. The molecular weights of these products were determined ebullioscopically in methanol.

Reactions involving ethylene glycol. Mixtures of one-half gram mole of *O*-aryl phosphorodichloridothioate with one-fourth to one gram mole of ethylene glycol, as indicated in Table III, were heated with agitation for eight hours at 55° under a pressure of about 100 mm. The reaction mixtures were taken up with benzene and washed with water in order to remove unreacted glycol. The benzene layers were separated and evaporated. The evaporation residues were recrystallized from methanol to give main products with yields, analyses, and melting points as shown in Table IV. The molecular weights of these products were determined cryoscopically in benzene.

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(13) W. J. Penney and G. B. B. M. Sutherland, *J. Chem. Phys.*, **2**, 498 (1934).

Selective Hydrogenation of Olefins with Ruthenium

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In common with the other platinum metals, ruthenium can be a very active hydrogenation catalyst, but its use has been limited, so far, mainly to carbonyl reduction,[1] to ring hydrogenation, especially where hydrogenolysis is to be avoided,[2] and to reduction of acids to alcohols.[3]

We examined ruthenium catalysts for the hydrogenation of olefins and discovered the catalyst was very selective. Monosubstituted olefins were reduced preferentially in the presence of di- and trisubstituted olefins, as shown in the following

COMPETITIVE HYDROGENATION OF OLEFINS BY RUTHENIUM ON CARBON

4-Methyl-1-pentene and 2-methyl-2-pentene	Selective
4-Methyl-1-pentene and 2-methyl-1-pentene	Selective
4-Methyl-1-pentene and 2-octene	Selective
4-Methyl-1-pentene and cyclohexene	Selective
2-Methyl-2-pentene and 2-methyl-1-pentene	Not selective
2-Methyl-2-pentene and 2-octene	Not selective
2-Methyl-2-pentene and 1-octene	Selective
2-Methyl-2-pentene and cyclohexene	Not selective
2-Methyl-1-pentene and 2-octene	Not selective
2-Methyl-1-pentene and 1-octene	Selective
2-Methyl-1-pentene and cyclohexene	Not selective
2-Octene and 1-octene	Selective
2-Octene and cyclohexene	Not selective
1-Octene and cyclohexene	Selective

(1) G. Gilman and G. Cohn, *Advances in Catalysis*, Academic Press Inc., New York, 1957, Vol. IX, pp. 733–742.

(2) (a) L. C. Behr, J. E. Kirby, R. N. MacDonald, and C. W. Todd, *J. Am. Chem. Soc.*, **68**, 1296 (1946). (b) A. E. Barkdoll, D. C. England, H. W. Gray, W. Kirk, Jr., and G. M. Whitman, *J. Am. Chem. Soc.*, **75**, 1156 (1953). (c) M. Freifelder and G. R. Stone, *J. Am. Chem. Soc.*, **80**, 5270 (1958).

(3) T. A. Ford, U. S. Patent 2,607,807 (August 19, 1952).

table. In each case the underlined olefin was completely reduced before any reduction of the other olefin. The catalyst showed no pronounced specificity toward mixtures of di- and tri-substituted olefins or toward mixtures of symmetrically and asymmetrically disubstituted olefins.

Ruthenium hydrogenated acetylenes readily but showed no selectivity. *Sym*-diphenylacetylene gave, on absorption of one mole of hydrogen, a mixture of starting material and diphenylethane.

In all of these experiments water was used as a solvent. Solvents for ruthenium hydrogenations at low pressure and room temperature seem to be virtually limited to water, water–acetic acid, or water-alcohol mixtures. Occasionally methanol or ethanol may be used satisfactorily. Ruthenium hydrogenations usually show a variable, and sometimes lengthy, induction period. This induction period can usually be eliminated entirely by shaking the catalyst and solvent together with hydrogen at room temperature and atmospheric pressure for an hour or two before adding the substrate.

EXPERIMENTAL

Competitive hydrogenation. One hundred ml. of water, 500 mg. of 5% ruthenium on carbon, and 10.0 ml. (0.064 mole) each of 1-octene and 2-octene were shaken at 32° and 42 p.s.i.g. After an induction period of 2 hr. during which time no hydrogen was absorbed, 0.064 mole of hydrogen was taken up in 20 min. The temperature rose from 32° to 35°. The shaker was stopped, the mixture filtered, the aqueous layer saturated with sodium chloride, and the organic layer separated and dried over sodium sulfate. The infrared spectrum of the product was identical with one of an equimolar mixture of 2-octene and octane. All other hydrogenations followed the same procedure, except that frequently the catalyst was shaken with hydrogen for 1 hr. before adding the substrates.

The catalyst was a commercial preparation, manufactured by Engelhard Industries, of 5% reduced metal on Norit.

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Relative Acidities of Butyrophenone and α-Ethylbutyrophenone[1]

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The ethylation of butyrophenone enolate gives a 90% yield of α-ethylbutyrophenone but no α,α-diethylbutyrophenone. Two factors contribute to this result: the relative rates, k_1 and k_2, for the alkylation of the two enolates and the equilibrium constant, K, for the reaction of butyrophenone enolate with α-ethylbutyrophenone.

$$\mathrm{PhCOCHEt^- + EtX \xrightarrow{k_1} PhCOCHEt_2 + X^-}$$

$$\mathrm{PhCOCHEt^- + PhCOCHEt_2 \overset{K}{\rightleftharpoons} PhCOCH_2Et + PhCOCEt_2^-}$$

$$\mathrm{PhCOCEt_2^- + EtX \xrightarrow{k_2} PhCOCEt_3 + X^-}$$

In excess ethyl iodide, independent measurements of specific rates for the alkylations gave $k_1/k_2 = 3.5$. Also, a preliminary experiment indicated that the reaction of sodio-butyrophenone with α-ethylbutyrophenone occurred to only a small extent in 26 hr. in ether solution.[3] There was some doubt as to whether equilibrium had been established in this time, for the reaction of this ketone with sodium triphenylmethide was known to be slow.

The equilibrium has now been approached from both directions and the butyrophenone anion has been studied when paired with both sodium and lithium cations. Equilibrium mixtures were quenched in deuterium oxide and the concentrations of the resulting four ketones determined by infrared spectroscopy. The reactions of both ketone-enolate pairs in equal initial concentrations gave product mixtures with almost identical absorption curves. The equilibrium as written is at least 90% to the left. The concentration equilibrium constant (K) at 30° in ethyl ether is $\lesssim 0.02$, a value which corresponds to at least two pK units difference in acidity for the two ketones. This value was not changed within the limits of the experimental error when lithium was substituted for sodium in the enolate.

These results are in accord with the acid-weakening effects of alkyl groups in other weakly acidic organic compounds.[4] The effect of the α-ethyl group in lowering the acidity of butyrophenone is essentially the same as the 50–100-fold lowering found for this group when in the *alpha-* position of malonic ester in ethanol solution.[5]

EXPERIMENTAL

All operations involving enolates were carried out at 30.00 ± 0.05° under nitrogen in an apparatus described previously.[3]

Materials. Anhydrous ether was Mallinckrodt analytical reagent distilled from ethyl Grignard reagent and stored under a slight positive pressure of nitrogen. The preparations of sodium triphenylmethide, butyrophenone and α-ethylbutyrophenone have been described.[3] Lithium hydride was obtained from Maywood Chemical Co. and ground to a powder in a nitrogen atmosphere. Deuterium oxide (>99.5%) was obtained from the Stuart Oxygen Co.

(1) Supported in part by a grant from the National Science Foundation.

(2) Du Pont Postgraduate Teaching Assistant, The Pennsylvania State University, 1955–56.

(3) H. D. Zook and W. L. Rellahan, *J. Am. Chem. Soc.*, **79**, 881 (1957).

(4) J. B. Conant and G. W. Wheland, *J. Am. Chem. Soc.*, **54**, 1212 (1932); W. K. McEwen, *J. Am. Chem. Soc.*, **58**, 1124 (1936); A. A. Morton, *Chem. Revs.*, **35**, 11 (1944).

(5) R. G. Pearson, *J. Am. Chem. Soc.*, **71**, 2212 (1949).

Butyrophenone-α-d and α-ethylbutyrophenone-α-d. To 4.05 g. (0.0273 mole) of butyrophenone was added 210 ml. (0.0273 mole) of 0.130*M* ethereal sodium triphenylmethide. The color change from deep red to light yellow was rapid and the end point was sharp when the calculated volume had been added. The enolate solution was stirred for 3 hr. with 1.5 ml. (0.075 mole) of deuterium oxide. The ether layer was washed well with water and distilled through a 6-plate column to give six fractions, 3.7 g., 90%, of butyrophenone-α-*d*, b.p. 61–62° at 2 mm., n_D^{25} 1.5175. The infrared spectrum contained characteristic peaks at 4.63μ and 11.10μ which were lacking in the spectrum of butyrophenone. Several major peaks characteristic of butyrophenone were missing.

The conversion of α-ethylbutyrophenone to its enolate is a slow reaction. An end point was obtained when stoichiometric amounts of ketone and sodium triphenylmethide were stirred for several hours at 30°. The enolate from 4.07 g. (0.0231 mole) of ketone was stirred for 16 hr. with 2 ml. (0.10 mole) of deuterium oxide to give seven fractions, 3.5 g., 83%, of α-ethylbutyrophenone-α-*d*, b.p. 72–73.5° at 1 mm., n_D^{25} 1.5093. The infrared spectrum contained characteristic peaks at 4.65μ and 11.22μ which were lacking in the spectrum of α-ethylbutyrophenone. Major peaks characteristic of this ketone were lacking. All spectra were determined in carbon tetrachloride solution. The spectrum of the deuterated ketone was unchanged by shaking an ethereal solution with dilute aqueous sodium hydroxide for 30 min. at room temperature. This experiment shows the absence of H-D exchange during the washing procedure used in the equilibrium studies.

Equilibrium studies. The reaction of sodio-α-ethylbutyrophenone with butyrophenone is typical. The enolate was prepared from 5.29 g. (0.0301 mole) of the ketone and 203 ml. (0.0301 mole) of 0.148*M* ethereal sodium triphenylmethide. The addition with stirring to give a satisfactory end point required 1 hr. The solution was stirred for an additional 3 hr. after which 4.50 g. (0.0304 mole) of butyrophenone was added. After 28 hr., the reaction was quenched by the addition of 4 ml. of deuterium oxide. The ether layer was washed with five 10-ml. portions of water, the last of which was neutral to litmus. The solution was dried over Drierite and diluted with carbon tetrachloride. All of the ether and a portion of the carbon tetrachloride were removed through a short column, and the residue was diluted to 50.0 ml. with carbon tetrachloride for infrared analysis.

In the reverse process, 0.026 mole of sodio-butyrophenone was stirred for 26 hr. with 0.026 mole of α-ethylbutyrophenone and quenched with 0.10 mole of deuterium oxide.

Lithio-butyrophenone was prepared by stirring and refluxing for 5 days a concentrated ethereal solution of the ketone with excess powdered lithium hydride. The solution was filtered through sintered glass and diluted to 0.107*M* with anhydrous ether. A solution of 181 ml. (0.019 mole) of the enolate was stirred for 117 hr. with 3.42 g. (0.019 mole) of α-ethylbutyrophenone, the reaction quenched with 4 ml. of deuterium oxide and extracted as described.

Spectra were measured on a Perkin-Elmer Model-21 spectrophotometer. The four ketones and triphenylmethane were found to obey Beer's law at the wave lengths used for analysis. When triphenylmethane was present, the concentration of this hydrocarbon was estimated by its absorbance at 6.69μ, a wave length at which the absorbances of the four ketones are negligible. The amounts of triphenylmethane obtained agreed within 3% with those calculated from the quantities of sodium triphenylmethide employed. Spectra of the product mixtures starting with equal concentrations of either ketone-enolate pair were practically identical. The equilibrium is far to the left as indicated by the characteristic peaks of butyrophenone and α-ethylbutyrophenone-α-*d* which appear as small shoulders on the strong peaks of α-ethylbutyrophenone and butyrophenone-α-*d*. Absorbances were measured at peaks characteristic of each of the four ketones. These absorbances were corrected for absorbance due to triphenylmethane when present. Solution of four simultaneous equations gave the equilibrium concentrations from which values of K ranging from 0.006 to 0.02 were calculated for both forward and reverse processes. The equilibrium is too far to the left to obtain a more precise value for the equilibrium constant from these data.

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Use of Girard's Reagent "T" in the Separation of Derivatives of Chlorophylls *a* and *b*

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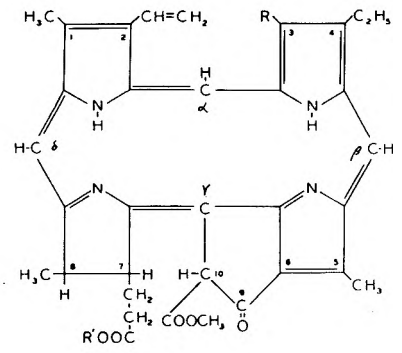
In view of the continuing interest in the chemistry of chlorophyll, we wish to report a new method for the separation of mixtures of *a* and *b* derivatives. The large scale preparative methods employed in this field separate chlorophyll derivatives according to their hydrochloric acid number[1] and their behavior toward buffers of different *p*H. The latter indicates the number of free carboxylic acid groups present.[2] In the method reported here, Girard's reagent "T" (carboxymethyltrimethylammonium chloride hydrazide)[3] is employed to resolve mixtures into groups of *a* compounds and *b* compounds, irrespective of their hydrochloric acid number or the number of carboxylic acid residues present. The 3-formyl group of the *b* compounds reacts readily with this reagent to form a water soluble derivative, whereas members of the *a* series, even those possessing a keto group, *i.e.*, pheophorbide *a* (I, R = CH_3; R′ = H) or purpurin 7*a* trimethyl ester (II, R = C(O)—$COOCH_3$) react very slowly if at all.

The experimental procedure is as follows: A mixture of *a* and *b* compounds containing about 15 mg. of the *b* member is dissolved in 30 ml. of a 90:10 (v/v) mixture of 95% ethanol:glacial acetic acid containing 150 mg. of Girard's reagent "T". The mixture is refluxed under nitrogen for 5 min., cooled, and poured into 1 l. of peroxide-free ether. (If refluxing is continued indefinitely some of the *a* derivative, if it possesses a keto group, does react.) This is then extracted with small (100ml.) portions of distilled water until the aqueous extract is colorless. The *a* derivative, free of even traces of *b* contamination, remains in the ether layer. Partial hydrolysis of esterified compounds may occur, but treatment with diazomethane is sufficient to re-esterify them completely. The *b*

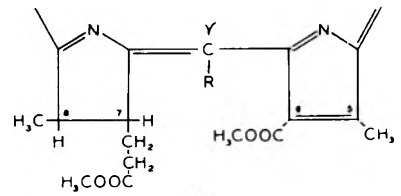
(1) R. Willstätter and A. Stoll, *Investigations on Chlorophyll*, translated from the German by F. M. Schertz and A. R. Merz, The Science Press Printing Co., Lancaster, Pa., 1928, pp. 237–245.

(2) M. J. Hendrickson, unpublished data.

(3) Purchased from Fisher Scientific Co.



I



II

fraction can be regenerated if desired by making the aqueous extract about 6% with respect to hydrochloric acid and heating at 85° for 15 min. It can then be driven into fresh ether and esterified.

This method has been tried on several different mixtures of *a* and *b* derivatives, *e.g.*, chlorin p_6 trimethyl ester (II, R = $COOCH_3$ in the *a* series) and *b*-chlorin p_6 trimethyl ester (II, R = $COOCH_3$, with a formyl group at position 3); purpurin 7*a* trimethyl ester and purpurin 7*b* trimethyl ester (II, R = C(O)—$COOCH_3$, with a formyl group at position 3), and has been found capable of effecting complete separations. We have been unable to separate pheophytin *a* (I, R = CH_3; R′ = phytyl) from pheophytin *b* (I, R = CHO; R′ = phytyl) however, presumably because the phytol residue renders the *b*-Girard compound somewhat ether soluble. Also, in the case of the pheophorbides (I, R = CH_3 or CHO; R′ = H), we are not certain that they do not suffer some slight degree of oxidation and/or allomerization at the 10- position, when the reaction is carried out as described. Although chromatographic analysis[4] shows only one *a* and one *b* component, and the respective phase tests are still positive, these two criteria alone are not conclusive proof, and examination of the products of a hot quick saponification under nitrogen (modified after Willstätter) should supply definitive evidence. It was noted however, that if the reflux time was extended to 20 min., an additional *a* and *b* component appeared on the chromatogram. The visible spectra of these compounds were similar to the respective pheophorbides, but they both gave a negative phase test.

The chlorophyll derivatives in the foregoing discussion were prepared according to Fischer and his co-workers.[5] They were characterized by means of their hydrochloric acid number, visible and infrared spectra, solubility in buffers of appropriate *p*H, and chromatographic behavior.

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(4) M. J. Hendrickson, R. R. Berueffy, and A. R. McIntyre, *Anal. Chem.*, 29, 1810 (1957).

(5) H. Fischer and A. Stern, *Die Chemie des Pyrrols*, Hälfte 2, Bd. II, Akademische Verlagsgesellschaft, Leipzig, 1940.

2-Alkenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazines

JOHN W. LYNN

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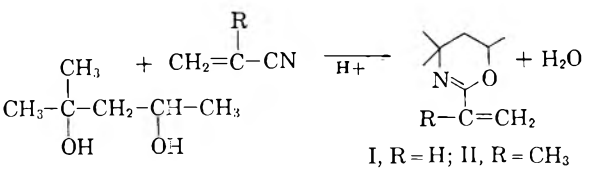
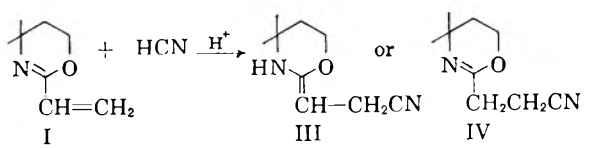
A novel polymerizable oxazine, 2-vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (I), was prepared by the reaction of acrylonitrile with 2-methyl-2,4-pentanediol in sulfuric acid; an extension of the general reaction described by Tillmanns and Ritter.[1] The 2-isopropenyl analog was also prepared by this reaction using methacrylo-



I, R = H; II, R = CH_3

nitrile. Similar 2-alkenyl-5,6-dihydro-1,3-oxazines may be prepared by the aluminum alkoxide catalyzed condensation of 1,3-alkanolamines with α,β-unsaturated esters.[2]

The addition of hydrogen cyanide to I in refluxing acetic acid gave 2-(2′-cyanoethylidene)-4,4,6-trimethyltetrahydro-1,3-oxazine (III). The reaction of HCN could take place by 1,4- addition to give III, or by 3,4-addition to give IV. That III is the product (by direct 1,4- addition or by



isomerization of initially formed IV) is clearly shown by the infrared spectrum. A sharp band at 3.00μ as well as absence of typical unconjugated C=N absorption at 6.25μ is in good agreement with structure III, and not at all in accord with IV.

(1) E. Tillmanns and J. J. Ritter, *J. Org. Chem.*, 22, 839 (1957).

(2) P. L. de Benneville and L. S. Luskin, U. S. Patent 2,831,858, April 22, 1958

EXPERIMENTAL[3]

2-Vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (I). A solution of 500 g. (4.7 moles) of 92% sulfuric acid was stirred at 6–7° during the addition of 56 g. (1.05 moles) of acrylonitrile over a 5-hr. period. The mixture was stirred at 8–10° and 118 g. (1.0 mole) of 2-methyl-2,4-pentanediol was added over a 4-hr. period. The reaction mixture was poured over 1000 g. of ice, treated with 470 g. (4.7 moles) of 40% sodium hydroxide, and washed 3 times with 1/3 volumes of chloroform. The remaining aqueous layer was brought to *p*H 10 with additional 40% sodium hydroxide and extracted with diethyl ether. Distillation of the extract gave 72 g., a 47% yield, of I (b.p. 75°/24 mm.; n_D^{30} 1.4605; n_{20}^{20} 0.9192; infrared maxima: 3.24, 5.37 (=CH_2), 6.05 (C=N—), 6.22 (C=C conugated), 7.22, 7.33 (*gem*-dimethyl), 8.5μ α,β-unsaturated ether).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.7; H, 9.81; N, 9.16. Found: C, 70.4; H, 9.8; N, 9.12.

Copolymer of I with vinylidene chloride. Vinylidene chloride and I in a 7 to 3 mole ratio were agitated in a sealed glass tube at 50° in the presence of 1% azo-bisisobutyronitrile catalyst for 6 hr. A greenish pliable solid polymer was obtained which contained 70.5% of I. The yield was 17%.

2-Isopropenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (II). The procedure was the same as that used for the preparation of I. II was obtained in 53% yield (b.p. 79°/20 mm.; n_D^{30} 1.4585).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.9; H, 10.18; N, 8.38. Found: C, 71.54; H, 10.03; N, 8.71.

2-(2'-Cyanoethylidene)-4,6,6-trimethyltetrahydro-1,3-oxazine (III). A solution of 153 g. (1.0 mole) of I, 200 cm.^{3} of glacial acetic acid, 34 g. (1.25 moles) of hydrogen cyanide and 1 g. of 2,4-dinitrobenzene was refluxed for 1 hr. during which time the kettle temperature rose from 30° to 115°. Distillation gave a 45% yield of III (b.p. 87°/1.3 mm.; n_D^{30} 1.4542; infrared maxima: 3.00 (—NH—), 4.45 (—C≡N), 6.00 (—C=C—), 8.60 (—C=C—O—).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.7; H, 8.80; N, 15.55. Found: C, 66.35; H, 8.60; N, 15.9.

Acknowledgment. The author is grateful to Mr. C. M. Lovell for infrared analyses and to Mr. Q. Quick for microanalyses.

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(3) All boiling points are uncorrected.

Potential Carcinostatic Agents. Benzimidazole Derivatives

WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

Received November 10, 1958

The need for larger amounts of 2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride ("benzimidazole mustard")[1] for clinical trials and the intended synthesis of derivatives of this nitrogen mustard made it desirable to look for a more convenient method of preparation than the one previously employed by us[1] and other investigators.[2,3] We wished to eliminate the use of 2-chloromethylbenzimidazole or its hydrochloride as intermediates because these substances are very irritating and sensitizing on the skin and therefore difficult to handle. Substituted 2-chloromethylbenzimidazoles would be expected to have the same disadvantage.

Hughes and Lions[4] had shown that glycine could not be condensed with *o*-phenylenediamine in the presence of 4*N* hydrochloric acid at reflux temperature, according to Phillips' method.[5] Of substituted glycines in which the basicity of the amino group had been depressed by acylation, hippuric acid did not react, and phthalimidoacetic acid only poorly. We found, however, that *N*,*N*-bis(2-hydroxyethyl)-glycine and *o*-phenylenediamine, refluxed together in 4*N* hydrochloric acid solution, gave a fairly good yield of 2-[bis-(2-hydroxyethyl)aminomethyl]-benzimidazole dihydrochloride, the precursor of the benzimidazole mustard.

Similarly, the reaction of *N*,*N*-bis(2-hydroxyethyl)glycine with substituted *o*-phenylenediamines, such as 4-chloro-,4,5-dichloro and 4,5-dimethyl-1,2-phenylenediamine led to the desired substituted 2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole dihydrochlorides which were converted into the corresponding bis(2-chloroethyl) compounds by means of thionyl chloride in the usual manner.

One of the benzimidazoles needed for testing, 1-methyl-2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride, was prepared by the old method, starting from 1-methyl-2-chloromethylbenzimidazole hydrochloride. This substance which is irritating to the skin, but to a lesser degree than the unmethylated compound, was brought to reaction with diethanolamine. The resulting 1-methyl-2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole was purified by means of its picrate and brought to reaction with thionyl chloride, yielding the "1-methylbenzimidazole mustard."

Preliminary studies[6] of the carcinostatic properties of the new compounds indicate that they are less effective against a number of experimental tumors in mice than the unsubstituted "benzimidazole mustard." The final results will be reported elsewhere.

(1) E. Hirschberg, A. Gellhorn, and W. S. Gump, *Cancer Research*, **17**, 904 (1957).

(2) A. R. Day, *Trans. N. Y. Acad. Sci.*, [2] **20**, No. 1, 3 (Nov. 1957).

(3) O. F. Ginzburg, B. A. Porai-Koshits, M. I. Krylova, and S. M. Lotareichik, *Zhur. Obshchet Khim.*, **27**, 411 (1957).

(4) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 209 (1938).

(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(6) We are indebted to Drs. A. Gellhorn and E. Hirschberg, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York 32, N. Y., for evaluation of the antitumor activity of the compounds.

EXPERIMENTAL*

N,N-Bis(2-hydroxyethyl)glycine. This compound was prepared from diethanolamine and chloroacetic acid as described by Khromov-Borisov and Remizov.[7] In order to obtain satisfactory yields, refluxing of the mixture should be carried out for 24 hr. instead of 3 to 4 hr.

2-[Bis(2-hydroxyethyl)aminomethyl]benzimidazole dihydrochloride. A mixture of 400 g. of *N,N*-bis(2-hydroxyethyl)-glycine, 280 g. of *o*-phenylenediamine, and 2350 ml. of 4*N* hydrochloric acid was refluxed for 10 hr. in a nitrogen atmosphere. Darco decolorizing carbon (40 g.) was added and the mixture refluxed for 30 min. After filtration, the liquid was evaporated under reduced pressure. The distillation was stopped when some crystals had precipitated; they were removed by filtration after cooling. The light pink crystals (12 g.) which did not melt up to 260° consisted mainly of *o*-phenylenediamine dihydrochloride[8] (calcd. 39.4% Cl; found 40.2% Cl); *o*-phenylenediamine could be obtained on treating the salt with sodium hydroxide solution.

The filtrate was concentrated *in vacuo* almost to dryness and the residue recrystallized from 1500 ml. of 90% ethanol. Soft, light orange colored crystals (305 g.) of m.p. 190–192° were obtained; recrystallization from 90% ethanol yielded 251 g. of the pure substance, m.p. 194–195°. Concentration of the mother liquors resulted in a second crop (101 g.); m.p. 190–192°.

2-[Bis-(2-hydroxyethyl)aminomethyl]-5(or 6)-chlorobenzimidazole dihydrochloride. Commercial *p*-chloro-*o*-phenylenediamine was purified by recrystallization from toluene, but it still had a brown color.

p-Chloro-*o*-phenylenediamine (71 g.), *N,N*-bis(2-hydroxyethyl)glycine (82 g.), and 500 ml. of 4*N* hydrochloric acid were refluxed for 4 hr. in a nitrogen atmosphere, 15 g. of Darco carbon was added, and refluxing continued for 2 hr. After filtration, the liquid was evaporated to dryness under reduced pressure. The remaining dark orange resin was taken up in 350 ml. of absolute ethanol. Ether was added to the solution until an oil started to separate. The mixture was kept at −10° for 3 days; the reddish crystals which had formed were separated and recrystallized from 350 ml. of ethanol, some Darco being added. The solid obtained (55 g.) was still reddish; another crystallization from 400 ml. of ethanol gave 38 g. of slightly pinkish crystals; m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{18}Cl_3N_3O_2$: Cl^-, 20.7; Cl (total), 31.1. Found: Cl^-, 21.0; Cl (total), 31.2.

2-[Bis(2-hydroxyethyl)aminomethyl]5,6-dichlorobenzimidazole dihydrochloride. 4,5-Dichloro-1,2-phenylenediamine (60.7 g.), prepared by catalytic reduction[9] of 4,5-dichloro-1,2-dinitrobenzene[10] or preferably of 4,5-dichloro-2-nitroaniline,[11] *N,N*-bis(2-hydroxyethyl)glycine (62 g.), and 450 ml. of 4*N* hydrochloric acid were agitated and refluxed for 10 hr. in a nitrogen atmosphere. The dark red solution was concentrated to dryness under reduced pressure. The remaining dark residue was refluxed for 30 min. with 500 ml. of absolute ethanol in the presence of about 10 g. of Darco carbon. Absolute ethanol (200 ml.) and ether (680 ml.) were added to the filtrate. The Darco and the filter were extracted with 300 ml. of boiling absolute ethanol, and 500 ml. of ether was added to the filtrate. The filtrates were combined and allowed to crystallize at −10°; the red solids were removed by filtration, washed with 40 ml. of ethanol and 140 ml. of ether, finally with ether. Yield: 71.7 g. The compound liquefied at 165° after a broad sintering range.

The product was then refluxed for 15 min. with 450 ml. water and 3 ml. of concentrated hydrochloric acid in the presence of 20 g. of Darco; the filtrate was again refluxed for 20 min. with 15 g. Darco. A slightly yellowish filtrate was obtained and concentrated to dryness at reduced pressure. The residue was dissolved in a refluxing mixture of 460 ml. of absolute ethanol and 20 ml. of water. Ether (480 ml.) was added to the warm filtrate. The whole was kept overnight at −10°. The crystals were separated by filtration, washed with ether and dried at 70° at 4 mm. Yield, 42.8 g. of a slightly yellowish solid; it softened at 160°, but did not form a clear melt when heated up to 178°. It was recrystallized from a mixture of 250 ml. of ethanol and 7 ml. of water. After standing overnight at −10°, the crystals were separated, washed with a little cold ethanol, and dried at 70° at 4 mm. Yield, 34.7 g.; m.p. 160–163° (turbid melt).

Anal. Calcd. for $C_{12}H_{17}Cl_4N_3O_2$: Cl^-, 18.8; Cl (total), 37.9. Found: Cl^-, 18.8; Cl (total), 37.7.

2-[Bis(2-hydroxyethyl)aminomethyl]5,6-dimethylbenzimidazole dihydrochloride. A mixture of 40.8 g. of 4,5-dimethyl-1,2-phenylenediamine,[12] 48 g. of *N,N*-bis(2-hydroxyethyl)-glycine and 294 ml. of 4*N* hydrochloric acid was refluxed for 10 hr. in a nitrogen atmosphere. A small amount of Darco was added to the solution and refluxing continued for 30 min. After filtration, the liquid was concentrated to dryness in vacuo. Ethanol (300 ml.) was added to the residue and the mixture refluxed for 30 min. Insoluble material was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The brown resin was dissolved in 110 ml. of absolute ethanol and the solution kept at −10° overnight. The white solid isolated was twice recrystallized from ethanol. Yield: 17 g.; m.p. 190–192° (turbid melt).

Anal. Calcd. for $C_{14}H_{23}Cl_2N_3O_2$: C, 50.0; H, 6.9; Cl, 21.4. Found: C, 49.7; H, 6.7; Cl, 21.0.

2-[Bis(2-hydroxyethyl)aminomethyl]-1-methylbenzimidazole dihydrochloride. A mixture of 90 g. of 2-chloromethyl-1-methylbenzimidazole hydrochloride,[4] 44 g. of diethanolamine, 34 g. of anhydrous sodium acetate, and 600 ml. of acetone was refluxed for 2 hr. and allowed to cool. After addition of 25 g. of anhydrous sodium carbonate, refluxing was continued for 3 hr. The mixture was cooled again; after 35 g. of sodium bicarbonate had been added it was refluxed for another 2 hr. The salt was removed by filtration and the filtrate freed from acetone by distillation. The oily residue was dissolved in 250 ml. of hot water and poured slowly with stirring into a solution of 100 g. of picric acid in 2000 ml. of boiling water. Next morning the crystalline picrate was separated by filtration, washed with cold water, and recrystallized from 1100 ml. of water. Yield, 65 g.; m.p. 142–143°.

The picrate was finely ground and triturated with 260 ml. of concentrated hydrochloric acid. The mixture was extracted with 400 ml. of benzene; the aqueous layer was separated and washed six times with small amounts of benzene in order to remove the picric acid completely. The aqueous solution was decolorized with Darco and the filtrate evaporated to dryness in vacuo. Recrystallization of the semisolid residue from 150 ml. of alcohol gave 31.7 g. of white crystals, m.p. 172–174°.

Anal. Calcd. for $C_{13}H_{21}Cl_2N_3O_2$: C, 48.4; H, 6.5; Cl, 22.1. Found: C, 48.1; H, 6.6; Cl, 22.2.

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* After this note was submitted, we learned of the publication of W. Knobloch, *Chem. Ber.*, **91**, 2557 (1958) in which he reports the synthesis of some of the compounds described by us. It should be mentioned that most of the melting points shown by Knobloch are not in agreement with ours.

(7) N. V. Khromov-Borisov and A. L. Remizov, *Zhur. Obshch. Khim.*, **23**, 598 (1953); see also M. Izumi, *Pharm. Bull. (Japan)*, **2**, 275 (1954).

(8) R. Kuhn and F. Zumstein, *Ber.*, **59**, 491 (1926).

(9) W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 3258 (1951).

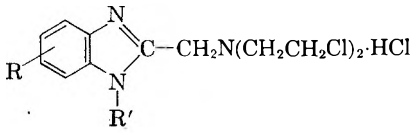
(10) R. Kuhn, F. Weygand, and E. F. Möller, *Ber.*, **76**, 1048 (1943).

(11) F. Beilstein and A. Kurbatow, *Ann.*, **196**, 225 (1879).

(12) We are grateful to Dr. Karl Folkers of Merck Sharp & Dohme Research Laboratories, Rahway, N. J., for a generous sample.

TABLE I

SUBSTITUTED 2-[BIS(2-CHLOROETHYL)AMINOMETHYL]BENZIMIDAZOLE HYDROCHLORIDES



R	R′	Yield, %	M.P., °C.	Analyses							
				Calculated				Found			
				C	H	N	Cl	C	H	N	Cl
5(or 6)-Chloro	H	45	146–147	41.97	4.37	12.24	41.40	41.86	4.23	12.07	41.52
5,6-Dichloro	H	49	171–173	38.17	3.73	11.13	46.95	38.24	3.85	11.26	47.01
5,6-Dimethyl	H	70	180–182	49.93	5.98	12.48	31.59	49.97	6.06	12.53	31.62
H	CH_3	61	137–138.5	48.37	5.58	13.03	33.03	48.47	5.60	13.12	32.8

2-[Bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride. This substance ("benzimidazole mustard") was obtained from the corresponding 2-hydroxyethyl compound by means of thionyl chloride, as had been described previously.[1] In order to obtain a pure product, several recrystallizations from ethanol are necessary in order to remove a lower melting by-product, which apparently is the dihydrochloride. It is less soluble in ethanol than the monohydrochloride and could be isolated from the first fractions of the ethanol recrystallization as a white crystalline substance, melting at 142–143° (after recrystallization from a small amount of ethanol).

Anal. Calcd. for $C_{12}H_{17}Cl_4N_3$: Cl, 41.2. Found: Cl, 41.4.

The substituted 2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochlorides were prepared by the same general procedure from the alcohols and thionyl chloride. The crude products were twice recrystallized from absolute ethanol; usually, ether was added to the alcoholic solutions until cloudiness appeared.

The yields, physical properties, and analyses of the compounds are presented in Table I.

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Methyl 2-Nitro-3-ethoxyacrylate and Related Compounds

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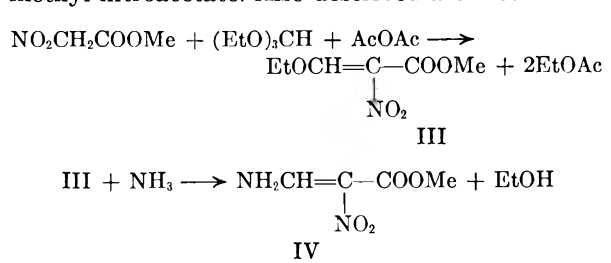
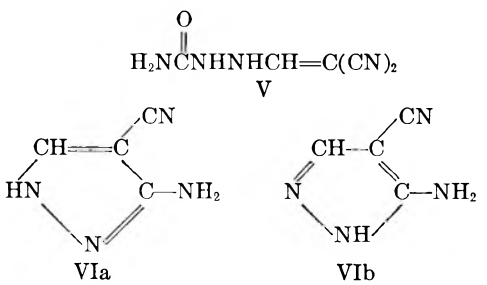
Active methylene compounds react with acetic anhydride and alkyl orthoformates to form alkoxymethylene derivatives.[1] The latter, in turn, readily undergo addition-elimination reactions with displacement of the alkoxyl group by nucleophilic agents. Thus, with ammonia ethoxymethylenemalononitrile, I, yields aminomethylenemalononitrile, II.[2] This note will serve to record the analogous synthesis of methyl 2-nitro-3-ethoxyacrylate, III, and methyl 2-nitro-3-aminoacrylate, IV, from methyl nitroacetate. Also described are methods of preparation and spectral data for several new derivatives of I.

$EtOCH{=}C(CN)_2$ I $NH_2CH{=}C(CN)_2$ II



The structure of the compound derived from I with semicarbazide was assigned by comparison of its ultraviolet spectrum with those of I, II, and the product of I with hydrazine. I, II, and the semicarbazide product, V, all showed high intensity maxima between 248 and 267 mμ with minima below 215 mμ. The product of I with hydrazine which has been shown[3] to be the cyclized 3 (or 5)-amino-4-cyanopyrazole, IVa or b, exhibited only inflections at 214 and 240 mμ superimposed on a high intensity shorter wave length band. On this basis V was uncyclized semicarbazidomethylenemalononitrile.



The spectra of III and IV did not bear the expected resemblance to those of the corresponding dinitriles. IV exhibited medium-low intensity maxima at 235 and 312 mμ while III showed only a low intensity inflection at 252 mμ. Elemental analyses, the formation of a phenylurea from IV and

(1) For leading references see R. G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951). A discussion of the mechanism is given by R. G. Jones, *J. Am. Chem. Soc.*, **74**, 4889 (1952).

(2) O. Diels, H. Gartner, and R. Kaack, *Ber.*, **55**, 3429 (1922).

(3) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

phenylisocyanate, and the conversion of III to a bis-hydrazine derivative, probably 2-nitro-3-hydrazinoacrylyl hydrazide, however, indicated that the assigned structures were probably correct.

EXPERIMENTAL[4]

Materials. Ethoxymethylenemalononitrile, I, is commercially available from Kay-Fries Chemicals, Inc., New York. With aqueous ammonia it gave aminomethylenemalononitrile, II, m.p. 143–145° (lit.[2] 146°). Methyl nitroacetate, b.p. 95–96° (18 mm.) was prepared in 32% over-all yield from nitromethane via dipotassium nitroacetate. The procedure has been described by Feuer, Hass, and Warren.[5]

Methyl 2-nitro-3-ethoxyacrylate, III. Two tenths mole (24.0 g.) methyl nitroacetate, heated overnight on the steam bath with 0.3 mole (44.4 g.) ethyl orthoformate and 0.5 mole (51.0 g.) acetic anhydride and the reaction mixture fractionated *in vacuo*, gave as a high boiling main cut 23.1 g. (66%) of III, a mobile yellow liquid, b.p. 119–121° (1.0 mm.).

Anal. Calcd. for $C_6H_9NO_5$: C, 41.11; H, 5.16; N, 8.00. Found: C, 41.04, 41.30; H, 4.99, 5.26; N, 7.62, 7.94.

Methyl 2-nitro-3-aminoacrylate, IV. Addition of 5.0 g. III to 20 ml. cold, stirred 28% ammonium hydroxide, filtration of the pale green solid which immediately precipitated, and washing the filter cake with cold ethyl acetate gave 3.85 g. (95%) crude IV, m.p. 154–156°. A single recrystallization from 200 ml. ethyl acetate furnished 2.75 g. (66%) of an analytical sample as clusters of cream colored needles, m.p. 163.2–163.6°.

Anal. Calcd. for $C_4H_6N_2O_4$: C, 32.89; H, 4.11; N, 19.16. Found: C, 33.03, 33.09; H, 4.16, 4.29; N, 18.53, 18.23, 18.98.

Methyl 2-nitro-3-(N'-phenylureido)acrylate. One half gram of IV, 1 g. phenylisocyanate, and 2 drops pyridine, heated 90 min. on the steam bath, taken up in hot chloroform, filtered, and cooled to crystallize, and the product recrystallized from ether-chloroform, yielded 250 mg. (28%) of chartreuse crystals, m.p. 180.2–182.2°.

Anal. Calcd. for $C_{11}H_{11}N_3O_6$: C, 49.81; H, 4.15; N, 15.84. Found: C, 49.59, 49.76; H, 4.39, 4.45; N, 15.60, 15.61.

2-Nitro-3-hydrazinoacrylyl hydrazide. Dropwise addition of 4.0 g. III in 4.0 ml. methanol to a cooled, swirled solution of 10 ml. 85% hydrazine hydrate in 10 ml. methanol caused immediate formation of a thick yellow slurry. The mixture, diluted with 25 ml. methanol, cooled, and filtered, and the product washed with methanol, and air dried yielded 3.20 g. (88%) of the hydrazino hydrazide, m.p. 232–234° (dec.). Recrystallization from a large quantity of methanol gave an analytical sample, m.p. 235–236° (dec.).

Anal. Calcd. for $C_3H_7N_5O_3$: C, 22.36; H, 4.35; N, 42.50. Found: C, 22.66, 22.68; H, 4.47, 4.57; N, 42.79, 42.57.

Semicarbazidomethylenemalononitrile, V. A solution of 4.88 g. (0.04 mole) I, 9.0 g. (0.08 mole) semicarbazide hydrochloride, and 8.2 g. (0.06 mole) sodium acetate trihydrate in 100 ml. 50% aqueous ethanol, allowed to stand overnight at room temperature, concentrated to 40 ml., and cooled, deposited 3.35 g. (56%) of a light tan solid, m.p. >360°. An analytical sample was obtained as clusters of fine white needles on recrystallization from ethanol.

Anal. Calcd. for $C_5H_5N_6O$: C, 39.72; H, 3.31; N, 46.34. Found: C, 39.61, 39.86; H, 3.46, 3.56; N, 46.97, 46.69.

Ultraviolet spectra. Solvent methanol. λ_{max} (log ϵ): *I*, 248 (4.11); *II*, 267 (4.17), 344 (3.11); *III*, 252[s] (3.18); *IV*, 235 (3.20), 312 (3.11); *V*, 249 (3.87); *VI*, 214[s] (4.03), 240[s] (3.81). Superscript s = shoulder or inflection.

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(4) All melting points are corrected. Microanalyses by Professor Katherine Gerdeman, Department of Chemistry, University of Maryland. Ultraviolet spectra were determined with a Cary Model 14 spectrophotometer using 1-cm. silica cells.

(5) H. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, 71, 3078 (1949).

Studies of Configuration. V. The Preparation and Configuration of *cis*-3-Methoxycyclopentanecarboxylic Acid

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Received November 13, 1958

In continuing the investigation of the ether–acid chloride rearrangement[1] we have undertaken the preparation of 3-methoxycyclopentanecarboxylic acid and have characterized the *cis* isomer.

The preparation of 3-oxocyclopentanecarboxylic acid has been previously described by Hope,[2] by Ingold, Shoppee, and Thorpe,[3] by Vaughn,[4] and more recently by Shemyakin and co-workers.[5] The addition of diethyl malonate to diethyl itaconate using a molar excess of diethyl malonate afforded tetraethyl 1,1,3,4-butanetetracarboxylate (I) in 93% yield. Sodium ethoxide in toluene converted I to triethyl 3-oxo-1,2,4-cyclopentanecarboxylate (II) in 66% yield. Hydrolysis and decarboxylation afforded 3-oxocyclopentanecarboxylic acid (III) in nearly quantitative yield. The procedure of Vaughn[4] in which the intermediates I and II are not isolated afforded 3-oxocyclopentanecarboxylic acid in 54% yield from diethyl itaconate.

Of several methods of reduction investigated, hydrogenation over Raney nickel of either the sodium salt of III or the methyl ester afforded the most tractable mixtures of *cis*- and *trans*-3-hydroxycyclopentanecarboxylic acid (IV). Crystallization from ether-pentane at low temperatures afforded 60% of a crystalline isomer, m.p. 50.4–51.8°. Evidence is presented below to show that this is the *cis*-isomer.

Conversion of 3-hydroxycyclopentanecarboxylic acid to its lactone was attended with some difficulty. Direct heating of crude IV resulted in polymerization and no lactone was obtained. Heating a dilute solution of the mixed isomers of IV in

(1) D. S. Noyce and H. I. Weingarten, *J. Am. Chem. Soc.*, 79, 3093, 3098 (1957).

(2) E. Hope, *J. Chem. Soc.*, 101, 892 (1912).

(3) C. K. Ingold, C. W. Shoppee, and J. F. Thorpe, *J. Chem. Soc.*, 1477 (1926).

(4) H. A. Vaughn, Jr., Dissertation, Columbia University; *Chem. Abstr.*, 51, 16314 (1957).

(5) M. M. Shemyakin, L. A. Shchukina, E. I. Vinogradova, M. N. Kolosov, R. G. Vdovina, M. G. Karapetyan, V. Ya. Rodionox, G. A. Ravdel, Yu. B. Shvetsov, E. M. Bamdan, E. S. Shaman, K. M. Ermolaev, and E. P. Semkin, *Zhur. Obshchei Khim.*, 27, 742 (1957); *Chem. Abstr.*, 51, 16313 (1957).

dibutyl ether gave a very small yield of lactone (3%). Using dibutyl phthalate as the solvent, the crystalline isomer was converted to the lactone of *cis*-3-hydroxycyclopentanecarboxylic acid (V) in 24% yield. Purification by sublimation gave material of m.p. 53.7–54.5°. The infrared spectrum of V showed a carbonyl peak at 5.62μ (1779 cm.$^{-1}$). A shift of about 0.02μ towards shorter wave lengths appears to be general in changing from a five-membered ring to the more constrained [2.2.1] bicyclic system, as exemplified by cyclopentanone (5.77μ) and camphor (5.75μ).

Hydrolysis of V afforded a pure sample of *cis*-3-hydroxycyclopentanecarboxylic acid (*cis*-IV), m.p. 52.2–52.9°, which showed no depression in melting point when admixed with the crystalline isomer of IV isolated above.

Conversion of the hydroxyl group of *cis*-IV to the methyl ether by a stereospecific method would give *cis*-3-methoxycyclopentanecarboxylic acid (*cis*-VI) of established configuration. Methyl iodide and silver oxide is the method of choice. Mislow[6] has shown that the use of an alcoholate and alkyl halide is frequently accompanied by some racemization, whereas methyl iodide and silver oxide gives material of high optical purity. He concludes that the silver oxide procedure gives optically pure material.

Methylation of *cis*-IV was carried out essentially by the method of Bonner[7] using a larger excess of methyl iodide and silver oxide, to give methyl *cis*-3-methoxycyclopentanecarboxylate which was not isolated but directly subjected to mild alkaline hydrolysis to afford *cis*-VI in 93% yield, which was characterized by analysis, neutralization equivalent, infrared spectrum, and preparation of the *p*-toluidide and the *p*-phenylphenacyl ester.

EXPERIMENTAL[8]

3-Oxocyclopentanecarboxylic acid (III). Diethyl malonate (2 moles), sodium (1 mole) in ether, and diethyl itaconate (1 mole) afforded *tetraethyl 1,1,3,4-butanetetracarboxylate* (I) in 93% yield, b.p. 153–156° (0.5 mm.), n_D^{21} 1.4420 (lit.[3] 198–199°/10 mm.). Hydrolysis of I afforded *1,2,4-butanetricarboxylic acid*, m.p. 121.2–121.8° (lit.[2] 122°). Treatment of I with sodium ethoxide in toluene afforded *ethyl 3-oxo-1,2,4-cyclopentanecarboxylate* (II) in 66% yield, b.p. 160–161° (1 mm.), n_D^{24} 1.4602 (lit.[3] 205–210°/15 mm.). Hydrolysis of II with refluxing 8% sulfuric acid afforded III in nearly quantitative yield, b.p. 140–145° (3.5 mm.) m.p. 57.9–59.3°, (lit.[2] b.p. 172–174°/10 mm., m.p. 62–64°). Crystallization from ether-hexane gave material of m.p. 62.7–63.3°. The procedure of Vaughn,[4] in which sodium hydride is used and no intermediates are isolated, afforded III in 54% yield from diethyl itaconate.

Also characterized were *ethyl 3-oxocyclopentanecarboxylate*, b.p. 95° (5.5 mm.) n_D^{22} 1.4518 (lit.[3] b.p. 109–111°/10 mm.), and *methyl 3-oxocyclopentanecarboxylate*, b.p. 94–98° (14 mm.) n_D^{23} 1.4565.

Methyl 3-hydroxycyclopentanecarboxylate. Methyl 3-oxocyclopentanecarboxylate, 25 g., in 40 ml. of absolute ethanol was reduced at 1700 p.s.i. and 100° with Raney nickel catalyst. Hydrogenation was complete in about 1 hr. The catalyst was removed by filtration, and the filtrate fractionally distilled to afford 25 g. (98.5%) of methyl 3-hydroxycyclopentanecarboxylate, b.p. 106° (15 mm.), n_D^{26} 1.4602–1.4612. A portion was redistilled and a center cut taken for analysis, n_D^{26} 1.4608.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.30; H, 8.41. Found: C, 58.51; H, 8.55.

3-Hydroxycyclopentanecarboxylic acid (IV). Ten grams of the acid III was neutralized with a slight excess of alcoholic sodium hydroxide, and hydrogenated at 2000 p.s.i. and 100° with Raney nickel catalyst. Reduction was complete in 1 hr. The catalyst was removed by filtration; most of the ethanol was removed by distillation, and the residue was acidified with dilute hydrochloric acid. The resulting solution was extracted with 4 portions of ether, the ether extracts dried with anhydrous sodium sulfate, and the ether removed by distillation. There was obtained 7.0 g. of residue. From an ether-pentane mixture, crystals (2.0 g., 20%) of crude IV were slowly deposited m.p. 39–43°.

cis 3-Hydroxycyclopentanecarboxylic acid (*cis*-IV). Methyl 3-hydroxycyclopentanecarboxylate, 10.0 g., was heated with dilute sodium hydroxide on a steam bath for 20 hr. The solution was acidified and continuously extracted with ether. The ether extracts, after drying, were concentrated to a small volume and pentane was added dropwise to turbidity. After cooling for 4 days at Dry Ice temperature, 2.4 g. (27%) of crystals, m.p. 37–44°, were deposited. After recrystallization from ether–pentane, the melting point is 50.4–51.8°. Systematic fractional crystallization afforded a total of 5.4 grams of *cis*-3-hydroxycyclopentanecarboxylic acid (*cis*-IV). The *p-bromophenacyl ester*[9] crystallized from hexane as white needles, m.p. 92.2–92.4°.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.41; H, 4.59; Br, 24.44. Found: C, 51.56; H, 4.63; Br, 24.42.

The *p-toluidide* of *cis*-IV was prepared by the method of Cheronis and Entriken[10] from the acid and *p*-toluidine. It was crystallized from aqueous methanol, m.p. 138.2–139.0°.

Anal. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39. Found: N, 6.56.

3-Oxo-2-oxabicyclo[2.2.1]heptane (V). A solution of 3.0 g. of *cis*-IV in 15 ml. of butyl phthalate was heated at 150° for 2 hr. The mixture was fractionally distilled to afford 0.72 g. of V, b.p. 92–93° (10 mm.), m.p. 50.5–52.2°. Attempts to recrystallize the waxy white solid failed. Sublimation at 10 mm. yielded waxy white crystals, m.p. 51.2–52.6°. The center fraction of a second sublimation was taken for analysis, m.p. 53.7–54.5°.

Anal. Calcd. for $C_6H_8O_2$: C, 64.29; H, 7.19. Found: C, 64.33; H, 7.29.

Hydrolysis of the lactone to cis-IV. Sublimed V (20 mg.) was treated with warm 0.5*N* sodium hydroxide. The solution was acidified immediately with hydrochloric acid, and extracted with 3 portions of methylene chloride. The combined extracts were dried with sodium sulfate, filtered, and the methylene chloride removed by evaporation. The residue was crystallized from ether-pentane, affording about 15 mg. of *cis*-IV, m.p. 52.2–52.9°, which showed no depression

(6) K. Mislow, *J. Am. Chem. Soc.*, **73**, 4043 (1951).

(7) W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3126 (1951); D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **76**, 768 (1954).

(8) All melting points are corrected; boiling points are uncorrected. Distillations were carried out through a two-foot modified Podbielniak column. Infrared spectra were recorded with a Baird recording infrared spectrometer. Analyses were performed by the Microanalytical Laboratory of the University of California.

(9) R. L. Shriner and R. C. Fuson, "*Systematic Identification of Organic Compounds*," John Wiley and Sons, New York, N. Y., 1948, p. 157.

(10) N. D. Cheronis and J. B. Entriken, "*Semimicro Qualitative Organic Analysis*," T. Y. Crowell Co., New York, N. Y., 1947, p. 208.

of m.p. when admixed with *cis*-IV isolated from the mixture of isomers.

The *p*-bromophenacyl ester was crystallized from hexane, m.p. 90.2–90.5°. It showed no depression in m.p. with the *p*-bromophenacyl ester prepared above.

cis-3-Methoxycyclopentanecarboxylic acid (*cis*-VI). In a 300-ml. flask, equipped with stirrer, reflux condenser, and drying tube, were placed 10 g. of glass beads, 20 g. of Drierite, 50 g. of freshly precipitated anhydrous silver oxide, 150 ml. of methyl iodide, and 4.0 g. of *cis*-IV. The mixture was heated under reflux with stirring for 3 days with the addition of methyl iodide when necessary to keep the volume constant. The crude isolated material still showed a slight hydroxyl band in the infrared spectrum, so the methylation was continued for an additional 2 days with fresh silver oxide and additional methyl iodide.

The crude product, isolated by filtration, washing, and evaporation of the low boiling fraction, was treated with 100 ml. of standardized 0.8*N* sodium hydroxide and heated on the steam bath. After 45 min. the theoretical amount of base had been used, as determined by titration of an aliquot. The solution was cooled, acidified, and extracted with five 100-ml. portions of ether. The dried ether solution was distilled to afford 4.1 g. (93%) of *cis*-3-methoxycyclopentanecarboxylic acid, b.p. 136–139° (10 mm.), n_D^{26} 1.4587.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.34; H, 8.34; OCH_3, 21.52; neut. equiv., 144. Found: C, 58.16; H, 8.32; OCH_3, 21.58; neut. equiv., 145.

The *p-toluidide* was prepared by the method of Cheronis and Entriken[10] and crystallized from aqueous methanol, m.p. 81.9°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.05; H, 8.22; N, 6.00. Found: C, 72.36; H, 8.04; N, 6.58.

The *p-phenylphenacyl ester* was crystallized from aqueous ethanol, m.p. 79.5–79.7°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.53; H, 6.57. Found: C, 74.36; H, 6.63.

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Perchlorates of Conjugate Acids of Azobenzene and Substituted Azobenzenes[1]

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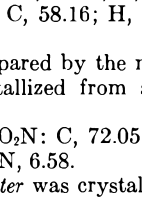
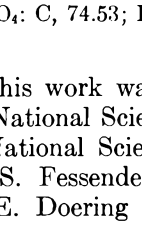
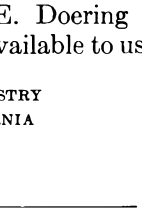
In an attempt to establish the structure of the conjugate acids of substituted azobenzenes, we have prepared the perchlorates of the conjugate acids of azobenzene, and of its 4-methoxy and 4,4′-dimethoxy derivatives.

TABLE I

ANALYSES AND PHYSICAL PROPERTIES OF THE PERCHLORATES

Substances	Decomposition Point, °C.[b]	Neutralization Equivalent		Analysis[a]					
				C		H		N	
		Found	Caled.	Found	Caled.	Found	Caled.	Found	Caled.
	198	284	283	50.80	50.98	4.00	3.92	9.66	9.91
	200	311	311	50.01	50.00	4.16	4.17	8.88	8.98
	205	337	343	49.22	49.20	4.52	4.42	8.06	8.19
	152	296	293	82.84	83.58	4.31	3.98	7.04	7.13

[a] Elemental analysis were performed by A. Bernhardt, Mülheim (Ruhr), Germany. [b] Uncorrected.

(1) This work has been supported by a Bonita Geho Memorial Grant for Cancer Research from the American Cancer Society. This support is gratefully acknowledged.

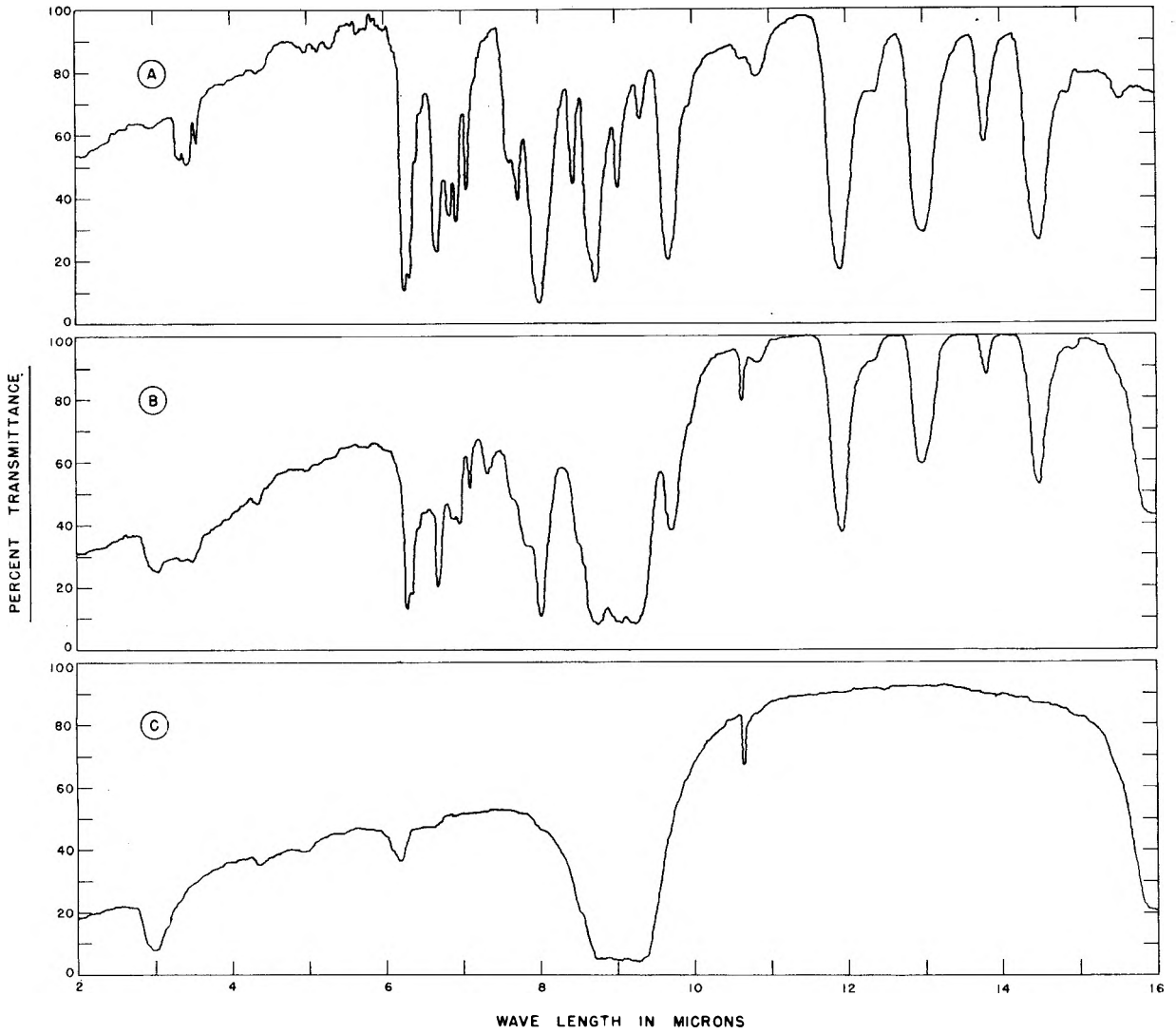
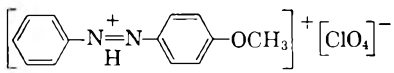


Fig. 1. Comparison of infrared spectra of (A) 4-methoxyazobenzene; (B) its salt with perchloric acid; (C) $NaClO_4$, all in KBr pellets.

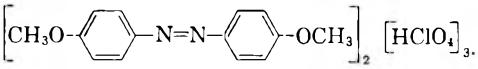
EXPERIMENTAL

Azobenzene (1 g.) was dissolved in 20 ml. of dioxane to which 50 ml. of 70% $HClO_4$ was added. Light yellow crystals precipitated and were collected on a sintered-glass filter. The perchlorate obtained was recrystallized from 70% $HClO_4$ (below 60°). The salt was highly hygroscopic, and decomposed slowly at 198°. The preliminary identification of the perchlorate was carried out by determining its neutralization equivalent, *i.e.* after hydrolysis in water the $HClO_4$ was titrated potentiometrically with standard NaOH. The results showed that exactly one equivalent of proton is associated with each mole of azobenzene. The identity of the compound was confirmed by elemental analysis, the results of which are summarized in Table I.

The perchlorate of the conjugate acid of 4-methoxyazobenzene was prepared in the same manner as that of azobenzene. After recrystallization from 70% $HClO_4$, the red crystals of the perchlorate of the conjugate acid of 4-methoxyazobenzene, decomposed slowly at 200°.



It is interesting to note the difference in the preparation of the perchlorate of the conjugate acid of 4,4′-dimethoxyazobenzene. Treatment of this compound under exactly the conditions described above, yielded very dark purple crystals which decomposed slowly at 152°. The neutralization equivalent and the elemental analysis suggested that this material was a single compound of the formula



When the perchlorate of the conjugate acid of 4,4′-dimethoxyazobenzene was prepared and recrystallized from a solution of lower acidity the monoperchlorate was obtained. 4,4′-Dimethoxyazobenzene (1 g.) was dissolved in 30 ml. of dioxane, and 10 ml. of 70% $HClO_4$ was added. The crude crystals were collected and recrystallized from 35% $HClO_4$. Golden purple crystals which decomposed at 205° were obtained. The analyses of the compounds are summarized in Table I.

Infrared spectra of the perchlorates were obtained by a Baird Model KM1 I.R. spectrophotometer. An example of the infrared spectrum is shown in Fig. 1.

DISCUSSION

We had hoped to find an NH stretching frequency, and to use this frequency to obtain infor-

mation concerning the nature of the NH bond. No NH frequency was found below 3000 cm $^{-1}$ Unfortunately, however, the spectrum of sodium perchlorate had a wide band at about 3200–3300 cm.$^{-1}$, which persisted in all the salts investigated here; this band was probably an overtone of a strong band at about 1600 cm.$^{-1}$ Consequently we were unable to observe any NH frequency in the conjugate acids of the azo compounds in the 3000–3400 cm.$^{-1}$ range, where we had anticipated that the absorption of the $\diagdown\overset{+}{\mathrm{N}}{=}\underset{\mathrm{H}}{\mathrm{N}}\diagup$ group[2] would lie.

The infrared spectra of the compounds investigated are strikingly similar to the spectra of the free bases. Unfortunately, however, the spectra of *cis*- and *trans*-azobenzenes are so similar, that no decision can be made on the basis of these spectra concerning the stereochemistry of the conjugate acids.

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(2) H. H. Jaffé and R. W. Gardner, *J. Am. Chem. Soc.*, **80**, 319 (1958).

The Oxidation of 3,5,5-Trimethyl-1,2-cyclohexanedione by Hydrogen Peroxide

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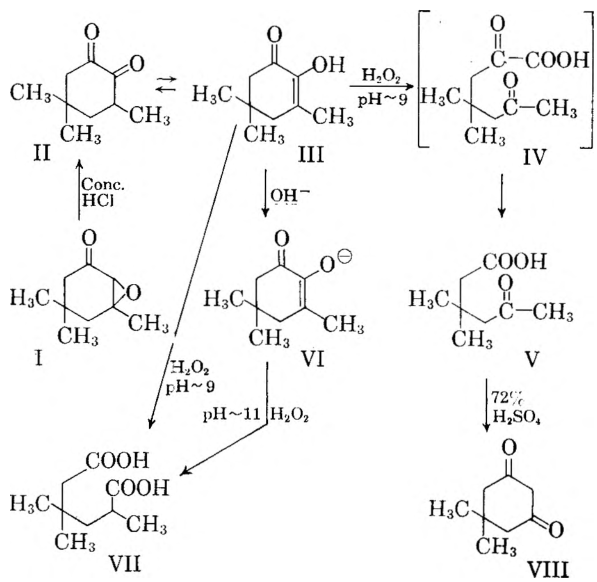
α-Diketones, on oxidation by hydrogen peroxide, are reported[1] to undergo cleavage according to the equation

$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R'} \xrightarrow{H_2O_2} \mathrm{RCOOH + R'COOH}$$

We have observed, however, that with the *cyclic* α-diketone, 3,5,5-trimethyl-1,2-cyclohexanedione (II), which, by spectroscopic evidence,[2] must exist mainly in an enolic form such as III, the product obtained with hydrogen peroxide depends on the *p*H.

Under mildly alkaline conditions (*p*H *ca.* 9), using excess hydrogen peroxide and adding alkali continuously to neutralize the acidic product, there was obtained a 26% yield of *crude* α,γ,γ-trimethyladipic acid (VII) and a 55% yield of 5-keto-3,3-dimethylhexanoic acid (V). This unexpected product was probably formed by way of the α-keto acid, IV, since carbon dioxide was evolved on acidification of the reaction mixture.[3] Its structure was indicated by physical constants and suitable analyses, and confirmed by its known[4] cyclization to dimedone (VIII).



When one molar equivalent of hydrogen peroxide was added dropwise to the enolate anion, VI (formed by charging equivalent amounts of II and alkali), a mixture resulted. Esterification of the material provided a 23% yield of diethyl α,γ,γ-trimethyl-adipate. This yield was based on unrecovered ketone.

The starting material used in this brief investigation was prepared in 65% yield from isophorone oxide (I) by treatment with cold concentrated hydrochloric acid. The oxide was prepared from isophorone in 84% yield by the action of alkaline peroxide in ethanol at 30–35°.

EXPERIMENTAL[5]

Isophorone oxide. A solution of 138 g. (1.0 mole) of isophorone (redistilled, b.p. 100–102°/20 mm.) in 1300 ml. of ethanol was charged to a 3-liter, round-bottom flask and treated with stirring with a solution of 15 g. of sodium hydroxide in 150 ml. of water. With stirring and cooling at 30–35° was added 165 g. (1.5 moles) of 30% hydrogen peroxide over a period of 20 min. After an additional hour, the mixture was diluted with 2 l. of water and extracted with three 300-ml. portions of chloroform. The combined chloroform extracts were washed with water, dried over magnesium sulfate, and distilled through a 1 × 50 cm. glass helices-packed column to give 129 g. (84% yield) of isophorone oxide, b.p. 68–69° (5 mm.), n_D^{20} 1.4539 [lit.[2a] values: b.p. 70–73° (5 mm.); n_D^{25} 1.4510].

3,5,5-Trimethyl-1,2-cyclohexanedione. To 500 ml. of concentrated hydrochloric acid stirred at 0–5° was added 100 g. (0.65 mole) of isophorone oxide. The mixture was stirred

(1) A. F. Holleman, *Rec. trav. chim.*, **23**, 169 (1904); J. Boeseken, *Rec. trav. chim.*, **30**, 142 (1911); E. Weitz and A. Scheffer, *Ber.*, **54B**, 2327 (1921).

(2) (a) R. L. Wasson and H. O. House, *J. Am. Chem. Soc.*, **79**, 1488 (1957); (b) H. S. French and E. T. Holden, *J. Am. Chem. Soc.*, **67**, 1239 (1945).

(3) α-Keto acids are readily cleaved by hydrogen peroxide; see ref. 1.

(4) T. Henshall, W. E. Silbermann, and J. G. Webster, *J. Am. Chem. Soc.*, **77**, 6656 (1955).

(5) All melting points are corrected.

in the cold for 3 hr. and then allowed to warm to room temperature over a 3-hr. period. After dilution with 1 l. of water, the solid product was collected by filtration, washed with water, and vacuum dried to a constant weight of 82 g., m.p. 80–85°. Recrystallization from petroleum ether afforded 65 g. (65% yield) of 3,5,5-trimethyl-1,2-cyclohexanedione, m.p. 91–92° (lit.[2a] m.p. 92–93°).

5-Keto-3,3-dimethylhexanoic acid. To a 1-l., 5-neck, round-bottom flask equipped with stirrer, thermometer, *p*H electrodes (connected to a Beckman *p*H meter), and dropping funnel was charged a solution of 38.5 g. (0.25 mole) of 3,5,5-trimethyl-1,2-cyclohexanedione in 300 ml. of methanol. The mixture was stirred at 40° and treated with a solution of 7 g. of potassium hydroxide in 30 ml. of water. One mole of 30% hydrogen peroxide was then added dropwise with cooling over a 15-min. period. During this addition, the meter reading changed from 11 to 8, while indicator paper showed a change from 10 to 7. There was next added dropwise a solution of 21 g. of potassium hydroxide in 90 ml. of water at such a rate as to maintain the meter reading at 9.8–10.0 (true *p*H *ca.* 9). After 1 hr., the alkali addition was complete and another 0.5 mole of hydrogen peroxide was added to compensate for the 0.5 mole loss by decomposition (oxygen evolution followed by means of a wet test meter connected to the system). The mixture was stirred for 1 hr. longer at a steady *p*H of 9.8; no further addition of alkali was necessary

After 12 hr., the mixture was diluted with 200 ml. of water and concentrated under vacuum to a volume of 150 ml. The concentrate was acidified with 30% sulfuric acid and extracted with three 100-ml. portions of chloroform. The combined chloroform extracts were washed with water, dried over magnesium sulfate, and concentrated to low volume on the steam bath. Claisen distillation gave 21.9 g. (55% yield) of 5-keto-3.3-dimethylhexanoic acid, b.p. 73–74° (0.2 mm.), n_D^{20} 1.4469 [lit.[6] values: b.p. 162° (25 mm.), $n_D^{19.5}$ 1.4465] and 11.1 g. of *crude* α,γ,γ-trimethyladipic acid, b.p. 130–135° (0.2 mm.).

Anal. Calcd. for the keto acid, $C_8H_{14}O_3$: C, 60.6; H, 8.9; neut. equiv., 158. Found: C, 60.4; H, 8.9; neut. equiv., 161.

The keto acid gave a positive iodoform test and a crystalline *2,4-dinitrophenylhydrazone* derivative, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{18}O_6N_4$: N, 16.5. Found: N, 16.4.

The keto acid was cyclized to *dimedone* by the procedure described in the literature[4]: a solution of 5.0 g. of the material in 50 ml. of 72% sulfuric acid was held at 130° for 2 hr. and then poured into 350 ml. of water to precipitate 2.6 g. of dimedone, m.p. and mixed m.p. 145–147°.

α,γ,γ-Trimethyladipic acid. To a stirred solution of 92 g. (0.60 mole) of 3,5,5-trimethyl-1,2-cyclohexanedione, 0.2 g. of magnesium sulfate (stabilizer), and 26 g. (0.65 mole) of sodium hydroxide in 500 ml. of water was added dropwise over 1 hr. 72 g. (0.65 mole) of 30.6% hydrogen peroxide. The temperature was held at 40–45° by means of a cooling bath; the *p*H, as determined by indicator paper, remained about 11 throughout the addition. After completion of the addition, the mixture was allowed to stir for 1 hr. longer before filtration was carried out to allow the recovery of 43 g. (0.28 mole) of starting diketone, m.p. and mixed m.p. 91–92°. Carbon dioxide was bubbled through the filtrate to neutralize excess caustic, and extraction with chloroform gave an additional 2.5 g. of crude starting material. After concentration of the aqueous solution to a volume of 150 ml., it was acidified with 30% sulfuric acid, saturated with solid ammonium sulfate, and extracted with five 200-ml. portions of ether. The combined ether extracts were washed with saturated ammonium sulfate solution, dried over magnesium sulfate, and concentrated to low volume on the steam bath.

Claisen distillation at 0.5 mm. pressure afforded *A*, b.p. 100–140° (11 g.), *B*, b.p. 140–150° (33 g.), and a residue of 3 g.

Fraction *B* represents a 56% yield of *crude* α,γ,γ-trimethyladipic acid based on unrecovered starting material.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.6; neut. equiv. 94. Found: C, 57.9; H, 8.1; neut. equiv. 120.

Attempts to secure pure acid by recrystallization were unsuccessful, so 24 g. of the crude material was esterified with ethanol using *p*-toluenesulfonic acid catalyst. Distillation of crude ester through a 0.7 × 50 cm. glass spiral-packed column at 5 mm. gave 12.8 g. (23% yield based on unrecovered diketone) of diethyl α,γ,γ-trimethyladipate, b.p. 115–117°, n_D^{20} 1.4361 (lit.[7] values: b.p. 124°/9 mm.; n_D^{20} 1.4330).

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.9; H, 9.9; sapon. equiv., 122. Found: C, 63.9; H, 9.7; sapon. equiv., 122.

The *free acid* was obtained by saponification of the ester with alcoholic sodium hydroxide. It was recrystallized from chloroform-isopentane by allowing the solution to stand for several hours at room temperature, then at 0° for several hours, and finally at −20°. From 10 g. of ester there was obtained 4.5 g. (60%) of recrystallized acid, m.p. 67.5–68.5° (lit.[7] m.p. 68.6–69.2°).

Anal. Calcd. for $C_9H_{16}O_4$: Neut. equiv., 94. Found: Neut. equiv., 95.

The *dianilide* was prepared via the acid chloride (not purified) and recrystallized from benzene, m.p. 162.5–163.5° (lit.[7] m.p. 162.8–163.3°).

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(6) M. Qudrat-I-Khuda, *J. Chem. Soc.*, 207 (1929).

(7) S. F. Birch and E. A. Johnson, *J. Chem. Soc.*, 1493 (1951).

Products of the Reaction between γ-Butyrolactone and Phenylmagnesium Bromide

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The reaction between phenylmagnesium bromide and γ-butyrolactone has been reported to yield 1,1-diphenylbutane-1,4-diol (I).[1] We have found that an increase in the concentration of acid used to decompose the Grignard adduct results in the formation of two other products, 2,2-diphenyltetrahydrofuran (II) and 1,1-diphenyl-1-butene-4-ol (III). These results are summarized in Table I.

$(C_6H_5)_2C(OH)CH_2CH_2CH_2OH$
I

$(C_6H_5)_2C\overline{CH_2CH_2CH_2O}$
II

$(C_6H_5)_2C{=}CH{-}CH_2CH_2OH$
III

Examples of the formation of cyclic ethers analogous to II seem to be rare in this type of reaction. This structure was assigned on the basis of the infrared spectrum, which shows the characteristic absorption of the tetrahydrofuran ring at about

(1) C. Weizmann and F. Bergmann, *J. Am. Chem. Soc.*, 60, 2647 (1938).

TABLE I

Acid Concentration	Product Yield, %		
	I	II	III
2.05*M*	80–90	—	—
3.50*M*	56–63	24–27	—
5.00*M*	35	16	15
6.50*M*	—	60	15
8.50*M*	—	—	26

1076 cm.$^{-1}$ and the absence of an olefinic double bond and a hydroxyl group. Also, this compound does not decolorize permanganate or add bromine. Its ultraviolet spectrum with the maximum at 211 mμ is almost identical to that of 2,2-diphenyl-4-*t*-butyltetrahydrofuran.[2]

It has been reported that the reaction between one mole of 2,4-dimethyl-2-hydroxypentanoic acid-4-lactone and three moles of phenylmagnesium bromide yielded 2,2,4-trimethyl-4-hydroxy-5,5-diphenyltetrahydrofuran.[3] In high dilution this reaction gave the trihydroxy open chain compound, 1,1-diphenyl-2,4-dimethylpentane-1,2,4-triol. With methylmagnesium iodide and γ-butyrolactone only 1,1-dimethylbutane-1,4-diol was reported to have been formed.[4] In this investigation it was shown that the course of the reaction is not affected by the molar ratio or the concentration of the reactants. It was also demonstrated that II is formed quantitatively from I by heating the diol above its melting point or by the action of mineral acid at room temperature. It is to be noted that neither of these procedures results in the conversion of I to III.

The unsaturated carbinol (III), which is formed when the Grignard adduct is hydrolyzed with strong hydrochloric acid (above 5.0*M*) can be obtained as the acetate by refluxing the adduct with acetic anhydride, followed by hydrolysis with hydrochloric acid of any concentration. This ester can be made, also, by refluxing a mixture of I and acetic anhydride in acetic acid.

Structure III was assigned to the unsaturated carbinol on the basis of its dibromo derivative, its oxidation with permanganate and ozone which yielded benzophenone, and its absorption spectra. The infrared spectrum does not show any absorption at 1650 cm.$^{-1}$ (characteristic of 1-butene). This eliminates the tertiary alcohol structure with a terminal double bond. The strong absorption at about 3335, 1600, and 1500 cm.$^{-1}$ indicates the presence of an associated hydroxyl group and a double bond in conjugation with a benzene ring. The ultraviolet spectrum shows the absorption maximum at 250 mμ with an ε value of 15,100 (log ε = 4.18), confirming the above conclusion regarding the position of the double bond.[5] Compound III was compared, also, to the isomeric tertiary unsaturated carbinol, 1,1-diphenyl-3-butene-1-ol, which was prepared by the method of Kharasch and Weinhouse[6] from allylmagnesium bromide and benzophenone. Permanganate oxidation of this compound yields 3-hydroxy-3,3-diphenylpropanoic acid. Its infrared spectrum shows the terminal methylene group (1650 cm.$^{-1}$) and a weaker absorption of the free hydroxyl group at 3500 cm.$^{-1}$ than the corresponding absorption of compound III at 3335 cm.$^{-1}$

The solid product formed by hydrolyzing the Grignard adduct with hydrochloric acid solutions of 3.5*M* and 5.0*M* (Table I) was shown to be a 70:30% mixture of I and II. This composition was assigned to this product on the basis of the similarity of its melting point (88–98°) to that of a synthetic mixture of the same composition. Also, the infrared spectra of these two mixtures are very similar, particularly, since they show approximately the same amount of absorption at 1076, 1447, 1487, 2685, 2950, 3015, 3340, and 3500 cm.$^{-1}$

EXPERIMENTAL

1,1-Diphenylbutane-1,4-diol (I). To the Grignard solution prepared in every case from 31.4 g. (0.2 mole) of bromobenzene and 4.8 g. (0.2 mole) of magnesium in 100 ml. of ether, a solution of 8.6 g. (0.1 mole) of γ-butyrolactone in 100 ml. of ether was added slowly either at 0° or at the reflux temperature of the mixture with vigorous stirring. Stirring was continued for 2 hr. To avoid formation of an agglomerated sticky product, the higher temperature is preferred. The alternate procedure, involving the addition of the ethereal solution of the Grignard reagent to the ethereal solution of the lactone, produced the same result. The cold reaction mixture was treated with 100 ml. of 2.05*M* hydrochloric acid. An equivalent amount of acetic acid gave the same result. The ethereal layer was separated and treated successively with water, 5.0% sodium hydroxide, and saturated sodium chloride before being dried over anhydrous calcium chloride. After removing the ether, 21.0–23.0 g. of crude material, m.p. 104–107°, was obtained. Recrystallization from light petroleum ether yielded 19.5–22.0 g. (80–90%) of I, m.p. 108–109°. This substance gave a bright red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44. Found: C, 79.56; H, 7.57.

The Schotten-Baumann reaction in dioxane-water solution yielded the monobenzoate, m.p. 123–124°. This product also gave a bright red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{23}H_{22}O_3$: C, 79.77; H, 6.36. Found: C, 79.81; H, 6.55.

1,1-Diphenyl-1-butene-4-ol (III). Decomposition of the Grignard adduct with 25.0 ml. of 8.5*M* hydrochloric acid yielded 5.8 g. (26.0%) of III, b.p. 135–137° (0.6 mm.), n_D^{25} 1.5948, D_{25}^{25} 1.1024; infrared spectrum of liquid film on salt plate: 3335, 1600, and 1500 cm.$^{-1}$; ultraviolet spectrum in 95% ethyl alcohol: 250 mμ, ε = 15,100 (log ε = 4.18).

(2) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951, Plate 118.

(3) M. Kohn, *Monatsh.*, **34**, 1729 (1913).

(4) A. Losanitsch, *Compt. rend.*, **153**, 390 (1911).

(5) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951, Plates 117 and 119.

(6) M. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.71; H, 7.14. Found: C, 85.62; H, 7.26.

Treatment of a carbon tetrachloride solution of III with bromine yielded the dibromo derivative, m.p. 96–97°.

Anal. Calcd. for $C_{16}H_{16}OBr_2$: C, 50.00; H, 4.17. Found: C, 50.28; H, 4.24.

Permanganate oxidation and ozonolysis of III yielded benzophenone, identified by its 2,4-dinitrophenylhydrazone and phenylhydrazone.

Distillation of III resulted in the formation of an appreciable amount of a viscous, nonvolatile residue, which was readily soluble in ether and gave a bright red color with concentrated sulfuric acid.

The reaction between allylmagnesium bromide and benzophenone yielded 1,1-diphenyl-3-butene-1-ol, b.p. 135–138° (0.5 mm.), n_D^{25} 1.5875, D_{25}^{25} 1.0756; infrared spectrum of liquid film on salt plate: 3500 and 1645 cm.$^{-1}$ Kharasch and Weinhouse reported the boiling point, 150–155° (3.0 mm.) and no other constants.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.71; H, 7.14. Found: C, 85.58; H, 7.35. This product yielded a dibromo derivative, m.p. 186–188°.

Anal. Calcd. for $C_{16}H_{16}OBr_2$: C, 50.00; H, 4.17. Found: C, 50.22; H, 4.32.

4,4-Diphenyl-3-butenyl acetate. The Grignard adduct was treated with 20.4 g. (0.2 mole) of acetic anhydride, and the mixture was allowed to stir for 2 hr. at the reflux temperature of the ethereal mixture. The cold mixture was then treated with 120.0 ml. of 1.7*M* hydrochloric acid. The ether layer, after being treated in the usual manner, yielded 14.5 g. (54.5%) of the unsaturated ester, b.p. 144–146° (0.8 mm.), n_D^{25} 1.5740, D_{25}^{25} 1.0960; infrared spectrum of liquid film on salt plate: 1735, 1600, and 1245 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.20; H, 6.76. Found: C, 81.27; H, 6.82.

Saponification of this ester in ethanolic potassium hydroxide yielded the unsaturated carbinol (III), which was identified by its physical constants and its dibromo derivative, m.p. 96–97°. The odor of ethyl acetate was also very prevalent in the saponification mixture.

Method 2. A mixture of 10.0 g. (0.041 mole) of I and 4.2 g. (0.041 mole) of acetic anhydride in 15 ml. of glacial acetic acid was refluxed for 1 hr. The cold mixture was diluted with 100 ml. of water and extracted with 150 ml. of ether in two portions. The ether solution of the ester was treated with water, sodium bicarbonate, and saturated sodium chloride before drying it over anhydrous sodium sulfate. After removing the ether and a small amount of forerun, 1.5 g. of viscous liquid, b.p. 110–122° (0.6 mm.) was distilled. This substance solidified on standing, m.p. 64–68°. It did not depress the melting point of a pure sample of II (68–69°). Further distillation produced 6.3 g. (66.0%) of the unsaturated acetate, b.p. 140–143° (0.6 mm.), n_D^{25} 1.5738.

2,2-Diphenyltetrahydrofuran (II). Decomposition of the Grignard adduct with 32.0 ml. of 6.5*M* hydrochloric acid yielded a viscous liquid, which on cooling in an ice bath for 4 hr. deposited 10.7 g. of crystals, m.p. 64–68°. Recrystallization from light petroleum ether gave 9.8 g. of II, m.p. 68–69°. Distillation of the liquid which was filtered from the crude solid yielded 3.5 g. of product, b.p. 100–120° (0.5 mm.) which solidified, m.p. 66–68°, bringing the total yield to 13.3 g. (59.5%). Compound II gave a bright red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.71; H, 7.14. Found: C, 85.45; H, 7.19; infrared spectrum in CCl_4: 1076 cm.$^{-1}$; ultraviolet spectrum in 95% ethyl alcohol: 211, 227, 252, 258, and 264 mμ.

Compound II did not decolorize permanganate or add bromine.

Distillation of the residue remaining after removing product II yielded 3.4 g. (15.0%) of III.

Method 2. Compound I (5.0 g.) was heated in an oil bath at 130° for 2 hr. On cooling, 4.5 g. (97%) of crystals, m.p. 66–68° was obtained. This product did not depress the melting point of II.

Method 3. A mixture consisting of 1.0 g. of I, 15.0 ml. of dioxane, 30.0 ml. of water, and 10.0 ml. of sulfuric acid was allowed to stand at room temperature for 6 hr. and then was poured into 200 ml. of water. This yielded 0.84 g. (92%) of product, m.p. 67–69°. This product did not depress the melting point of compound II.

Mixture of 1,1-diphenylbutane-1,4-diol (I) *and 2,2-diphenyltetrahydrofuran* (II). Decomposition of the Grignard adduct with 60.0 ml. of 3.5*M* hydrochloric acid yielded 20.0–22.0 g. (80–90%) of crude material, m.p. 88–98 . This product has the same melting point as a synthetic mixture of I and II in a 70:30 weight ratio. The infrared absorption curves of the two mixtures are very similar, showing approximately the same amount of absorption at 1076, 3340, and 3500 cm.$^{-1}$ in particular.

Attempts to separate the two components of the mixture by four crystallizations from cyclohexane yielded a fraction, m.p. 61–75° (pure II, m.p. 68–69°) and another product, m.p. 99–106° (pure I, m.p. 108–109°).

Mixture of 1,1-diphenylbutane-1,4-diol (I), *2,2-diphenyltetrahydrofuran* (II), *and 1,1-diphenyl-1-butene-4-ol* (III). Decomposition of the Grignard adduct with 43.0 ml. of 5.0*M* hydrochloric acid gave a product, which on cooling for 4 hr. in an ice bath deposited 12.3 g. (51.0%) of crystals, m.p. 86–96°, which is the 70:30% mixture of I and II. The liquid which was obtained by filtration was distllled, yielding 3.5 g. (15.0%) of compound III.

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Polarographic Reduction of Some Aliphatic Ketones

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Aliphatic ketones are reduced at a dropping mercury electrode only at fairly negative potentials. Neiman and Markina[1] reported the half-wave potentials of acetone and methyl ethyl ketone as −2.20 and −2.25 v., respectively, in 0.025 *M* tetramethylammonium iodide solution. Von Stackelberg and Stracke[2] reported the reduction of acetone and cyclohexanone in 0.05*M* tetraethylammonium iodide–75% dioxane, with half-wave potentials of −2.45 v. and −2.46 v., respectively. The number of electrons involved in the electrode process has not been measured for such ketones. However, diffusion current values reported in the literature[2] suggest a one-electron electrode process. On the other hand, it is known that it is difficult to obtain bimolecular reduction products from aliphatic ketones other than acetone when the reduction is carried out either chemically or electrolytically.[3,4] Swann[4] has reported that electrolytic

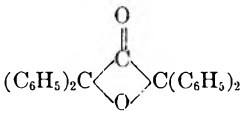
(1) M. B. Neiman and Z. V. Markina, *Zavodskaya Lab.*, **13**, 1177 (1947).

(2) M. von Stackelberg and W. Stracke, *Z. Elektrochem.*, **53**, 118 (1949).

(3) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, 1954, p. 711.

reduction of acetone to pinacol can be effected in alkaline solution, but that the reaction is not general for aliphatic ketones. No pinacol was obtained, for example, upon electrolytic reduction of either methyl ethyl ketone or di-*n*-propyl ketone.

We have investigated the polarographic reduction of a series of aliphatic ketones and have isolated the products obtained in several instances when the electrolyses were carried out on a macro scale. The compounds studied were acetone, methyl cyclopropyl ketone, 1-phenylpropanone-2 (I), 1,3-diphenylpropanone-2 (II), 1,1,3-triphenylpropanone-2 (III), 1,1,3,3-tetraphenylpropanone-2 (IV), and the unusual molecule 2,2,4,4-tetraphenyl-3-oxetanone[5] (V). Macroelectrolyses were carried out with II, IV and V.



V

The results of the polarographic studies are summarized in Table I. It will be noted that the half-wave potentials obtained in ethanol are slightly more positive than those in dioxane, although the values are not widely different. This variation may arise from differences in liquid junction potentials in the two solvents. The values obtained for acetone and cyclohexanone are more negative than those reported by Neiman and Markina[1] and von Stackelberg and Stracke,[2] but are in more reasonable agreement with the values of the latter workers.

The half-wave potentials of the phenyl-substituted acetones become increasingly more positive as phenyl groups are substituted for hydrogen atoms in acetone. The oxetanone, V, has a half-wave potential of approximately −2.0 v., an unusually positive value for an aliphatic ketone. This compound also gives a larger diffusion current than the other ketones and there is a slight separation into two waves. Although the separation is not sharp, we have reported separate half-wave potentials in Table I.

TABLE I

HALF-WAVE POTENTIALS OF ALIPHATIC KETONES
(All $E_{1/2}$ Values Are Negative)

Compound	Dioxane[a] $E_{1/2}$	Dioxane[a] i_d/C	Ethanol[b] $E_{1/2}$	Ethanol[b] i_d/C
Acetone	2.61	2.0	2.53	3.2
Methyl cyclopropyl ketone	—	—	2.55	2.4
Cyclohexanone	2.54	2.2	—	—
I	2.45	2.5	2.34	3.0
II	2.22	2.4	2.10	2.6
III	2.16	2.3	—	—
IV	2.13	2.5	2.05	2.6
V	1.94	2.5	1.91	2.6
	2.05	2.5	2.08	1.7

Various attempts were made to determine by coulometric measurements the number of electrons involved in the electrode process. The experimental difficulties encountered when working at very negative potentials prevented conclusive evidence from being obtained. Best results were obtained with compound IV, but the volume correction for the blank was of the same order as the volume anticipated for reduction of the carbonyl group. A value of $n = 1.0$ was obtained for this compound but the data cannot be considered conclusive. Determinations were also run with the oxetanone, V, but the results were scattered, the values being nonintegral and considerably greater than two (see below). Evidence based on the polarographic diffusion currents indicate a one-electron electrode process for all compounds except V, but again data at such high potentials are inconclusive.

Controlled potential macroelectrolyses of II and IV gave the secondary alcohols, indicating, of course, an over-all two-electron process. From II essentially a quantitative yield of 1,1-diphenylpropanol-2 was obtained,[6] while the reduction of IV gave essentially 1,1,3,3-tetraphenylpropanol-2 (VI) as the product. There was no evidence in either case of a bimolecular reduction product.

The macroelectrolysis of the oxetanone, V, apparently produced a mixture of products. As mentioned above, coulometric measurements of the number of electrons gave scattered, nonintegral values, considerably greater than two. Infrared analyses of the product and comparison with the spectra of pure samples of VI and of 2,2,4,4-tetraphenyl-3-oxetanol (VIII) indicated the presence of VII and another compound (or compounds) of structure similar to VI. The presence of the latter structure presumably resulted from opening of the oxetane ring. This ring has been found to open under the attack of chemical reducing agents,[7] yielding structures similar to VI. Such behavior would account for the scattered coulometric results.

EXPERIMENTAL

The polarographic data were obtained with a Leeds and Northrup Electro-chemograph Type E. Half-wave potentials were corrected for IR drop and for lag caused by galvanometer damping. The electrolysis cell was the usual H-type but in order to prevent the possibility of contamination of the cell solution by potassium ion a mercury-tetrabutylammonium chloride reference was used, the tetrabutylammonium chloride being at a concentration of 1*M*. The agar plug was saturated with 1*M* tetrabutylammonium chloride. The potential of this reference cell was measured

(4) S. Swann, Jr., in Weissberger's *Technique of Organic Chemistry*, Interscience Publishers, Inc., New York, 1956, Vol. II, p. 426.

(5) G. B. Hoey, D. O. Dean, and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 391 (1955).

(6) Since the infrared spectra of pure 1,1-diphenylpropanol-2 and of the reduction product of II were identical, the highest order of impurity would be 5%.

(7) B. L. Murr, G. B. Hoey, and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 4430 (1955).

against a saturated calomel electrode and all half-wave potentials were corrected to refer to the latter electrode.

The original runs were made with a solvent consisting of 75% dioxane–25% water, the supporting electrolyte being 0.05*M* tetrabutylammonium chloride. This was the solvent used by von Stackelberg and Stracke.[2] The dioxane was purified by the method of Hess and Frahm.[8] Later 80% ethanol–20% water was found to be a suitable solvent and was considerably more convenient than dioxane. A higher concentration of supporting electrolyte was used with the alcohol solutions, the cell solutions being 0.10*M* in both tetrabutylammonium chloride and tetrabutylammonium hydroxide. Blanks run with these solutions showed that appreciable decomposition of the supporting electrolyte did not occur below about −2.6 volts. The concentration of ketone in all cases was 0.001*M*. A single capillary of Corning Marine barometer tubing was used. The value of $m^{2/3}t^{1/6}$ was 1.63 determined in 80% ethanol with an open circuit, and 1.45 at −2.40 v.

The macroelectrolyses were carried out using a potentiostat of the Lingane-Jones type.[9] A hydrogen-oxygen coulometer was used in the coulometric measurements. The cell, electrodes, and experimental procedures were essentially those recommended by Lingane.[10] In most cases identification of a product was carried out by comparison of its infrared spectrum to that of the authentic compounds.

The samples of III, IV, and V[5] were kindly furnished us by Dr. Charles T. Lester. The samples of polarographically pure tetrabutylammonium hydroxide and chloride were obtained from Southwestern Analytical Chemical Corp. All other organic reagents were Eastman white label products and were used without further purification.

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(8) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(9) J. J. Lingane and S. L. Jones, *Anal. Chem.*, **22**, 1169 (1950).

(10) J. J. Lingane, *Electroanalytical Chemistry*, 2nd Ed., Interscience Publishers, Inc., New York, 1958, p. 251.

Alkylation of Some Diacylhydrazines[1]

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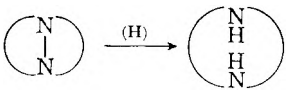
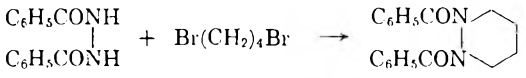
This report summarizes the preliminary work in a program aimed at the synthesis of bicyclic hydrazines (I) and conversion of the latter by hydrogenolysis to large ring diamines (II). The recent report[3] of the successful completion of a similar



I II

study has prompted us to terminate our own work n this area and to submit a brief account of experiments related to the syntheses of the precursors of the bicyclic hydrazines (I).

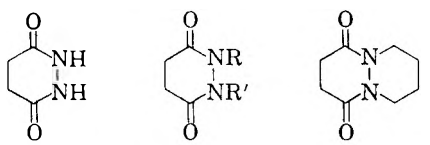
Like Stetter and Spangenberger we were unable to effect the alkylation of 1,2-dibenzoylhydrazine with trimethylene bromide. We found, however, that 1,2-dibenzoylhydrazine and tetramethylene bromide in basic solution yield 1,2-dibenzoylhexahydropyridazine (III). The structure of III was established by its carbon, hydrogen analysis,



III

its insolubility in basic solution, and its melting point.[4] Similar results have been obtained by using 1,2-diacetyl- and 1,2-diisobutyrylhydrazine.[3]

Alkylation of cyclic succinhydrazide (IV) by dimethyl sulfate in basic solution yielded 1,2-dimethylhexahydropyridazine-3,6-dione (Va), previously prepared by the hydrogenation of *N,N'*-dimethylmaleic hydrazide.[5] Alkylation of IV with



IV a. R = R' = CH_3 V VI
b. R = H; R' = C_2H_5

ethyl iodide, however, yielded a product (Vb) bearing only one ethyl group. Assignment of structure Vb to the product is supported by the C, H analysis, the decreased melting point of the product relative to that of the starting material,[4] and the fact that the product could be extracted from acidic solution, but not from basic solution, in accord with the acidic properties of acylhydrazines containing the –CONH– group. Attempts to alkylate IV with tetramethylene bromide yielded a product, presumed to be VI. Although the product could not be purified sufficiently to yield satisfactory analytical results, the melting point (179–181°) agrees well with that (179–180°) reported[3] for VI, which was prepared from piperidazine and succinic anhydride. Extraction of the product from basic solution, and the decrease in the melting point relative to the starting material[4] is additional evidence in support of structure VI.

The cyclic succinhydrazide (IV) was prepared by catalytic hydrogenation of maleic hydrazide.[6] However, consistently successful reductions were obtained only if the latter compound was refluxed with a small quantity of Raney nickel before use.

(1) Taken from the M.S. thesis of R. J. Landborg, State University of Iowa, August 1957.

(2) Present address: Union Carbide Research Institute, 32 Depot Plaza, White Plains, N. Y.

(3) H. Stetter and H. Spangenberger, *Ber.*, **91**, 1982 (1958).

(4) A decrease in m.p. usually accompanies substitution of an alkyl group for the peptide hydrogen of an acylhydrazine, R. L. Hinman and M. C. Flores, *J. Org. Chem.*, **24**, 660 (1959).

(5) K. Eichenberger, A. Staehelin, and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954).

(6) H. Feuer, G. B. Bachman, and E. H. White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).

Attempts to prepare the cyclic succinhydrazide by alternative methods, such as the reaction of diethyl succinate and hydrazine at high dilution, intramolecular cyclization of succindihydrazide in refluxing butyl cellosolve, and the reaction of hydrazine with *N*-benzylsuccinimide were unsuccessful.

EXPERIMENTAL[7]

1,2-Dibenzoylhexahydropyridazine. A solution of 1.8 g. (0.008 mole) of tetramethylene bromide in 30 ml. of absolute alcohol was added slowly with stirring to a refluxing solution of 2 g. (0.008 mole) of dibenzoylhydrazine[8] in 100 ml. of 60% ethanol. Sufficient concentrated sodium hydroxide was added throughout the reaction to maintain a *p*H of 8–9. After 8 hr. the alcohol was removed by distillation during which water was added to replace the alcohol. The aqueous solution was extracted several times with chlorofrom and the combined extracts dried over anhydrous sodium sulfate. After removal of the solvent by evaporation, the residue (0.5 g., 20%) consisted of white crystals melting at 124–127°. An analytical sample was prepared by recrystallization from a mixture of hexane and chloroform followed by 2 sublimations. The melting point of the hygroscopic crystals was raised to 130°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.46; H, 6.15; N, 9.51. Found: C, 73.06; H, 6.08; N, 8.99.

Only starting material was isolated from the reaction of 1,2-dibenzoylhydrazine and trimethylene bromide under similar conditions.

Hexahydropyridazine-3,6-dione. This compound was prepared by catalytic reduction of maleic hydrazide by a modification of the method of Feuer, Bachman, and White.[6] Practical grade maleic hydrazide was recrystallized from water, refluxed with 4% of its weight of Raney nickel in water, and recrystallized again from water. By use of this procedure the amount of platinum oxide catalyst necessary for the reduction of maleic hydrazide could be reduced to half that previously required, the reaction time shortened, and the reductions made consistently successful. The product, which was obtained in 70–80% yield, consisted of white needles, m.p. 277° (lit.[6] m.p. 277–278°). High pressure reductions using Raney nickel catalyst gave starting material or a mixture of products. Only starting material was isolated from the reduction at room temperature using aluminum amalgam.[6]

1,2-Dimethylhexahhyropyridazine-3,6-dione. A solution of 4.0 g. (0.034 mole) of dimethyl sulfate in 75 ml. of 50% ethanol was added with stirring over a period of 4 hr. to a refluxing solution of 2 g. (0.017 mole) of cyclic succinhydrazide in 60 ml. of 50% alcohol. The reaction mixture was maintained at a *p*H of 8–9 by the addition of small amounts of concentrated aqueous sodium hydroxide. At the end of the reaction time the alcohol was removed by distillation during which water was added to replace the alcohol. The remaining aqueous solution was extracted several times with chloroform and the combined extracts were dried over anhydrous sodium sulfate. The average yield of crude product after the evaporation of the solvent was 0.4 g. (16%). After recrystallization from a mixture of hexane and chloroform and 2 sublimations, the melting point of the purified compound was 104–105° (lit.[5] m.p. 104–105°). The compound was highly hygroscopic.

Alkylation of hexahydropyridazine-3,6-dione with ethyl iodide. The above alkylation was carried out substituting 5.3 g. (0.034 mole) of ethyl iodide in 30 ml. of ethanol for the dimethyl sulfate solution. After recrystallization from a mixture of hexane and chloroform and 2 sublimations, 0.3 g. (12%) of white crystals melting at 140–142° was obtained. The compound analyzed for 1-ethylhexahydropyridazine-3,6-dione.

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.70; H, 7.04. Found: C, 50.66; H, 7.10.

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(7) Melting points are uncorrected.

(8) H. H. Hatt, *Org. Syntheses*, Coll. Vol. II, 208 (1943).

Polyphosphoric Acid–Catalyzed Reaction of Anisole with γ-Butyrolactone

Herbert O. House and Ronald J. McCauley

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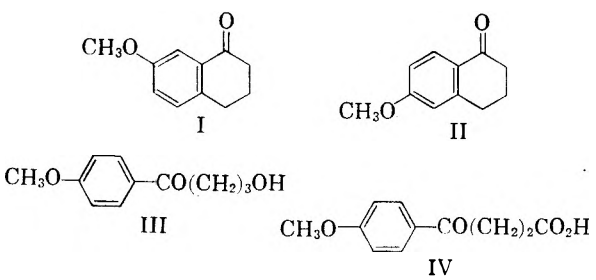
The reaction of γ-substituted-γ-butyrolactones with benzene and alkyl-substituted benzenes in the presence of aluminum chloride has served to produce γ-aryl-γ-substituted butyric acids.[1,2] The comparable reaction of benzene with γ-butyrolactone in the presence of excess aluminum chloride afforded α-tetralone in one step.[3] These observations suggested that 7- (or 6-) alkoxy-1-tetralones might be prepared directly by the reaction of alkoxybenzenes with γ-butyrolactone in the presence of polyphosphoric acid.[4,5]

The reaction of anisole with γ-butyrolactone in the presence of polyphosphoric acid was found to yield neither of the expected tetralones I or II, but rather a hydroxy ketone which has infrared and ultraviolet spectra compatible with structure III. This structure was confirmed by oxidation of the product to form the keto acid IV.



EXPERIMENTAL[6]

γ-Hydroxy-p-methoxybutyrophenone (III). A mixture of 6.14 g. (0.0568 mole) of anisole and 4.876 g. (0.0568 mole) of

(1) J. F. Eijkman, *Chem. Weekblad*, **1**, 421 (1904).

(2) D. D. Phillips, *J. Am. Chem. Soc.*, **77**, 3658 (1955).

(3) C. E. Olson and A. R. Bader, *Org. Syntheses*, **35**, 95 (1955).

(4) For a review of cyclizations effected in the presence of polyphosphoric acid, see F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 321 (1958).

(5) A successful intermolecular acylation of anisole reported by N. C. Deno and H. Chafetz [*J. Org. Chem.*, **19**, 2015 (1954)] may have involved a γ,γ-disubstituted butyrolactone as an intermediate.

γ-butyrolactone was added, with stirring, to 100 g. of polyphosphoric acid which have been heated to 50°. The resulting mixture was heated to 85–90° with stirring for 8 hr. and then poured onto ice and extracted with four portions of ether. The combined extracts were washed with sodium bicarbonate, dried over sodium sulfate, and concentrated. The residue, when cooled, solidified as yellow needles, m.p. 35–48°, yield 5.53 g. (50%). Recrystallization from an ether-hexane mixture and from ethanol afforded the pure hydroxy ketone as white needles, m.p. 48–49°. The infrared spectrum[7] of the product has bands at 3400 cm.$^{-1}$ (associated O—H) and 1670 cm.$^{-1}$ (conj. C=O); the ultraviolet spectrum[8] has maxima at 218 mμ (ε 10,300) and 272 mμ (ε 14,600).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.88; H, 7.30.

A solution of 0.0518 g. (0.00027 mole) of the keto alcohol in 10 ml. of reagent acetone was cooled in a Dry Ice–acetone bath and treated, dropwise and with stirring, with a solution of 0.044 g. (0.00044 mole) of chromium trioxide and 0.15 ml. of concentrated sulfuric acid in 1.8 ml. of water. The mixture was allowed to warm to room temperature and stand over a 4-hr. period. The reaction mixture was concentrated, diluted with water, and extracted with ether. The ether solution was extracted with three 20-ml. portions of 5% aqueous sodium bicarbonate. Acidification of the combined bicarbonate extracts afforded 0.0329 g. (57%) of β-(*p*-methoxybenzoyl)propionic acid, m.p. 146–147°, which was identified by a mixed melting-point determination with an authentic sample. More vigorous oxidation of the keto alcohol with chromic acid in boiling acetic acid afforded *p*-anisic acid, identified by a mixed melting-point determination with an authentic sample, in 19% yield.

7-Methoxy-1-tetralone (I). β-(*p*-Methoxybenzoyl)propionic acid, m.p. 146–147° (lit.[9] 144.5–146.5°), was converted to γ-(*p*-methoxyphenyl)butyric acid, m.p. 60–60.8° (lit.[10] 61–62°) in 82% yield by low-pressure hydrogenolysis[10] in acetic acid solution at 65° in the presence of a 10% palladium-on-carbon catalyst and in 88% yield by high-pressure hydrogenolysis[11] of aqueous solution of the sodium salt of the acid at 200° in the presence of copper chromite catalyst. The reaction of 11.98 g. (0.0618 mole) of γ-(*p*-methoxyphenyl)-butyric acid with 150 g. of polyphosphoric acid at 90–93° for 15 min. followed by appropriate manipulations afforded 10.17 g. (93.5%) of 7-methoxy-1-tetralone, m.p. 56–62°. The pure tetralone, which crystallized from aqueous ethanol as pale yellow plates melting at 60.9–62° (lit.[9] 61–62.5°), has a band in the infrared[12] at 1685 cm.$^{-1}$ (conj. C=O) and exhibits ultraviolet[8] maxima at 222 mμ (ε 19,600), 253 mμ (ε 8900) and 323 mμ (ε 3100). The product formed a semicarbazone, m.p. 222–223.1° dec. (lit.[13] 224–226° dec.), in 72% yield and a crude 2,4-dinitrophenylhydrazone, m.p. 280–284°, in 99.5% yield. The pure *2,4-dinitrophenylhydrazone of 7-methoxy-1-tetralone* crystallized from ethyl acetate as red prisms, m.p. 285–286°. The ultraviolet spectrum[7] of the 2,4-dinitrophenylhydrazone has a maximum at 385 mμ (ε 31,400).

Anal. Calcd. for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.57; H, 4.39; N, 15.62.

The 2,4-dinitrophenylhydrazone of 6-methoxy-1-tetralone, m.p. 233–234° (lit.[14] 236–238°), has an ultraviolet[7] maximum at 396 mμ (ε 29,200).

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(6) The infrared spectra were determined with either a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(7) Determined in chloroform solution.

(8) Determined in 95% ethanol solution.

(9) D. G. Thomas and A. H. Nathan, *J. Am. Chem. Soc.*, **70**, 331 (1948).

(10) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **71**, 1036 (1949).

(11) This procedure developed by L. F. Fieser and W. H. Daudt, *J. Am. Chem. Soc.*, **63**, 782 (1941), was found to be more convenient in the present study.

(12) Determined in carbon tetrachloride solution.

(13) A. Muller, M. Meszaros, M. Lempert-Sreter, and I. Szara, *J. Org. Chem.*, **16**, 1003 (1951).

(14) F. J. Villani, M. S. King, and D. Papa, *J. Org. Chem.*, **18**, 1578 (1953).

The Triterpenes of *Heliabravoa chende*[1]

Maurice Shamma and Paul D. Rosenstock

Received December 18, 1958

A sample of the water-insoluble, "nonglycosidic", extracts of the giant Mexican cactus *Heliabravoa chende* (formerly *Lemaireocereus chende*),[2] kindly supplied by Prof. Carl Djerassi, was investigated for triterpenes. The sample was composed mostly of neutral material (A), and a small fatty acid fraction (B) which gave a negative Liebermann-Burchard test. Saponification of the neutral material (A) with 15% methanolic potassium hydroxide yielded an acid fraction (C) and a neutral fraction (D).

The acidic fraction (C) which was crude and only partly crystalline was washed several times with hexane. The hexane-insoluble residue, which proved to be oleanolic acid (I), was purified as its methyl ester (II).

Chromatography of the neutral fraction (D) over alumina gave oleanolic aldehyde (III) followed by erythrodiol (IV).

The presence of oleanolic aldehyde in *Heliabravoa chende* deserves special attention since this is the first instance of this triterpene being found in nature. However, its 3-acetyl derivative (V) had previously been prepared by Ruzicka and Schellenberg via a Rosenmund reduction of oleanolic acid chloride acetate.[3] In our hands, crude oleanolic aldehyde was obtained as a yellowish solid, m.p. 112–186°, which could best be purified as the acetate. Oleanolic aldehyde was also reduced in very high yields by lithium aluminum hydride to erythrodiol.

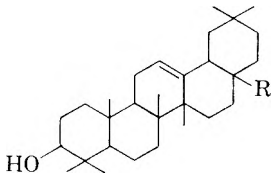
An interesting aspect of the present study is that oleanolic aldehyde is one more pentacyclic triterpene which should be added to the impressive

(1) This investigation was supported by a research grant (No. G5105) from the National Science Foundation.

(2) Helia Bravo and Don K. Cox, *Cactaceas Y Succulentas Mexicanas*, **3**, 3 (1958).

(3) L. Ruzicka and H. Schellenberg, *Helv. Chim. Acta*, **20**, 1553 (1937).

list of this class of compounds found in cacti.[4] Furthermore, oleanolic aldehyde conforms to the rule of possible oxygenation in cactus triterpenes only at C-15, 16, 21, 22, 28, and 30, besides the 3β-hydroxyl group.[4]



I. R = COOH
III. R = COH
IV. R = CH_2OH

EXPERIMENTAL

All infrared spectra on solids were run as potassium bromide pellets. All chromatograms employed acid-washed Brockman activity II-III alumina (*p*H 7). All melting points are uncorrected. All rotations were taken in chloroform. All triterpenes exhibited a triplet peak at 12.11, 12.24, and 12.46 μ due to the C-12,13 double bond. Elemental analyses are by Alfred Bernhardt Mikroanalytisches Laboratorium, Mulheim, Germany, and by Geller Microanalytical Laboratories, Bardonia, N. Y.

A solution of water-insoluble *H. chende* extracts (100 g.) in ether was extracted with three 500-ml. portions of 10% potassium hydroxide. The combined base extracts were neutralized and extracted with ether to yield a dark brown oil (B, 2.72 g.) that consisted of fatty acids which were not characterized. Extraction with 10% hydrochloric acid gave no acid-soluble substance. Evaporation of the ether then gave 97 g. of neutral, water-insoluble material (A).

Hydrolysis of neutral fraction A. The neutral fraction (A) was heated under reflux for 6 hr. with 5 l. of 15% potassium hydroxide in methanol. The solution was then evaporated to half volume, cooled, and acidified with concentrated hydrochloric acid. The precipitated potassium chloride was filtered and washed copiously with ether. The combined filtrate and washings were evaporated to dryness, the residue dissolved in 2 l. of ether, filtered, and extracted 4 times with a total of 2 l. of 10% sodium hydroxide. The organic layer was dried, filtered, and evaporated to yield an orange-brown neutral mass (D, 69.5 g.).

The combined sodium hydroxide extracts were acidified with concentrated hydrochloric acid and extracted with ether. The ether washings were evaporated to yield an olive drab mass (C, 27 g.).

Oleanolic acid (I). In a typical run 500 mg. of the acidic fraction (C) was extracted with 3 separate 25-ml. portions of hot hexane, and then stirred for 5 min. with 50 ml. of cold hexane. The tan hexane-insoluble residue (200 mg.) was crude oleanolic acid (I). The hexane-soluble fraction was composed mainly of fatty acid material which was not further characterized.

Methyl oleanolate (II) was produced when an ether solution of crude oleanolic acid (456 mg., 1 mmole) was treated with an excess of ethereal diazomethane. The crude product was chromatographed in 4:1 benzene-hexane on 50 g. of alumina. Elution with 99:1 benzene-ether yielded 433 mg. (92%) of white solid, m.p. 190–196°. A recrystallization from methanol-water netted 428 mg. of white crystalline solid, m.p. 196–198°. Analytical sample m.p. 199–200°, $[\alpha]_D$ +75°.

Anal. Calcd. for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 79.32; H, 10.90.

This compound had an infrared spectrum identical to that of an authentic sample of methyl oleanolate.[5]

Acetylation of methyl oleanolate (II) with acetic anhydried in pyridine and 2 recrystallizations from methanol-ethyl acetate gave *methyl acetyl oleanolate* (VI), m.p. 222.5–223°, $[\alpha]_D$ +70°.

Anal. Calcd. for $C_{33}H_{52}O_4$: C, 77.29; H, 10.22. Found: C, 77.59; H, 10.13.

This compound gave an undepressed mixed melting point with an authentic sample of methyl acetyl oleanolate.

Lithium in liquid ammonia reduction of methyl oleanolate (VI). Reduction of methyl oleanolate (II) (150 mg., 0.032 mmole) with lithium in liquid ammonia[6] gave oleanolic acid (I), m.p. 304–308°. Two recrystallizations from aqueous methanol raised the melting point to 309–310°, $[\alpha]_D$ +80°.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.79.

A 39-mg. (26%) yield of *erythrodiol* (IV), m.p. 208–217°, was also obtained from the reduction. Two recrystallizations from aqueous ethanol gave m.p. 230–231°.

Acetylation of the above oleanolic acid (I) with acetic anhydride in pyridine followed by 3 recrystallizations from aqueous ethanol gave *oleanolic acid acetate* (VII), m.p. 266–268°, $[\alpha]_D$ +76°.

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.29; H, 10.22. Found: C, 77.59; H, 10.13.

Chromatography of neutral fraction (D). Part of the crude neutral fraction (D) (5.5 g.) was chromatographed on 400 g. of alumina. Elution with 2:3 benzene-hexane yielded a yellow oil (1.8 g., 33%), which appeared to be a fatty acid ester, gave a negative Liebermann-Burchard test, and was not further investigated. Subsequent elution with ether washed the remaining 3.5 g. of material off the column. The ether eluate was rechromatographed in 1:1 ether-benzene on 300 g. of alumina. Elution with 1:9 ether-benzene yielded *oleanolic aldehyde* (III) (1.05 g., 19%) as a yellowish solid, m.p. 112–186°. Employment of 4:1 ether-benzene then gave impure *erythrodiol* (IV) (2.24 g., 41%) as a white solid, m.p. 207–219°. Two recrystallizations from aqueous ethanol gave m.p. 230–231°, $[\alpha]_D$ +75°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.15; H, 11.03.

The erythrodiol isolated at this stage gave an undepressed mixed melting point with the erythrodiol isolated from the lithium in liquid ammonia reduction of methyl oleanolate (II). In addition, the infrared spectra of the 2 compounds were identical.

Acetylation of erythrodiol (IV) with acetic anhydride in pyridine and crystallization from ethanol-water gave *erythrodiol diacetate* (VIII), m.p. 179–184°. The analytical sample exhibited m.p. 186–188°, $[\alpha]_D$ +58°.

Anal. Calcd. for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.74; H, 10.13.

Acetylation of crude oleanolic aldehyde (III) with acetic anhydride in pyridine followed by chromatography on alumina and elution with 3:1 benzene-hexane yielded *oleanolic aldehyde acetate* (IX), m.p. 215–217°. Several recrystallizations from methanol gave m.p. 225–228°. Infrared peaks at 5.78–5.80 (ester and aldehyde superimposed), 8.07 (acetoxy), and 6.1 μ (double bond), in addition to the previously mentioned triterpene peaks.

Oleanolic aldehyde acetate oxime (X). To a solution of crude oleanolic aldehyde acetate (161 mg., 0.33 mmole) in 2 ml. of dry pyridine and 3 ml. of absolute ethyl alcohol was added hydroxylamine hydrochloride (69.5 mg., 1 mmole). The solution was heated under reflux for 6 hr., the solvent mixture evaporated, and the residue dissolved in 30 ml. of ether. The ether solution was extracted with three 15-ml. portions of 10% hydrochloric acid, once with 15 ml. of water,

(4) C. Djerassi, *Festschrift Prof. Dr. Arthur Stoll*, Birkhauser, Basel, 1957, p. 330.

(5) The authors are indebted to Dr. Carl Djerassi for supplying all compounds for comparison studies.

(6) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, 80, 217 (1958).

and dried. The crude product was chromatographed in 99:1 benzene-ether on 5 g. of alumina. Elution with 3:7 benzene-hexane yielded unreacted oleanolic aldehyde acetate (66 mg., 41%), m.p. 207–214°. Subsequent elution with ether yielded oleanolic aldehyde acetate oxime (X) (84 mg., 52%), m.p. 175–186°. Further purification of the latter fraction by recrystallizations from methanol-water yielded a colorless crystalline analytical sample, m.p. 189–200° dec.

Anal. Calcd. for $C_{32}H_{51}O_3N$: C, 77.21; H, 10.33. Found: C, 76.95; H, 10.10.

Infrared peaks at 2.93 (hydroxyl), 5.74 (ester), 8.07 (acetoxy), and 6.1 μ (double bonds), in addition to the previously mentioned triterpene peaks.

Reduction of oleanolic aldehyde (III) with lithium aluminum hydride in ether resulted in a 99% yield of erythrodiol (IV), m.p. 216–221°. Recrystallizations from methanol-water gave m.p. 230–232°.

The erythrodiol obtained above gave an undepressed mixed melting point with the erythrodiol obtained either naturally, or by metallic reduction of methyl oleanolate (II). Furthermore, the infrared spectra of these samples were identical.

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Derivatives of Some Cycloalkylcarbinols

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During the synthesis of a series of compounds for a study of cycloalkylmethylbromides, it became necessary to characterize a number of cycloalkylcarbinols. A survey of the literature showed that a number of these carbinols had been synthesized and characterized. No systematic approach to the subject, however, could be found. It was the object of this work to prepare several derivatives of the alcohols with which we were concerned. The derivatives chosen for the characterization were the phenylurethanes, the α-naphthylurethanes, and the 3,5-dinitrobenzoates.

The phenylurethane of cyclopentylcarbinol has been reported to melt at 110°[1] and 108–108.5°[2] while that of cyclohexylcarbinol was reported to melt at 82°[3] and 74–75°.[4] The α-naphthylurethane of cyclohexylcarbinol has been reported to melt at 109.4–110.2°[2] and 109–110.2.°[5] The melting point of the 3,5-dinitrobenzoate of cyclohexylcarbinol has been reported as 94°.[6]

EXPERIMENTAL

The alcohols used in this work were prepared by the lithium aluminum hydride reduction of the corresponding ethyl cycloalkane carboxylates with the exception of cycloheptylcarbinol, which was prepared from the butyl ester. The esters were dropped slowly into a rapidly stirred refluxing ether solution of a slight excess of lithium aluminum hydride. The alcohols were isolated after decomposition of the excess hydride and the reaction complex. The alcohols were purified by fractional distillation under reduced pressure.

The urethane derivatives were prepared from equimolar quantities of the alcohol and isocyanate. The reagents were mixed and heated on a steam bath for 0.5 hr. The resulting solids were removed and recrystallized from petroleum ether until the melting points were constant.

The 3,5-dinitrobenzoate esters were prepared by mixing the alcohol with a 10% molar excess of 3,5-dinitrobenzoyl chloride and heating the mixture over a low flame for 5–10 min. After cooling, excess acidic materials were removed from the precipitate by washing with 5% sodium bicarbonate solution. The crude esters were repeatedly recrystallized from ethanol-water mixture to constant melting points.

MELTING POINTS OF CYCLOALKYLCARBINOL DERIVATIVES

Compound	M.P.	Analysis			
		Calcd.		Found	
		C %	H, %	C, %	H, %
Cyclobutylcarbinol					
Phenylurethane	65.0–66.5°	70.21	7.38	70.10	7.33
α-Naphthylurethane	112.0–112.5	75.26	6.72	75.57	6.72
3,5-Dinitrobenzoate	98.5–99.5	51.42	4.32	51.27	4.33
Cyclopentylcarbinol					
Phenylurethane	104.5–106.5	71.19	7.83	71.31	7.85
α-Naphthylurethane	85.0–86.0	75.80	7.12	75.65	6.96
3,5-Dinitrobenzoate	89.5–90.5	53.05	4.80	53.06	4.76
Cyclohexylcarbinol					
Phenylurethane	82.5–83.5	72.06	8.22	72.03	8.18
α-Naphthylurethane	108.0–109.0	76.28	7.48	76.21	7.50
3,5-Dinitrobenzoate	95.0–96.0	54.53	5.24	54.69	5.22
Cycloheptylcarbinol					
Phenylurethane	61.0–62.0	72.83	8.57	72.64	8.45
α-Naphthylurethane	84.5–85.5	76.72	7.81	76.54	7.67
3,5-Dinitrobenzoate	79.0–80.0	55.89	5.64	55.49	5.63

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Decolorizing charcoal was used when it was necessary to remove colored impurities from the esters.

The derivatives were dried under vacuum over phosphorus pentoxide and paraffin chips for 12 hr. at the temperature of boiling chloroform before the final melting points were determined.

All melting points were determined with the Koffler Microhotstage melting point apparatus using the calibrated thermometer supplied with the apparatus.

Carbon-hydrogen analyses were performed by Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Ill.

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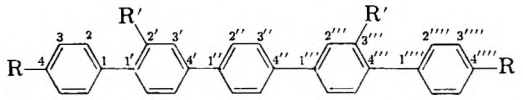
Communications TO THE EDITOR

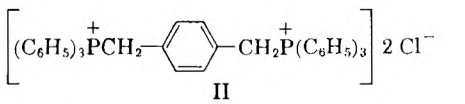
Synthesis of *p*-Quinquephenyl, 4,4''''-, and 2',3'''-Dimethyl-*p*-quinquephenyl

Sir:

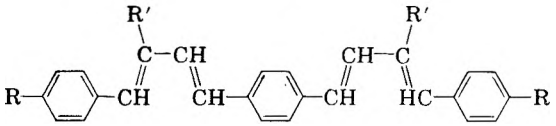
Previous syntheses of *p*-quinquephenyl (I; R = R' = H) have involved the reaction of biphenyllithium with cyclohexandione-1,4 followed by dehydration and air oxidation[1]; the Gatterman coupling reaction of benzenediazonium formate with copper[2]; the Ullmann coupling of 4-iodoterphenyl and 4-iodobiphenyl with silver[2]; the catalytic reduction of *p*-dibromobenzene[3]; and the Friedel-Crafts reaction of cyclohexene with terphenyl, followed by dehydrogenation.[4] These have yielded trace or, at best, poor yields of the hydrocarbon. We now wish to report the preparation of *p*-quinquephenyl and two derivatives utilizing the Wittig reaction for the synthesis of intermediates.



I



II



III

p-Xylylene dichloride when allowed to react with triphenylphosphine in refluxing dimethylformamide was converted in 95% yield to *p*-xylylene-bis(triphenylphosphonium chloride) [II, m.p. > 400°; *Anal.* Calcd. for $C_{44}H_{38}P_2Cl_2$: Cl, 10.16. Found: Cl (total), 10.04, 10.00; Cl (ionic), 10.15, 10.00, and for the dihydrate, calcd. for $C_{44}H_{38}P_2Cl_2 \cdot 2H_2O$: C, 71.8; H, 5.7; Cl, 9.7. Found: C, 71.6, 71.8; H, 5.9, 5.9; Cl (ionic) 9.7, 9.8; Cl (total), 9.6, 9.8].

Reaction of II with cinnamaldehyde in ethanol with lithium ethoxide as base gave a 75% yield of a mixture of *cis* and *trans* isomers of 1,4-bis(4-phenylbutadienyl)benzene[5] (III; R = R' = H; m.p. 290–293°; *Anal.* Calcd. for $C_{26}H_{22}$: C, 93.4; H, 6.6; Found: C, 93.3, 93.3; H, 6.5, 6.6), which was isomerized to all *trans* configuration with iodine.

The method reported by Lohaus[6] for the conversion of 1,4-diphenylbutadiene to terphenyl was adapted to the synthesis of quinquephenyl (I, R = R' = H). III (R = R' = H) was readily condensed with diethyl acetylenedicarboxylate in *o*-dichlorobenzene. Saponification gave a brilliant yellow solution containing potassium tetrahydroquinquephenyl tetracarboxylate. This substance was oxidized and decarboxylated by reaction with potassium fericyanide to give a 52% yield, after sublimation, of *p*-quinquephenyl, m.p. 385–390°.

Reaction of the bis-"ylide" derived from II with substituted cinnamaldehydes should ultimately lead to derivatives of *p*-quinquephenyl. When *p*-methylcinnamaldehyde was employed, 1,4-bis[4(*p*-tolyl)butadienyl]benzene (III; R = CH_3, R' = H; m.p. 315–320°; *Anal.* Calcd. for $C_{28}H_{26}$: C, 92.77; H, 7.23. Found: C, 92.6, 92.7; H, 7.14, 7.52) resulted. This was converted to 4,4''''-dimethyl-*p*-quinquephenyl (I; R = CH_3, R' = H; m.p. 400°; *Anal.*, Calcd. for $C_{32}H_{26}$: C, 93.62; H, 6.38. Found: C, 93.59, 93.65; H, 6.48, 6.57). 1,4-Bis(3-methyl-4-phenylbutadienyl)benzene (III; R' = CH_3, R = H; m.p. 235–237°; *Anal.* Found: 92.81, 92.77, H, 7.51, 7.31) was prepared by reaction of II with α-methylcinnamaldehyde. This was converted to 2',3'''-dimethyl-*p*-quinquephenyl (I; R' = CH_3, R = H; m.p. 217–218°; *Anal.* Found: C, 93.57, 93.61; H, 6.43, 6.46).

This is by far the best preparative method for *p*-quinquephenyl reported to date. The methylated compounds represent the first derivatives of this hydrocarbon synthesized, and by an unambiguous route.

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