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Reaction of the Methiodide of *N,N*-Dimethylaminomethylferrocene with Potassium Cyanide to Form Ferrocylacetonitrile[1]

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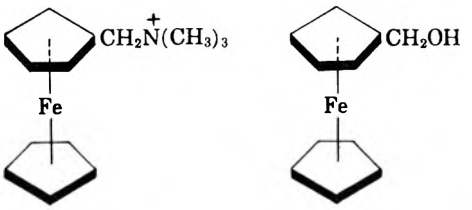
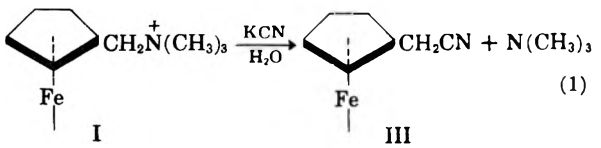
The methiodide of *N,N*-dimethylaminomethylferrocene was treated with potassium cyanide to afford ferrocylacetonitrile. This nitrile was converted to various derivatives. Evidence is presented for the structures of these compounds. An anomalous Leuckart reaction is reported.

The displacement of trimethylamine from quaternary ammonium ion I by hydroxide ion to form alcohol II has previously been described.[2]



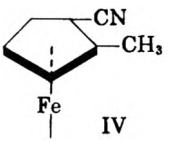
I II

The analogous displacement reaction with the cyanide ion to give nitrile III is described in the present paper.



I III (1)

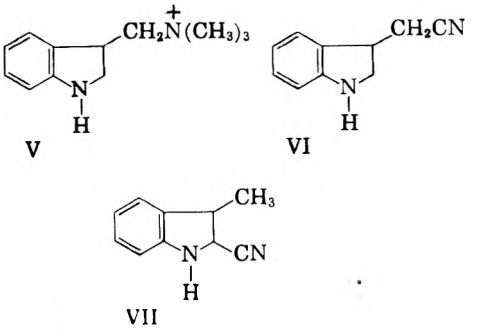
Before presenting the evidence that this nitrile has structure III, it should be mentioned that the erroneous structure IV for this nitrile was assigned recently in a communication.[3]



IV

This structural misinterpretation arose in the preparation of the tertiary amine from the reduction product of the nitrile employing the Eschweiler-Clarke modification of the Leuckart reaction.[4] This transformation has now been found to follow an anomolous course (see below).

It should also be mentioned that quaternary ammonium ion V has been observed by other workers[5] to produce with sodium cyanide both nitrile VI (60%) and nitrile VII (14%), which would be analogous to the ferrocene nitriles III and IV respectively.



V VI VII

(1) Supported by the Office of Ordnance Research, U. S. Army. Presented before the Southeastern Regional Meeting of the American Chemical Society, Nov. 15, 1957, Durham, N. C.

(2) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, 22, 355 (1957).

(3) C. R. Hauser, J. K. Lindsay, D. Lednicer, and C. E. Cain, *J. Org. Chem.*, 22, 717 (1957).

(4) See M. L. Moore, *Org. Reactions*, 5, 303, 307 (1949).

(5) See H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, 70, 1857 (1948).

Evidence for nitrile III. The nitrile prepared according to Equation 1 was hydrolyzed to the corresponding acid (VIII) which was reduced to the alcohol (IX) as indicated in Equation 2.

$$\underset{\text{III}}{RCH_2CN} \xrightarrow[C_2H_5OH]{KOH} \underset{\text{VIII}}{RCH_2COOH} \xrightarrow{LiAlH_4} \underset{\text{IX}}{RCH_2CH_2OH} \quad (2)$$

The acid obtained in this manner not only had a melting point in good agreement with that reported for acid VIII prepared from acetylferrocene (Wilgerodt reaction),[6] but its infrared spectrum was identical with that of a sample of acid VIII synthesized by this method.[7] Moreover, the acid exhibited an ultraviolet spectrum having ε maximum at 320 mμ, which is close to that of 323 mμ observed for hydroxymethyleneferrocene, and considerably different from that shown by ferrocenecarboxylic acid. This may be considered evidence for the lack of conjugation of the carboxyl group with the ring as in structure VIII.

Also, nitrile III was reduced to the corresponding primary amine X which was exhaustively methylated to form quaternary ammonium ion XI. This quaternary ion underwent β-elimination with potassium amide in liquid ammonia to form vinylferrocene (XII) as described previously.[8]

$$\underset{\text{III}}{RCH_2CN} \xrightarrow{LiAlH_4} \underset{\text{X}}{RCH_2CH_2NH_2} \xrightarrow[\text{(excess)}]{CH_3I}$$

$$\underset{\text{XI}}{RCH_2CH_2\overset{+}{N}(CH_3)_3} \xrightarrow[\text{liq. } NH_3]{KNH_2} \underset{\text{XII}}{RCH{=}CH_2} \quad (3)$$

The conversion of the nitrile III to vinylferrocene as represented by Equation 3 confirms its two-carbon sidechain.

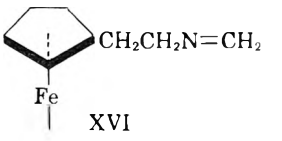
It should be pointed out that quaternary ammonium ion I, from which nitrile III was prepared (Equation 1), may be obtained from ferrocene in two convenient steps,[2] and that nitrile III should be a useful intermediate for the synthesis of not only the derivatives shown above but also of other compounds. A study is in progress on certain condensations involving the reactive methylenic hydrogens of this nitrile.

Anomalous Leuckart reaction. When the primary amine X prepared by the reduction of nitrile III was treated with formaldehyde and formic acid by the common method for effecting the *N,N*-dimethylation of primary amines,[4] a tertiary amine (XIII) was obtained. This tertiary amine produced a methiodide (XIV) that was different from, but isomeric with, the methiodide XI prepared by the exhaustive methylation of primary amine X. Whereas the methiodide XI underwent β-elimination with potassium amide to form vinylferrocene (Equation 3), the unidentified methiodide XIV produced a new tertiary amine XV that was homologous with tertiary amine XIII.

$$\text{X} \xrightarrow[HCO_2H]{HCHO} \underset{\text{XIII}}{C_{13}H_{19}FeN} \xrightarrow{CH_3I}$$

$$\underset{\text{XIV}}{C_{14}H_{19}Fe\overset{+}{N}CH_3I^-} \xrightarrow{KNH_2} \underset{\text{XV}}{C_{15}H_{21}FeN}$$

Apparently in the acidic medium of the first step of this series of reactions, there occurred a reaction other than (or in addition to) the expected *N,N*-dimethylation. It might be thought that the presumably first formed methylene derivative XVI underwent cyclization involving the ferrocene nucleus, since an acid catalyzed cyclization of similar Schiff bases from β-phenylethylamines has been reported.[9] However, the analytical data for our products have not been consistent with cyclic structures that might be expected from XVI.



XVI

EXPERIMENTAL[10]

Ferrocylacetonitrile (III). A solution of 84.4 g. (0.22 mole) of the methiodide of *N,N*-dimethylaminomethylferrocene[11] and 85 g. of potassium cyanide in 850 ml. of water was brought to reflux. Within 5 min. the copious evolution of trimethylamine was noted as an oil separated from the solution. At the end of 2 hr., the reaction mixture was cooled and extracted with ether. The ethereal solution was then washed well with water, percolated through anhydrous sodium sulfate, and taken to dryness. The solid residue thus obtained was recrystallized from hexane to afford 47.9 g. (95%) of the nitrile as bright yellow crystals, m.p. 76–79°. Since this compound darkens quickly on standing it is advisable to use it as soon as possible after preparation.

A small sample was recrystallized from hexane to a constant m.p. of 81–83°.

Anal. Calcd. for $C_{12}H_{11}NFe$: C, 64.03; H, 4.93; N, 6.22; Fe, 24.81. Found: C, 64.00; H, 4.98; N, 6.05; Fe, 24.52.

Ferrocylacetic acid (VIII). A suspension of 34.3 g. (0.15 mole) of the nitrile (III) in 340 ml. of ethanol was added to a solution of 85 g. of potassium hydroxide in 850 ml. of water. The reaction was then brought to reflux. After the evolution of ammonia had ceased (5 hr.), ethanol was removed *in vacuo* to bring the volume to about 100 ml. The residual suspension was dissolved in 800 ml. of water, extracted twice with ether and filtered. Acidification of the alkaline solution with 85% phosphoric acid afforded flaky

(6) P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

(7) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957); a sample of their acid was supplied by Dr. Rinehart.

(8) C. R. Hauser, J. K. Lindsay, and D. Lednicer, *J. Org. Chem.*, **23**, 358 (1958).

(9) J. S. Buck, *J. Am. Chem. Soc.*, **56**, 1769 (1934).

(10) All melting points are uncorrected and reported as obtained on a Fisher-Johns apparatus. All analyses are by Galbraith Laboratories, Knoxville, Tenn.

(11) See. Ref. 2. This compound was prepared from ferrocene generously supplied by Linde Air Products Co. (Dr. R. L. Pruett), Tonawanda, N. Y.

golden crystals. The product was collected by filtration and dried to yield 35.0 g. (94%) of ferrocylacetic acid, m.p. 152–156° (dec.); lit.,[4] 150–152°.

The analytical sample, m.p. 152–155° (dec.) was obtained by sublimation at 130–135° at 0.2 mm.

Anal. Calcd. for $C_{12}H_{12}O_2Fe$: C, 59.05; H, 4.96; Fe, 22.88. Found: C, 59.13; H, 5.07; Fe, 22.78.

2-Ferrocylethanol (IX). Ferrocylacetic acid (24.4 g., 0.10 mole) was placed in a Soxhlet extractor attached to a flask containing a stirred refluxing suspension of 4.1 g. of lithium aluminum hydride in 450 ml. of ether. The heating was continued until all the acid had dissolved (12 hr.). The reaction mixture (ice-cooled) was then treated with water and 400 ml. of 20% hydrochloric acid. The ethereal layer was quickly separated, washed with 5% aqueous sodium hydroxide and water, and then dried over sodium sulfate. The oil which remained when the ether was removed was dissolved in 600 ml. of 30–60° petroleum ether. When this was cooled in ice, the alcohol (19.7 g., 86%) was deposited as light orange needles, m.p. 32.5–33.5°.

Three recrystallizations in the manner described above afforded alcohol of m.p. 41–41.5°.

Anal. Calcd. for $C_{12}H_{14}OFe$: C, 62.61; H, 6.13; Fe, 24.27. Found: C, 62.70; H, 6.04; Fe, 24.11.

β-Ferrocylethylamine (X). A suspension of 20.0 g. (0.54 mole) of lithium aluminum hydride in 1 l. of ether was stirred under reflux for 1 hr. A solution of 77 g. (0.35 mole) of the nitrile in 500 ml. of ether was then added at such a rate as to produce gentle refluxing. After an additional 2 hr. reflux, the reaction mixture was cooled in ice, and 20 ml. of water, 15 ml. of 20% aqueous sodium hydroxide, and 90 ml. of water were added consecutively. The ethereal layer was then decanted from the solid and the latter washed several times with more ether. The combined extracts were then saturated with hydrogen chloride; the resulting salt was separated by decantation under nitrogen. The solid (still soaked with ether) was added to 2*N* sodium hydroxide and the mixture extracted with ether. The ethereal layer was then dried over sodium sulfate and evaporated *in vacuo* to afford 70 g. of dark brown oil. Distillation at 0.5 mm. afforded 51.2 g. (66%) of the primary amine, b.p. 118–120°.

A sample was redistilled at the same pressure to afford the amine, n_D^{25} 1.6155.

Anal. Calcd. for $C_{12}H_{15}NFe$: C, 62.91; H, 6.60; N, 6.11; Fe, 24.38. Found: C, 62.79; H, 6.88; N, 6.04; Fe, 24.15.

Treatment of a sample of the product with saturated alcoholic picric acid afforded the picrate as purple crystals, dec. 185° (dark, 180°).

Anal. Calcd. for $C_{18}H_{18}N_4O_7Fe$: C, 47.18; H, 3.96; N, 12.23; Fe, 12.19. Found: C, 47.28; H, 4.05; N, 12.34; Fe, 12.08.

N,N,N-Trimethyl-β-ferrocylethylammonium iodide (XI). A solution of 1 g. (0.005 mole) of the primary amine (X) in 10 ml. of acetonitrile was treated with 10 ml. of methyl iodide. Evolution of heat was noted. After 30 min. a solution of 0.84 g. (0.01 mole) of sodium bicarbonate in water was added. The two-phase reaction mixture was then stirred for 2 hr., and at the end of this time poured into 100 ml. of ether. The resulting tan precipitate was collected by filtration and recrystallized from water, to afford 1.30 g. (65%) of the quaternary iodide, m.p. 237°. Further recrystallization raised the m.p. of the salt to 240° (dec.).

A small sample (0.2 g.) was treated with 2 ml. of saturated alcoholic picric acid. The quaternary picrate was deposited as ruby red crystals, m.p. 150–152°.

Anal. Calcd. for $C_{21}H_{24}O_7N_4Fe$: C, 50.41; H, 4.84; N, 11.20; Fe, 11.16. Found: C, 50.63; H, 4.77; N, 11.00; Fe, 9.90.

Reaction of primary amine X with formic acid and formaldehyde. To a solution of 34.4 g. (0.15 mole) of the primary amine, in 39.3 g. (0.75 mole) of formic acid, 33.6 ml. (0.45 mole) of 37% formaldehyde was cautiously added. After the frothing had subsided the reaction mixture was warmed on a steam bath for 8 hr. The dark mixture was then cooled, treated with 75 ml. of 4*N* hydrochloric acid and evaporated to a dark syrup *in vacuo*. This was dissolved in water, and made basic with 40% sodium hydroxide. The amine was taken up in ether, washed with water, and dried. The oil which remained (35 g.) when the solvent was removed was distilled at 0.7 mm. to afford 24.2 g. (63%) of dark amber product XIII, b.p. 123–125°.

The b.p. of the analytical sample was 113° at 0.35 mm.

Anal. Calcd. for $C_{14}H_{19}NFe$: C, 65.38; H, 7.45; N, 5.45; Fe, 21.72. Found: C, 65.19; H, 7.32; N, 5.43; Fe, 21.37.

The picrate of this compound was obtained as golden plates, m.p. 160–161° (dec.), in the usual manner.

Anal. Calcd. for $C_{20}H_{22}N_4O_7Fe$: C, 49.40; H, 4.56; N, 11.52; Fe, 11.49. Found: C, 49.29; H, 4.69; N, 11.66; Fe, 11.31.

Methiodide XIV *of* XIII was formed by cautiously adding 13 ml. of methyl iodide to a solution of 13 g. of the tertiary amine in 25 ml. of methanol. The solid which came out when the solution was cooled was collected by filtration to afford 18.3 g. of the methiodide, m.p. 258° (dec.).

A sample was recrystallized from methanol ether to afford golden needles, m.p. 258° (dec.).

Anal. Calcd. for $C_{15}H_{22}NIFe$: C, 45.14; H, 5.56; N, 3.51; Fe, 13.99. Found: C, 45.34; H, 5.58; N, 3.51; Fe, 14.15.

Reaction of methiodide XIV *with potassium amide.* To a solution of 0.058 mole of potassium amide in 200 ml. of liquid ammonia there was added in portions over 30 min. 11.6 g. (0.029 mole) of the quaternary salt. Each addition was accompanied by a transient red color. At the end of 2 hr. a small amount of ammonium chloride was added to the brown reaction mixture and the solvent allowed to evaporate. The residue was washed several times with ether and the washes were combined. The ethereal solution was then washed with water, dried, and the solvent removed. A red oil having a strong amine odor XV remained (6.0 g., 77%). The infrared spectrum of this exhibits no N—H band but does suggest a ferrocene derivative substituted in one ring only.

One-half gram of the amine was treated with saturated ethanolic picric acid to give 0.83 g. (90% assuming XV to be a homolog of XIII) of orange crystals, m.p. 130–138°. This was recrystallized from ethanol to a constant m.p. of 138–140°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7Fe$: C, 50.41; H, 4.84; N, 11.20; Fe, 11.16. Found: C, 50.20; H, 4.88; N, 11.29; Fe, 11.24.

The methiodide was prepared from 5.25 g. of the amine in 15 ml. of acetonitrile and 5 ml. of methyl iodide. The salt (5.9 g., 74%) was deposited as orange crystals, charring at 178°. A sample was recrystallized three times from acetonitrile-ether.

Anal. Calcd. for $C_{15}H_{26}NIFe$: C, 46.51; H, 5.86; N, 3.39; Fe, 13.52. Found: C, 46.26; H, 5.67; N, 3.41; Fe, 13.64.

DURHAM, N. C.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Reactions of α-Ketols Derived from Tertiary Acetylenic Carbinols. I. Preparation and Low Pressure Hydrogenation[1]

G. F. HENNION AND E. J. WATSON[2]

Received October 18, 1957

A general procedure has been developed for the hydration of tertiary acetylenic carbinols and has been used for the preparation of six α-ketols in high yields from the corresponding commercially available carbinols. The ketols were easily converted to the *vic*-glycols by low pressure hydrogenation using a platinum oxide catalyst in the presence of alkali.

Acetylenic carbinols are converted to the corresponding α-ketols by hydration in acidic aqueous solution in the presence of dissolved mercuric salts.[3] The reaction has been accomplished in various ways, sometimes in good yield and sometimes not, and no general procedure has yet been recommended. Since assorted tertiary acetylenic carbinols are now commerically available and hold promise as intermediates for syntheses, especially in the pharmaceutical field, renewed interest in these compounds is evident in the current literature. The hydration reaction, for example, has been employed as the first step in the preparation of simple analogs of cortisone.[4]

$$RR'C(OH)-C\equiv CH + H_2O \longrightarrow RR'C(OH)-COCH_3$$

Since acetylenic compounds (including most of the carbinols) commonly are not water soluble, experience in this laboratory has shown that the hydration reactions are best carried out in mixed aqueous solvents, notably well in aqueous methanol.[5] It has now been found that use of aqueous methanol containing only a 50% excess of water over that required by theory, with sulfuric acid and mercuric oxide as catalysts, provides an excellent general procedure which permits easy recovery of the product in high yield. The reaction is best carried out at a temperature near the reflux point, usually self-maintained since it is very exothermic. Surprisingly, an induction period is frequently observed and it is therefore imperative that the acetylenic carbinol be added to the aqueous methanol-catalyst mixture in small amount at first, delaying further addition until reaction is evident. Otherwise unreacted carbinol may accumulate so that the reaction finally becomes very vigorous and entirely uncontrollable.

The general procedure described below is a mild one and in special cases more strenuous conditions may be needed. Thus diisopropylethynylcarbinol did not respond to this method; in this case hydration may be achieved (in 40–50% yield) by boiling with 20% aqueous sulfuric acid containing mercuric oxide.[6] When the acetylenic alcohol is particularly sensitive to acids, as in the case of phenylmethylethynylcarbinol, control of acid concentration and temperature become more critical.[5c]

α-Ketols have been converted to the corresponding glycols by reduction with sodium in ethanol,[7] by hydrogenation in the presence of Raney nickel at high pressure,[8] by reaction with lithium aluminum hydride,[6] and, in a few cases, by low pressure hydrogenation with platinum oxide catalyst.[4c] The low pressure method was chosen for further study.

When 1-acetylcyclohexanol was hydrogenated as previously described by Stacy and Mikulec,[4c] reaction proceeded very slowly as reported. Addition of acid suppressed reaction completely. On the other hand, addition of a small amount of ethanolic sodium hydroxide resulted in the desired acceleration.

The ketols are described in Table I and the glycols in Table II.

EXPERIMENTAL

Hydration of acetylenic carbinols. A two-liter, three-neck flask was fitted with a mercury-sealed stirrer and a reflux condenser. In the flask was placed 15 grams of red HgO and a solution of 10 ml. of concd. H_2SO_4 in 135 ml. (7.5 moles) of water. The warm mixture was stirred for three to five min. and then 385 ml. of methanol was added. A bright yellow suspension formed. The third neck of the flask was closed with a stopper bearing a thermometer and an addition funnel. The catalyst mixture was heated to 60–65°.

(1) Paper LXVIII on substituted acetylenes; previous paper, G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).

(2) Eli Lilly Co. Fellow, 1954–1956. Abstracted in part from the Ph.D. Dissertation of E. J. W.

(3) For review and references see A. W. Johnson, *Acetylenic Compounds. Vol. I. The Acetylenic Alcohols*, Edw. Arnold Co., London, 1946, pp. 102–105.

(4) (a) J. D. Billimoria, N. F. Maclagan, *J. Chem. Soc.*, 3067 (1951); 2626 (1953); 3257 (1954); 1126 (1955). (b) D. Papa, H. F. Ginsberg, and F. J. Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954). (c) G. W. Stacy and R. A. Mikulec, *J. Am. Chem. Soc.*, **76**, 524 (1954).

(5) (*a*) G. F. Hennion, R. J. Thomas, K. N. Campbell, R. B. Davis, D. E. Maloney, and B. R. Fleck, *J. Am. Chem. Soc.*, **60**, 718 (1938); (*b*) **71**, 2813 (1949); (*c*) **77**, 3253 (1955).

(6) W. J. Hickenbottom, A. A. Hyatt, and M. B. Sparke, *J. Chem. Soc.*, 2529 (1954).

(7) (a) A. Favorski, *J. Russ. Phys. Chem. Soc.*, **44**, 1347 (1912); *Chem. Abstr.*, **7**, 984 (1913). (b) I. N. Nazarov and A. N. Elizarova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 195 (1940); *Chem. Abstr.*, **36**, 742 (1942).

(8) (a) G. Bernard and J. Colonge, *Bull. soc. chim. France*, **12**, 356 (1945). (b) E. D. Bergmann, U. S. Patent 2,539,806 (1951); *Chem. Abstr.*, **45**, 6655 (1951). (c) E. D. Bergmann and D. F. Herman, *J. Appl. Chem.*, **3**, 42 (1953).

TABLE I

α-KETOLS, RR'C(OH)COCH$_3$, FROM TERTIARY ACETYLENIC CARBINOLS

R	R'	Yield (%)	B.P. (°C./Mm)	n_D^{25}	Reference
CH_3	CH_3	81	46–47/21	1.4129	[a]
CH_3	C_2H_5	80	54–56/21	1.4198	[b]
C_2H_5	C_2H_5	88	61–62/20	1.4231	[c]
CH_3	i-C_4H_9	94	69–70/17	1.4260	[d]
—$CH_2(CH_2)_3CH_2$—		91	105–107/26	1.4660	[e]
CH_3	C_6H_5	92[g]	78–85/1.4[g]	1.5180[g]	[f]

[a] M. S. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1952), gives b.p. 137°, n_D^{26} 1.4176; E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3131 (1953), give b.p. 49–51°/17 mm., n_D^{24} 1.4158. [b] G. F. Hennion *et al.*, (ref. 5b), give b.p. 70–73°/50 mm., n_D^{25} 1.4200. [c] R. Locquin and W. Sung, *Compt. rend.*, **176**, 516 (1923), give b.p. 56–57°/13 mm., n_D^{11} 1.4303. [d] D. Papa *et al.*, (ref. 4b), give b.p. 68–70°/12 mm., n_D^{23} 1.4300. [e] G. W. Stacy and R. A. Mikulec (ref. 4c), give b.p. 92–94°/15 mm., n_D^{25} 1.4670. [f] G. F. Hennion and R. Fleck (ref. 5c), give b.p. 99–100°/3 mm., n_D^{25} 1.5215. [g] This ketol could be prepared in good yield only by applying the method of Hennion and Fleck.[5c] The yield and physical constants are for once distilled product suitable for hydrogenation. In all other cases physical constants were determined after redistillation.

TABLE II

vic-GLYCOLS, RR'C(OH)CH(OH)CH$_3$, FROM α-KETOLS

R	R'	Yield (%)[a]	B.P. (°C./Mm.)	n_D^{25}	d^{25}	Ref.
CH_3	CH_3	88	173–174/ atm.	1.4361	0.9688	[b]
CH_3	C_2H_5	94	63/0.5	1.4440	0.9638	[c]
C_2H_5	C_2H_5	97	109/24	1.4503	0.9612	[d]
CH_3	i-C_4H_9	99	111/21	1.4450	0.9285	[e]
—$CH_2(CH_2)_3$-CH_2—		96	87/1.4	1.4840		[f]
CH_3	C_6H_5	78	106/1.6	1.5301		[g]

[a] Yields are for once distilled products; physical constants were determined after redistillation. [b] I. N. Nazarov and A. N. Elizarova, (ref. 7b), give b.p. 170–176°, n_D^{17} 1.4290. *Cf.*, Beilstein, 4th ed., Vol. I, p. 482. [c] H. van Risseghem, *Bull. soc. chim. France*, 177 (1952), gives b.p. 93°/15 mm., d^{15} 0.9750. [d] D. Gauthier, *Compt. rend.*, **152**, 1100 (1911), gives b.p. 105°/17 mm. [e] E. D. Bergmann (refs. 8b,c), gives b.p. 84–85°/7 mm., n_D^{20} 1.4455, d^{20} 0.9157. [f] G. W. Stacy and R. A. Mikulec, (ref. 4c), give b.p. 120–121°/10 mm., n_D^{25} 1.4843, d^{25} 1.0422. [g] T. I. Temnikova, *J. Gen. Chem. U.S.S.R.*, **8**, 1022 (1938); *Chem. Abstr.*, **33**, 3777 (1939), gives b.p. 153.5–154.5°/17 mm.

The acetylenic carbinol (5 moles) was placed in the funnel and about 5 to 10 ml. was admitted to the flask after the heat source had been removed. Either immediately or after a short induction period, the reaction mixture became clear and nearly colorless and the temperature began to rise.

When the initial portion of the acetylenic carbinol had reacted, a white cloudy suspension formed and the temperature began to drop slowly. The remainder of the acetylenic carbinol then was added dropwise at such a rate as to maintain the temperature at about 65°. It is important to ascertain that the reaction actually has started by observing the rise in temperature and the appearance of the cloudy suspension. If these are not observed, the reaction mixture is refluxed for 5 to 10 min., allowed to cool to 60–65° and the procedure repeated. The reaction mixture gradually becomes darker during the reaction and metallic mercury appears (grey sludge). The addition requires about 4 hr. The reaction mixture was allowed to cool overnight and the next day was refluxed for 0.5 hr. After allowing the reaction mixture to cool, 100 grams of anhydrous sodium carbonate was added to neutralize the acid and to absorb most of the excess water. Although the reaction mixture can be filtered immediately, it is best to allow the solids to settle overnight.

As much of the liquid as possible was decanted through a Büchner funnel. The reaction flask and the solid material were washed with about 30 ml. of methanol and this was poured through the filter. The filtrate was transferred to a two-liter flask for distillation. Anhydrous potassium carbonate (5 g.) was added to suppress acidification due to the thermal decomposition of small amounts of organomercury compounds. Methanol was removed by distillation through a helix-packed column at atmospheric pressure and the residual liquid was distilled at an appropriate pressure. Some water and a small amount of organic material usually distilled over before the desired product and all such foreruns were discarded. The ketol was then redistilled.

2-Methyl-2,3-butanediol. 3-Hydroxy-3-methyl-2-butanone (25.5 g., 0.25 mole) in 100 ml. of ethanol was hydrogenated in the Parr low pressure apparatus using 0.25 g. of PtO_2 as catalyst. Hydrogen uptake (0.25 mole) was complete in one hour. A second run was carried out under the same conditions. The reaction mixtures were filtered and each hydrogenation vessel was rinsed twice with 10 ml. portions of ethanol, the solvent then being poured through the filter. The combined filtrates were placed in a dropping funnel and gradually admitted to a heated 100-ml. Claisen flask in order to remove the ethanol. The residual liquid was distilled to give 46.1 g. (88% yield) of 2-methyl-2,3-butanediol, b.p. 169–172°, n_D^{25} 1.4345.

2-Methyl-2,3-butanediol monophenylurethane. 2-Methyl-2,3-butanediol (2.08 g., 0.02 mole) in a 50-ml. Erlenmeyer flask was treated with 2.38 g. of phenyl isocyanate overnight at room temperature. The clear, hard glass which formed was induced to crystallize by scratching. One recrystallization from CCl_4 gave 2.8 g. (63% yield) of crystals, m.p. 128–130° (lit.[9] m.p. 125.5°).

3-Methyl-2,3-pentanediol. 3-Hydroxy-3-methyl-2-pentanone (29.0 g., 0.25 mole) in 60 ml. of ethanol was hydrogenated as previously described using 0.25 g. of PtO_2 and 1 ml. of 0.1*N* NaOH in ethanol. The theoretical amount of hydrogen was absorbed in 100 min. In another experiment, identical except for the addition of 3 ml. of 0.1*N* base, hydrogen uptake was complete in 45 min. The reaction mixtures were filtered, all filtrates and washings combined, and the ethanol distilled off. The residual liquid, upon distillation at reduced pressure, gave 55.8 g. (94% yield) of 3-methyl-2,3-pentanediol, b.p. 68–70° at 2.7 mm., n_D^{25} 1.4438. Without the addition of base, the hydrogenation required 5 hr.

3-Methyl-2,3-pentanediol monophenylurethane. When the glycol was treated with phenyl isocyanate as previously described, there was obtained, after one recrystallization from CCl_4, a 55% yield of white crystals, m.p. 131–133°. An additional recrystallization from CCl_4 raised the m.p. to 134–136°.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 65.64; H, 8.09.

3-Ethyl-2,3-pentanediol. 3-Hydroxy-3-ethyl-2-pentanone (39.1 g., 0.3 mole) in 75 ml. of ethanol was hydrogenated using 0.30 g. of PtO_2 and 10 ml. of 0.1*N* base, 3 hr. 40 min. being required. The time required for hydrogenation was not shortened in another run using 20 ml. of base. 3-Ethyl-2,3-pentanediol was obtained from the two runs in 90% and in 97% yield, respectively, b.p. 105–109° at 24 mm., n_D^{25} 1.4498 and 1.4490.

No crystalline phenylurethane or α-naphthylurethane could be prepared.

3,5-Dimethyl-2,3-hexanediol. When 3-hydroxy-3,5-dimethyl-2-hexanone (43.3 g., 0.3 mole) was hydrogenated using

(9) L. S. Dedusenko, *J. Gen. Chem. U.S.S.R.*, **9**, 1294 (1939); *Chem. Abstr.*, **34**, 715 (1940).

75 ml. of ethanol, 0.30 g. of PtO_2 and 20 ml. of 0.1*N* base, hydrogen uptake was complete in 40 min., and upon distillation 43.5 g. (99% yield) of 3,5-dimethyl-2,3-hexanediol was obtained, b.p. 110–113° at 23 mm., n_D^{25} 1.4446.

1-(1'-Hydroxyethyl)cyclohexanol. Hydrogenation of 1-acetylcyclohexanol (42.6 g., 0.3 mole) using 75 ml. of ethanol, 0.30 g. of PtO_2, and 5 drops of 0.1*N* ethanolic NaOH took 30 min. (without base, 2 runs required 3 hr. each). Upon distillation there was obtained 41.7 g. (96% yield) of 1-(1'-hydroxyethyl)cyclohexanol, b.p. 75–85° at 0.8 mm., n_D^{25} 1.4828.

No phenylurethane or α-naphthylurethane could be prepared. However, esterification with 3,5-dinitrobenzoic acid using the method of Brewster[10] gave the monoester in 94% yield, m.p. 122–125° after one recrystallization from ethanol (lit.[4c] m.p. 122.5–123.5°).

2-Phenyl-2,3-butanediol. Hydrogenation of 25.3 g. (0.15 mole) of 3-hydroxy-3-phenyl-2-butanone in 50 ml. of ethanol using 0.20 g. of PtO_2 and 10 drops of 0.1*N* NaOH in ethanol required 1 hr. 40 min. and gave 19.9 g. (78% yield) of 2-phenyl-2,3-butanediol, b.p. 106–113° at 2.0 mm. When no base was used, hydrogenation required 5.5 hr. Because of the possibility of hydrogenolysis a sample was submitted for analysis.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.90; H, 8.77.

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NOTRE DAME, IND.

(10) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Reactions of α-Ketols Derived from Tertiary Acetylenic Carbinols. II. Bromination and Bimolecular Transannular Dehydration[1]

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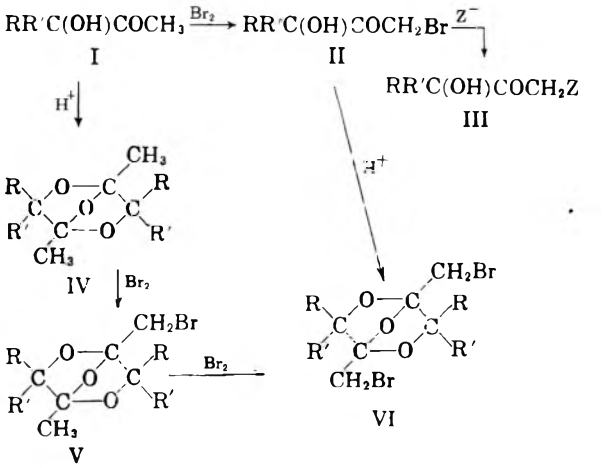
α-Ketols, $RR'C(OH)COCH_3$, derived from tertiary acetylenic carbinols, have been found to be susceptible to a bimolecular condensation reaction in the presence of acid leading to 1,4-dimethyl-3,3,6,6-tetraalkyl-2,5,7-trioxabicyclo[2.2.1]heptanes (IV). This reaction often intervenes seriously in the bromination of the ketones so that most of the bromination product is the corresponding 1,4-bis(bromomethyl)trioxabicycloheptane (VI) rather than the anticipated bromomethyl ketone (II).

Since a variety of α-ketols are readily accessible in high yield from commercially available tertiary acetylenic carbinols,[3] efforts are under way in this laboratory to develop syntheses from the ketols. One obvious approach to this end is provided by bromination followed by various nucleophilic displacement reactions, I → II → III, as shown below (Z = −OH, −OCOR, $-NR_2$, etc.) We wish to report now our experience with the bromination step, I → II.



At the outset of this work interest focused chiefly on dihydroxyacetone-type end products (III, Z = −OH; simple analogs of cortisone) since a significant amount of similar work had been reported by Billimoria and Maclagen,[4] especially in the case of 1-acetylcyclohexanol [I, R and R' = $-(CH_2)_5-$]. The latter compound was found to brominate readily in carbon tetrachloride solution. When the solvent was removed and the residue subjected to hydrolysis under mild conditions (with sodium formate in methanol), a crystalline product, m.p. 101–111°, was recovered. Several crystallizations raised the melting point to 115–118°, indicating immediately that the product was not 1-hydroxyacetylcyclohexanol,[4] m.p. 86–87°, but rather an unidentified dimeric bromination product mentioned by Billimoria.[4] This substance surpris-

(1) Paper LXIX on substituted acetylenes; previous paper, ref. (3).

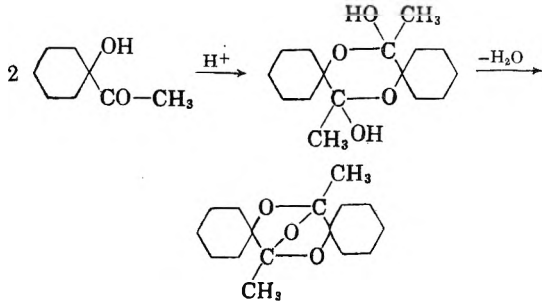
(2) Eli Lilly Co. Fellow, 1954–1956. Abstracted from a portion of the Ph.D. Dissertation of E. J. W.

(3) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 656 (1958).

(4) J. D. Billimoria and N. F. Maclagen, *J. Chem. Soc.*, 3067 (1951); 3257 (1954). See also D. Papa, H. F. Ginsberg, and F. J. Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954) and G. W. Stacy, R. A Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, **76**, 524 (1954); **79**, 3587 (1957).

ingly showed no carbonyl or hydroxyl absorption in the infrared, contained bromine but was stable to alkaline hydrolysis, did not react with acetic anhydride or with semicarbazide, etc. This evidence, coupled with analysis and molecular weight determination, showed the product to be 1,4-bis-(bromomethyl) - 3,3,6,6 - bis(pentamethylene)-2,5,7-trioxabicyclo[2.2.1]heptane[5] (VI, R and R′ = $-(CH_2)_5-$).

In order to determine whether this product arose *via* II or IV, 1-acetylcyclohexanol in carbon tetrachloride was treated with HBr (also with HCl) and facile conversion to 1,4-dimethyl-3,3,6,6-bis(pentamethylene)-2,5,7-trioxabicyclo[2.2.1]heptane[6] (IV, R and R′ = $-(CH_2)_5-$) was observed. These findings are in accord with the fact that certain α-hydroxyketones spontaneously cyclize to 2,5-dihydroxy-1,4-dioxanes;[7a] subsequent transannular dehydration is, of course, possible[7b] in the instances cited above, for example:



Similar experiments were then carried out with 3-hydroxy-3-methyl-2-butanone (I, R = R′ = CH_3). Treatment with acids under mild conditions gave the known 1,3,3,4,6,6-hexamethyl-2,5,7-trioxabicyclo[2.2.1]heptane[8] (IV, R = R′ = CH_3) while bromination in carbon tetrachloride yielded the corresponding dibromo substitution product (VI, R = R′ = CH_3) previously prepared by Scheibler and Fischer.[9]

Bromination of 3-hydroxy-3-ethyl-2-pentanone (I, R = R′ = C_2H_5) in carbon tetrachloride, however, gave a 45% yield of the bromoketone (II, R R′ = C_2H_5) indicating that the cyclization reactions to IV and/or VI may be subject to steric hindrance by the groups R and R′. Other examples of the action of bromine and of acid on α-ketols are cited in the Experimental section. It will be noted that a monobromo derivative of the trioxabicycloheptane type (V, R = R′ = CH_3) was isolated from two of the experiments.

The influence of solvents on the bromination step (I → II) was examined in a preliminary manner and it was observed that the bromoketones (II) may be obtained, although not in high yield, when the reaction is carried out in acetic acid, in ether or along with dioxane in ether. In two instances cited in the Experimental section the bromoketones were hydrolyzed successfully to known dihydroxyacetone-type end products (III, Z = −OH).

EXPERIMENTAL

The α-ketols used were prepared from acetylenic carbinols as described in the previous paper.[3]

Bromination of 1-acetylcyclohexanol in CCl_4 and attempted hydrolysis. 1-Acetylcyclohexanol (44.0 g., 0.31 mole) and 250 ml. of CCl_4 were placed in a 500-ml. Erlenmeyer flask. Bromine (17 ml., 53 g., 0.33 mole) was added followed by 2 ml. of 48% HBr and 3 ml. of glacial acetic acid. HBr evolution began after 10 min. The flask was then placed in an ice bath. Bromination was complete in another 10 min. The clear, yellow solution was poured into a separatory funnel with an equal volume of ice water. The organic layer was separated and washed with $NaHCO_3$ solution until there was no more effervescence. The neutral reaction mixture was placed in a 1-l. flask with 35 g. (0.51 mole) of sodium formate and 150 ml. of methanol. The mixture was refluxed for 15 hr., then cooled in an ice-salt bath and filtered through a sintered glass funnel. Solvents were removed by distillation until solid began to settle out. The solid isolated was proved to be sodium formate, 3.42 g. The filtrate was placed in the refrigerator and a white solid crystallized slowly. When dry this second white solid weighed 11.2 g., m.p. 95–100°. After one recrystallization from ethanol it weighed 7.0 g., m.p. 101–111°. A second crop weighed 1.31 g., m.p. 99–103°. Three additional recrystallizations of the solid from ethanol raised the m.p. to 115–118°. This substance was identified as 1,4-bis(bromomethyl)-3,3,6,6-bis(pentamethylene)-2,5,7-trioxabicyclo[2.2.1]heptane[5] as explained above.

Anal. Calcd. for $C_{16}H_{24}Br_2O_3$: C, 45.30; H, 5.70; Br, 37.68. Found: C, 45.36; H, 5.75; Br, 37.58.

When the experiment was repeated with the omission of the attempted hydrolysis, 34.6 g. of product (53% yield) was obtained, m.p. 106–111°.

Bromination of 3-hydroxy-3-methyl-2-butanone in CCl_4. Bromine (13 ml., 40 g., 0.25 mole) in 100 ml. of CCl_4 was added in small portions to a solution of 12.8 g. (0.125 mole) of 3-hydroxy-3-methyl-2-butanone in 100 ml. of CCl_4. Bromination was rapid after a 5-min. induction period and the temperature rose to 45°. A small upper layer (water) appeared at the end of the reaction. The mixture was washed with ice water and neutralized with $NaHCO_3$ solution as above. The solvent was removed by distillation first at atmospheric pressure and finally at reduced pressure. The residue was dissolved in ethanol, cooled, and enough water added to cause an oil to separate. The oil was redissolved by heating and the solution cooled slowly yielding 18.1 g. (42% yield) of a white solid, m.p. 54–64°. Recrystallization from 40 ml. of 90% methanol gave 1,4-bis(bromomethyl)-3,3,6,6-tetramethyl-2,5,7-trioxabicyclo[2.2.1]heptane, m.p. 66–68° (lit.[9] m.p. 64–65°).

Anal. Calcd. for $C_{10}H_{16}Br_2O_3$: C, 34.91; H, 4.69; Br, 46.46. Found: C, 35.07; H, 4.87; Br, 46.63.

Bromination of 3-hydroxy-3-methyl-2-pentanone in CCl_4. In a 500-ml. Erlenmeyer flask was placed 58.1 g. (0.5 mole) of 3-hydroxy-3-methyl-2-pentanone in 100 ml. of CCl_4. A solution of 26 ml. (0.5 mole) of bromine in 75 ml. of CCl_4 was then added in small portions. Bromination was rapid at room

(5) Alternative name: 8,16-bis(bromomethyl)-8,16-epoxy-7,15-dioxadispiro[5.2.5.2]hexadecane.

(6) Alternative name: 8,16-dimethyl-8,16-epoxy-7,15-dioxadispiro[5.2.5.2]hexadecane.

(7) (a) J. C. Sheehan, R. C. O'Neill, and M. A. White, *J. Am. Chem. Soc.*, **72**, 3376 (1950). (b) I. Elphimoff-Felkin and B. Tchoubar, *Bull. soc. chim. France*, 551 (1952).

(8) G. F. Hennion and J. F. Froning, *J. Am. Chem. Soc.*, **62**, 653 (1940).

(9) H. Scheibler and A. Fischer, *Ber.*, **55**, 2903 (1922). Structures assigned by these authors have since been shown to be incorrect: see ref. (8) and I. N. Nazarov and A. N. Elizarova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 203 (1940); *Chem. Abstr.*, **36**, 744 (1942).

temperature. A cold water bath was used to hold the reaction temperature at about 35°. The reaction mixture was poured into a funnel containing 500 ml. of ice water. The layers were separated and the CCl_4 layer washed with water again, then with $NaHCO_3$ solution and finally with brine. After drying over anhydrous Na_2SO_4, the material was filtered into a flask and the CCl_4 removed by distillation at reduced pressure. A little MgO was added to the distilling flask and the residual liquid distilled to give 52.3 g. of a liquid, b.p. 113–120° at 0.7 mm., n_D^{25} 1.5050 (56% yield of 1,4-bis(bromomethyl)-3,6-dimethyl-3,6-diethyl-2,5,7-trioxabicyclo[2.2.1]heptane). This material was redistilled into six fractions: (*1*) b.p. 89–108° at 0.75 mm., 2.02 g., n_D^{25} 1.5018; (*2*) b.p. 108–112° at 0.75 mm., 2.21 g., n_D^{25} 1.5020; (*3*) b.p. 112° at 0.75 mm. to 114° at 0.35 mm., 4.58 g., n_D^{25} 1.5030; (*4*) b.p. 114–116° at 0.35 mm., 12.05 g., n_D^{25} 1.5049; (*5*) b.p. 116° at 0.35 mm., 12.84 g., n_D^{25} 1.5053; (*6*) b.p. 116–120° at 0.35 mm., 11.97 g., n_D^{25} 1.5058. Material from fractions (*4*), (*5*), and (*6*) was redistilled and a center cut taken for analysis, b.p. 114° at 0.7 mm., n_D^{25} 1.5058.

Anal. Calcd. for $C_{12}H_{20}Br_2O_3$: C, 38.73; H, 5.42; Br, 42.95. Found: C, 38.25; H, 5.35; Br, 44.14.

1-Bromo-3-hydroxy-3-methyl-2-pentanone. A. By bromination in acetic acid. In a one-liter Erlenmeyer flask was placed 85.8 g. (0.738 mole) of 3-hydroxy-3-methyl-2-pentanone in 100 ml. of glacial acetic acid and 25 ml. of water. A solution of 120 g. (0.75 mole) of bromine in 200 ml. of glacial acetic acid and 50 ml. of water was added to the ketol solution. About 2–3 ml. of 48% HBr was added and the reaction mixture heated to 50°. After about 4–5 hr. the reaction mixture was a clear, pale yellow color. The solution was poured into a separatory funnel containing 1 liter of ice water and 500 ml. of ether. The ether layer was separated and washed with 500 ml. of water. The two water layers were combined and extracted with 500 ml. of ether which was then combined with the original ether layer. The combined ethereal extract was treated with water to which solid $NaHCO_3$ was added until there was no more effervescence. The water layer was drained off, the ether layer was washed with brine, and then dried over Na_2SO_4. A little MgO was added as a stabilizer.

The ethereal solution was then filtered into a separatory funnel and gradually added to a heated Claisen flask so that ether could be removed by distillation. A little MgO was added to the residual liquid and it was distilled under reduced pressure into six fractions: (*1*) b.p. 29.5° at 1.5 mm. to 67° at 1.0 mm., 3.14 g., n_D^{25} 1.4490; (*2*) b.p. 67–74° at 0.9 mm., 4.0 g., n_D^{25} 1.4751; (*3*) b.p. 74° at 0.9 mm. to 82° at 0.85 mm., 15.37 g., n_D^{25} 1.4799; (*4*) b.p. 82° at 0.85 mm. to 85.5° at 0.75 mm., 52.6 g., n_D^{25} 1.4838; (*5*) b.p. 85.5–88° at 0.75 mm., 14.85 g., n_D^{25} 1.4885; (*6*) b.p. 88° at 0.75–0.8 mm., 9.42 g., n_D^{25} 1.4952. Combined weight of fractions *3,4,5*, and *6* was 92.2 g., a 64% yield of 1-bromo-3-hydroxy-3-methyl-2-pentanone. Redistillation gave 73.6 g., 45% yield, of material b.p. 73° at 0.55 mm. to 81° at 0.35 mm., n_D^{25} 1.4822 [lit.[10] b.p. 43–45° (oil bath temp.) at 0.005 mm., n_D^{25} 1.4831].

B. *By bromination with dioxane dibromide in ether.* In a 500-ml. flask was placed 50 ml. of dioxane. Bromine (22 ml., 0.43 mole) was added, the mixture cooled in an ice bath, and diluted with 200 ml. of ether. To the slurry thus formed was added a solution of 51.5 g. (0.44 mole) of 3-hydroxy-3-methyl-2-pentanone in 100 ml. of ether. Decolorization took 2–3 min. The mixture was washed and dried as usual and the ether was removed by distillation. The residual liquid was distilled giving: fraction (*1*), b.p. 32° at 3.5 mm. to 74° at 1.5 mm., 10.9 g., n_D^{25} 1.4619; fraction (*2*), b.p. 74° at 1.5 mm. to 84° at 1.3 mm., 37.4 g., n_D^{25} 1.4865. Fraction (*2*) represents a 45% yield of the bromoketol. This portion was redistilled into five fractions: (*1*) b.p. 78° at 2.6 mm. to 79° at 2.5 mm., 1.15 g., n_D^{25} 1.4760; (*2*) b.p. 79–83° at 2.5 mm., 4.40 g., n_D^{25} 1.4808; (*3*) b.p. 83–83.5° at 2.5 mm., 6.25 g., n_D^{25} 1.4820; (*4*) b.p. 83.5–81° at 2.5 mm., 8.14 g., n_D^{25} 1.4826; (*5*) b.p. 81–84° at 2.5 mm., 6.22 g., n_D^{25} 1.4830.

A sample of fraction (*4*) was analyzed.

Anal. Calcd. for $C_6H_{11}BrO_2$: C, 36.94; H, 5.69; Br, 40.97. Found: C, 36.42; H, 5.72; Br, 41.87.

Another experiment, identical with the above except that the bromine was added to a solution of dioxane in ether, gave a 48% yield of the bromoketol.

Bromination of 3-hydroxy-3-ethyl-2-pentanone. A. *In CCl_4.* One-half mole (65.1 g.) of 3-hydroxy-3-ethyl-2-pentanone was brominated in CCl_4 as described above. Distillation *in vacuo* provided three fractions: (*1*) b.p. 30° at 1.8 mm. to 55° at 1.2 mm., 7.4 g., n_D^{25} 1.4295; (*2*) b.p. 55° at 1.2 mm. to 74° at 1.0 mm., 12.4 g., n_D^{25} 1.4600; (*3*) b.p. 74° at 1.0 mm. to 86° at 1.3 mm., 47.7 g., n_D^{25} 1.4827; residue, 16.5 g. Fraction (*3*) represents a 45% yield of 1-bromo-3-hydroxy-3-ethyl-2-pentanone.

B. *In acetic acid.* The experiment was repeated in acetic acid as described above. Two distillations gave 36.5 g. (35% yield), b.p. 76–79° at 1.3 mm., n_D^{25} 1.4782 (lit.[11] b.p. 116–118° at 15 mm., n_D^{17} 1.4788).

Bromination of 3-hydroxy-3-methyl-2-butanone in ether followed by reaction with 10% NaOH. A two-liter, three-neck flask was fitted with a mercury-sealed, motor-driven stirrer, a reflux condenser, and a stopper bearing both an addition funnel and a thermometer. Ether (500 ml.) was added and the flask was cooled in an ice bath. Bromine (80 g., 0.5 mole) was added and stirring started. Then 51.1 g. (0.5 mole) of 3-hydroxy-3-methyl-2-butanone was added and the bromination conducted as above. In the funnel was placed 400 ml. of a 10% NaOH solution. About 180 ml. of this was added, in small portions, rather rapidly, the rate of the addition being determined by the ability of the cooling bath to prevent the ether from refluxing too vigorously. At this point several drops of phenolphthalein solution were added. The addition of NaOH solution was continued, the solution being allowed to discharge the pink color before more alkali was added. The neutral solution required about two days to separate into two distinct layers. The layers were separated, the ethereal layer dried and the ether removed by distillation. The yellowish residual liquid was distilled at reduced pressure to give 18.9 g. of a liquid, b.p. 117–126° at 22 mm., n_D^{25} 1.4655. The reaction was repeated and yielded another 23.03 g., b.p. 80–90° at 3.5 mm., n_D^{25} 1.4632–1.4676. The combined fractions were subjected to two more distillations and the product was finally collected in three fractions: (*1*) b.p. 111° at 15 mm., 11.68 g., n_D^{25} 1.4651; (*2*) b.p. 111–111.5° at 15 mm., 10.02 g., n_D^{25} 1.4649; (*3*) b.p. 111.5–112° at 15 mm., 12.45 g., n_D^{25} 1.4648.

The infrared spectrum and elementary analysis showed the product to be 1-bromomethyl-3,3,4,6,6-pentamethyl-2,5,7-trioxabicyclo[2.2.1]heptane (V, R = R′ = CH_3).

Anal. Calcd. for $C_{10}H_{17}BrO_3$: C, 45.30; H, 6.46; Br, 30.14. Found: C, 45.81; H, 6.64; Br, 30.24.

This compound was also prepared as follows. In a 500-ml. flask was placed 250 ml. of ether to which was added 40 g. (0.25 mole) of bromine with cooling by an ice bath. After the solution had cooled to below 20°, 46.6 g. (0.25 mole) of 1,3,3,4,6,6-hexamethyl-2,5,7-trioxabicyclo[2.2.1]heptane was added. Decolorization was rapid. After the ethereal solution was washed, the ether was removed by distillation. The residual liquid was distilled into seven fractions: (*1*) b.p. 27° at 4.8 mm., to 37.5° at 3.7 mm., 7.69 g., n_D^{25} 1.4178; (*2*) b.p. 37.5° at 3.7 mm. to 40° at 4.5 mm., 4.11 g., n_D^{25} 1.4178; (*3*) b.p. 40° at 4.5 mm. to 78° at 3.9 mm., 1.64 g., n_D^{25} 1.4183 (total 13.44 g., 29% recovery of starting material); (*4*) b.p. 80–81° at 4.2 mm., 0.72 g., n_D^{25} 1.4572; (*5*) b.p. 81–85° at 4.2 mm., 13.06 g., n_D^{25} 1.4677; (*6*) b.p. 85° at 4.2 mm. to 86° at 4.5 mm., 12.09 g., n_D^{25} 1.4677; (*7*) b.p. 86° at 4.5 mm. to 91° at 4.0 mm., 8.13 g., n_D^{25} 1.4689 (total, fractions *5* to *7*, 33.28 g., 52% yield).

(10) G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, 79, 3587 (1957).

(11) J. Colonge and L. Cumet, *Bull. soc. chim. France*, 842 (1947).

Preparation of 1,4-dimethyl-3,3,6,6-bis(pentamethylene)-2,5,7-trioxabicyclo[2.2.1]heptane.[6] A. *From 1-acetylcyclohexanol and HBr.* 1-Acetylcyclohexanol (28.4 g., 0.2 mole) in 100 ml. of CCl_4 was treated with HBr from a tank until the solution was saturated. After standing overnight, the mixture had an insoluble upper layer (water). The CCl_4 solution was washed with water and with $NaHCO_3$ solution until neutral and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure leaving a residue of oily solid. Methanol was added to take up the oil and the solid was recovered by filtration. White crystals were thus obtained, m.p. 101–108°. Recrystallization from a methanol-chloroform mixture gave 10.5 g. (40% yield), m.p. 104–109°.

B. *From 1-acetylcyclohexanol and HCl.* The above procedure was repeated on the same scale using HCl gas. The product weighed 17.3 g., m.p. 103.5–110°. An additional 3.1 g. was obtained by concentration of the filtrate and had m.p. 103.5–108.5°. Total weight was 20.4 g., 77% yield.

C. *From 1-acetylcyclohexanol and toluenesulfonic acid.* A mixture of 71.1 g. (0.5 mole) of 1-acetylcyclohexanol, 250 ml. of petroleum ether (Skellysolve F), and 2 g. of *p*-toluenesulfonic acid in a 500-ml. flask provided with a Dean-Stark trap and reflux condenser was subjected to heating for removal of water by azeotropic distillation in the usual way. After two days, 3.8 ml. of water had been removed (theory, 4.5 ml.). The solution was cooled, filtered through a 2.5 cm. layer of anhydrous K_2CO_3, and the petroleum ether was removed by distillation. A tan colored solid resulted, weight 64.5 g. (97% yield) which was recrystallized from methanol-chloroform to give a white, crystalline material, m.p. 105–109°.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.25; H, 10.05.

Preparation of 1,3,3,4,6,6-hexamethyl-2,5,7-trioxabicyclo-[2.2.1]heptane. A. *From 3-hydroxy-3-methyl-2-butanone and HCl.* A solution of 104.4 g. (1.02 moles) of 3-hydroxy-3-methyl-2-butanone in 200 ml.of CCl_4 was saturated with HCl gas. The reaction mixture soon became cloudy and a small upper layer of water subsequently appeared. The reaction mixture was neutralized with anhydrous K_2CO_3, enough being used to absorb the water. The mixture was filtered and the filtrate was dropped into a heated 200-ml. flask from a separatory funnel, the solvent being removed by distillation. The residual liquid was distilled at reduced pressure to give fraction (*1*), b.p. 53° at 29 mm. to 62° at 22 mm., 36.3 g., n_D^{25} 1.4158 and fraction (*2*), b.p. 62–64° at 22 mm., 31.7 g., n_D^{25} 1.4166. Fraction (2) represents a 33% yield of product.

B. *From 3-hydroxy-3-methyl-2-butanone and toluenesulfonic acid.* A mixture of 51.1 g. (0.5 mole) of 3-hydroxy-3-methyl-2-butanone, 200 ml. of petroleum ether (Skellysolve F), and 2 g. of *p*-toluenesulfonic acid was subjected to azeotropic distillation using a Dean-Stark trap as described above. After 24 hr., 4.0 ml. of water had been collected (theory, 4.5 ml.). After neutralization, filtration, and removal of solvent, the residue was distilled *in vacuo*, yielding 38 g. of product (82% yield), b.p. 60–66° at 22 mm., n_D^{25} 1.4168 (lit.[8] b.p. 81–82° at 50 mm., n_D^{20} 1.4199).

1,3,4,6-Tetramethyl-3,6-diethyl-2,5,7-trioxabicyclo[2.2.1]-heptane. 3-Hydroxy-3-methyl-2-pentanone (58.1 g., 0.5 mole) was subjected to the azeotropic dehydration as described above. After 3 days, 2.8 ml. of water was collected (theory, 4.5 ml.). Distillation gave 13.0 g. (22.4%) of recovered ketol, b.p. 30–90° at 24 mm., n_D^{25} 1.4230 and 36.7 g. (68.5% yield) of product, b.p. 90–100° at 24 mm., n_D^{25} 1.4311. Redistillation gave material with b.p. 94.5–95° at 22 mm., n_D^{25} 1.4316.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.44; H, 10.48.

1,3,4,6-Tetramethyl-3,6-diisobutyl-2,5,7-trioxabicyclo[2.2.1]-heptane. 3-Hydroxy-3,5-dimethyl-2-hexanone (72.1 g., 0.5 mole) was subjected to the azeotropic dehydration as described above. After 3 days, the reaction mixture yielded 12.3 g. of recovered ketol, b.p. 74–120° at 14 mm., n_D^{25} 1.4259 and 41.8 g. (62% yield) of product, b.p. 120–126° at 14 mm., n_D^{25} 1.4388. Redistillation gave material with b.p. 131° at 21 mm., n_D^{25} 1.4390.

Treatment of the same ketol with HCl gave only a 23% of product with 56% recovered ketol.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 71.06; H, 11.18. Found: C, 71.49; H, 11.15.

Attempted reaction of 3-hydroxy-3-ethyl-2-pentanone with toluenesulfonic acid. When 3-hydroxy-3-ethyl-2-pentanone (65.1 g., 0.5 mole) was subjected to the azeotropic dehydration for one week, only the starting material was recovered, 56.2 g. (86%) b.p. 62–65° at 21 mm., n_D^{25} 1.4230.

Bromination of 1-acetylcyclohexanol in ether followed by reaction with 10% NaOH. 1-Acetylcyclohexanol (71.1 g., 0.5 mole) was treated with bromine in ether and then, without isolation of product, with 10% NaOH as described above. When the ether was removed by distillation, 1-hydroxyacetylcyclchexanol crystallized and was collected in the following fractions: (*1*) 15.1 g., m.p. 87–88.5°; (*2*) 4.9 g., m.p. 80–87°; (*3*) 11.3 g., m.p. 83–84°; (*4*) 2.6 g., m.p. 82–84°. Total weight was 33.9 g. (43% yield). The first three fractions were combined and recrystallized from ether to give 21.6 g., m.p. 88–89° (lit.[4] m.p. 86–87°).

1,3-Dihydroxy-3-methyl-2-pentanone. In a 500-ml. flask was placed 30.1 g. (0.47 mole) of KOH (C.P. analyzed, 87.9% KOH) and 150 ml. of absolute methanol. The solution was cooled and 37.7 g. (0.51 mole) of purified ethyl formate was added. The mixture was refluxed for 2 hr. At the end of this time, 73.5 g. (0.377 mole) of 1-bromo-3-hydroxy-3-methyl-2-pentanone was added. The reaction mixture was boiled under reflux for 17 hrs., cooled in an ice-salt bath and filtered through a Büchner funnel. When the solvent was removed by distillation some crystalline material was present. The oil was taken up in $CHCl_3$ and the solid filtered off. The $CHCl_3$ was removed and the residual liquid was distilled *in vacuo* into seven fractions: (*1*) b.p. 39° at 2.6 mm. to 81° at 2.0 mm., 0.80 g., n_D^{25} 1.4420; (*2*) b.p. 81° at 2.0 mm. to 82° at 1.75 mm., 3.29 g., n_D^{25} 1.4489; (*3*) b.p. 82° at 1.75 mm. to 82° at 1.5 mm., 6.39 g., n_D^{25} 1.4497; (*4*) b.p. 82° at 1.5 mm. to 84° at 1.4 mm., 10.46 g., n_D^{25} 1.4508; (*5*) b.p. 84–83.5° at 1.4 mm., 8.50 g., n_D^{25} 1.4520; (*6*) b.p. 82° at 2.6 mm. to 100° at 2.7 mm., 5.01 g., n_D^{25} 1.4541; (*7*) b.p. 100° at 2.7 mm. to 102° at 3.0 mm., 1.09 g., n_D^{25} 1.4754. Weight of fractions (*2*) through (*6*) is 33.65 g. (68% yield). When this material was redistilled there was obtained 26.36 g. (53%) of liquid b.p. 96° at 0.7 mm., n_D^{25} 1.4528–1.4531 (lit.[10] b.p. 25° (bath temp.) at 0.005 mm., 51–58° at 0.1–0.25 mm., n_D^{25} 1.4537).

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NOTRE DAME, IND.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Reactions of α-Ketols Derived from Tertiary Acetylenic Carbinols. III. The Preparation of 4-Methyl-4,5,5-trisubstituted-2-oxazolidinones[1]

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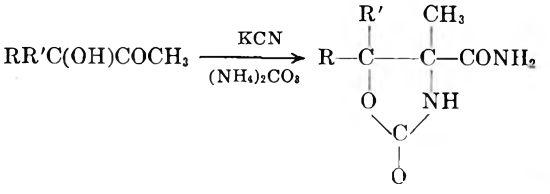
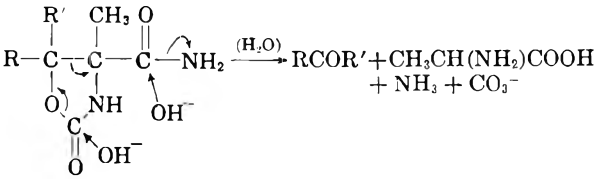
α-Ketols, $RR'C(OH)COCH_3$, react with potassium cyanide and ammonium carbonate in aqueous alcohol solution to produce 4-carbamyl-4-methyl-5,5-disubstituted-2-oxazolidinones, $RR'C(O)CO(NH)C(CH_3)CONH_2$. Acid hydrolysis converts the latter to the corresponding 4-carboxylic acids in 65–80% yields. Alkaline hydrolysis proceeds by a reverse aldol type reaction producing ketones, RCOR', and alanine. Attempts to prepare α-amino-β-hydroxy acids by hydrolysis of the oxazolidinones were unsuccessful.

The reaction of potassium cyanide and ammonium carbonate with six α-ketols, $RR'C(OH)COCH_3$, obtained by hydration of the corresponding tertiary acetylenic carbinols, has been studied in connection with attempts to prepare α-amino-β-hydroxy acids *via* the intermediate hydantoins.[3] Crystalline products were readily obtained in good yield and they analyzed correctly in all instances for the expected hydantoin structures. Examination of these substances, particularly their behavior when subjected to hydrolysis, quickly revealed, however, that they are 4-carbamyl-4-methyl-5,5-disubstituted-2-oxazolidinones, formed according to the following equation.



Hydrolysis with hot 4–5*N* hydrochloric acid converted these substances to the corresponding 4-carboxylic acids. The latter could be reconverted to the starting materials by treatment with thionyl chloride and then with aqueous ammonia. Similarly, treatment of the acids with thionyl chloride followed by reaction with methanol produced methyl esters identical with those obtained by direct esterification. It is noteworthy that the oxazolidinone ring survives these reactions so well. This was not the case, however, when the 4-carbamyl compounds were hydrolyzed in alkaline media. In all such instances they were completely degraded, apparently by a reverse aldol type reaction as indicated below.



It is interesting to compare these results with those of Henze and Craig.[4] They treated benzoylcarbinyl acetate with potassium cyanide and ammonium carbonate in aqueous ethanol, obtaining 4-carbamyl-4-phenyl-2-oxazolidinone. Dilute hydrochloric acid hydrolysis of the latter produced the corresponding 4-carboxylic acid. Hydrolysis of both the amide and the acid, the former by dilute sodium hydroxide, the latter by either dilute alkali or 9*N* hydrochloric acid, led to the formation of α-amino-β-hydroxy-α-phenylpropionic acid. Apparently no cleavage was observed.

This contrasts with our results in which alkaline hydrolysis leads to complete degradation, and in which degradation has also been observed as a side reaction in the acidic hydrolysis of the 4-carbamyl compounds to the corresponding 4-carboxy compounds. In no case has it been possible to obtain the desired α-amino-β-hydroxy acids.

Preliminary work indicates that the α-ketol methyl ethers react in the expected manner with potassium cyanide and ammonium carbonate to produce hydantoins. In the one case studied, 3-phenyl-3-methoxy-2-butanone gave a 26% yield of 5-methyl-5-(α-methoxy-α-phenethyl)hydantoin.

The new compounds prepared are described in Table I.

EXPERIMENTAL

α-Ketols. 3-Methyl-3-hydroxy-2-butanone, 3-methyl-3-hydroxy-2-pentanone, 3-ethyl-3-hydroxy-2-pentanone, 1-acetylcyclohexanol, 3,5-dimethyl-3-hydroxy-2-hexanone, and 3-phenyl-3-hydroxy-2-butanone were prepared by hydration of *t*-acetylenic carbinols.[5] 3-Phenyl-3-methoxy-2-butanone was prepared as previously described.[6]

(1) Paper LXX on substituted acetylenes; previous paper, G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 658 (1958).

(2) Eli Lilly Co. Fellow, 1955–1956. Abstracted from a portion of the Ph.D. Dissertation of F. X. O'S.

(3) K. Pfister *et al.*, *J. Am. Chem. Soc.*, **77**, 697 (1955); E. Ware, *Chem. Revs.*, **46**, 403 (1950).

(4) H. Henze and W. Craig, *J. Org. Chem.*, **10**, 16 (1945).

(5) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 656 (1958).

(6) G. F. Hennion and B. R. Fleck, *J. Am. Chem. Soc.*, **77**, 3253 (1955).

TABLE I

4-METHYL-4,5,5-TRISUBSTITUTED-2-OXAZOLIDINONES

RR′C(—O—CO—NH—)C(CH$_3$)—CO—X

Cpd.	R	R′	Yield, %	M. P., °C.[a]
		A. Amides (X = NH$_2$)		
I	CH$_3$	CH$_3$	34	208–209
II	CH$_3$	C$_2$H$_5$	31	224–226
III	C$_2$H$_5$	C$_2$H$_5$	72	175–177
IV	—CH$_2$—(CH$_2$)$_3$—CH$_2$—		79	253–254
V[b]	CH$_3$	*i*-C$_4$H$_9$	39	192–194
VI[b]	CH$_3$	*i*-C$_4$H$_9$	19	176–178
VII	CH$_3$	C$_6$H$_5$	24	222–224
		B. Acids (X = OH)		
VIII	CH$_3$	CH$_3$	74	206–207
IX	CH$_3$	C$_2$H$_5$	80	206–207
X	C$_2$H$_5$	C$_2$H$_5$	66	177–179
XI	—CH$_2$—(CH$_2$)$_3$—CH$_2$—		73	205–206
XII[c]	CH$_3$	*i*-C$_4$H$_9$	74	186–187
XIII[c]	CH$_3$	*i*-C$_4$H$_9$	69	195–196
XIV	CH$_3$	C$_6$H$_5$	72	198–199
		C. Esters (X = OCH$_3$)		
XV	CH$_3$	CH$_3$	58	99–100
XVI	—CH$_2$—(CH$_2$)$_3$—CH$_2$—		33	129–131
XVII	CH$_3$	*i*-C$_4$H$_9$	68	89–90

[a] All melting points are uncorrected. [b] Compounds V and VI are diastereoisomers. [c] Diastereoisomers, XII from V and XIII from VI.

TABLE II

IDENTIFICATION OF 4-METHYL-4,5,5-TRISUBSTITUTED-2-OXAZOLIDINONES

Compound	Name
I	4-Carbamyl-4,5,5-trimethyl-2-oxazolidinone
II	4-Carbamyl-4,5-dimethyl-5-ethyl-2-oxazolidinone
III	4-Carbamyl-4-methyl-5,5-diethyl-2-oxazolidinone
IV	4-Carbamyl-4-methyl-5,5-pentamethylene-2-oxazolidinone
V, VI	4-Carbamyl-4,5-dimethyl-5-isobutyl-2-oxazolidinone
VII	4-Carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone
VIII	4-Carboxy-4,5,5-trimethyl-2-oxazolidinone
IX	4-Carboxy-4,5-dimethyl-5-ethyl-2-oxazolidinone
X	4-Carboxy-4-methyl-5,5-diethyl-2-oxazolidinone
XI	4-Carboxy-4-methyl-5,5-pentamethylene-2-oxazolidinone
XII, XIII	4-Carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone
XIV	4-Carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone
XV	4-Carbomethoxy-4,5,5-trimethyl-2-oxazolidinone
XVI	4-Carbomethoxy-4-methyl-5,5-pentamethylene-2-oxazolidinone
XVII	4-Carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone

Preparation of 4-carbamyl-4,5,5-trisubstituted-2-oxazolidinones. The procedure used was essentially that described by Henze[7] for the preparation of hydantoins from carbonyl compounds. In most cases the product readily crystallized from the cooled reaction mixture and was usually recrystallized from aqueous ethanol.

In a typical preparation, 108 g. (0.75 mole) of 3,5-dimethyl-3-hydroxy-2-hexanone, 65 g. (1 mole) of potassium cyanide, 288 g. (2.5 moles) of ammonium carbonate, and one liter of 50% ethyl alcohol were placed in a 2-liter 3-neck flask fitted with a thermometer and an air condenser. As a precaution against the evolution of hydrogen cyanide, a trap containing sodium hydroxide solution was connected to the top of the condenser and the reaction was run in the hood. The reaction mixture was maintained at 55–60° for 6 hr. and then allowed to cool overnight. The white crystalline product was filtered off, washed with 200 ml. of distilled water, and air dried. Two crystallizations from aqueous ethanol yielded 47.2 g. of 4-carbamyl-4,5-dimethyl-5-isobutyl-2-oxazolidinone (V), m.p. 192–194°. The filtrate and washings were combined and refrigerated overnight yielding another 16.1 g. of product, m.p. 192–194° after two crystallizations from aqueous ethanol. The total yield was 63.3 g. (39%).

The mother liquor then was concentrated by distillation to *ca.* one-third volume. A third crop of solid was obtained which, after crystallization from ethyl acetate, yielded 30 g. (19%) of the low melting diastereoisomer (VI), m.p. 176–178°.

Preparation of 4-carboxy-4,5,5-trisubstituted-2-oxazolidinones. These compounds were prepared by refluxing the 4-carbamyl-4,5,5-trisubstituted-2-oxazolidinones for 2 to 4 hr. in 4 to 5*N* hydrochloric acid. The product precipitated out upon cooling of the reaction mixture and was usually recrystallized from aqueous ethanol.

In a typical preparation, 10 g. (0.0426 mole) of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone was refluxed in 100 ml. of 5*N* hydrochloric acid for 3.5 hr. At the termination of reflux, a small amount of acetophenone, detectable as oily droplets in the reaction mixture, was steam distilled out. A 2,4-dinitrophenylhydrazone derivative was prepared, affording 2 g. of orange crystals, m.p. (corr.) 248.5–249.5° (lit.[8] m.p. 250°) after crystallization from ethyl alcohol–ethyl acetate. The formation of acetophenone indicates a small amount of side reaction involving ring cleavage similar to that observed in alkaline hydrolysis.

The reaction mother liquor, upon cooling, yielded 7.2 g. (72%) of 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone (XIV) melting with decomposition at 198–199°. Crystallization from aqueous ethanol did not raise the melting point.

Conversion of 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone to the corresponding 4-carbamyl compound. One gram of powdered 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone (XIV) was refluxed with 5 ml. of thionyl chloride for 5 min. The hot solution then was added dropwise with shaking to 25 ml. of ice cold aqueous ammonia, producing a brown precipitate which was filtered off and dried. The product (0.8 g.) was crystallized twice from aqueous ethanol, the hot solutions being decolorized with activated charcoal (Norit A), yielding 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone (VII), m.p. 222–224°. Mixture with the 4-carbamyl compound (VII) obtained from the α-ketol did not depress the melting point and the infrared spectra of the compounds obtained by both methods were identical.

Preparation of 4-carbomethoxy-4,5,5-trisubstituted-2-oxazolidinones. Method A. Direct esterification was accomplished by refluxing the acid with anhydrous methanol containing 3% dry hydrogen chloride. In a typical preparation, 5 g. of 4-carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XII) was refluxed for 9 hr. with 100 ml. of anhydrous methanol

(7) H. Henze *et al.*, *J. Am. Chem. Soc.*, **71**, 2220 (1949).

(8) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, New York, 3rd ed., p. 263.

TABLE III

ANALYTICAL DATA

Compound	Mol. Formula	Calcd. C	Calcd. H	Calcd. N	Obsd. C	Obsd. H	Obsd. N	Neut. Equiv. Calcd.	Neut. Equiv. Obsd.
I	$C_7H_{12}N_2O_3$	48.83	7.03		49.31	7.17			
II	$C_8H_{14}N_2O_3$	51.60	7.58		51.38	7.17			
III	$C_9H_{16}N_2O_3$	53.98	8.06	13.99	53.72	7.88	13.98		
IV	$C_{10}H_{16}N_2O_3$	56.58	7.60	13.20	56.32	7.86	13.08		
V	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.08	56.01	8.40	13.20		
VI	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.08	56.28	8.43	13.16		
VII	$C_{12}H_{14}N_2O_3$	61.52	6.02	11.96	61.89	6.07	11.40		
VIII	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.42	6.67	8.00	173.2	174.1
IX	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.69	7.18	7.26	187.2	188.3
X	$C_9H_{15}NO_4$	53.72	7.51	6.96	54.16	8.01	7.00	201.2	200.1
XI	$C_{10}H_{16}NO_4$	56.33	7.09	6.57	56.63	7.16	6.43	213.2	216.2
XII	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	56.39	8.09	6.25	215.2	216.1
XIII	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	56.05	8.19	6.38	215.2	215.9
XIV	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.53	5.58	6.02	235.2	235.3
XV	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.08	7.12	7.34		
XVI	$C_{11}H_{17}NO_4$	58.12	7.54	6.16	58.39	7.61	6.00		
XVII	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.82	8.53	6.02		

containing 3% dry hydrogen chloride. The mixture, after standing overnight, was concentrated by distillation *in vacuo* to a gummy residue. The residue was dissolved in 100 ml. of chloroform, filtered, and the filtrate dried overnight in the refrigerator with anhydrous sodium sulfate. The solution then was filtered and the filtrate distilled *in vacuo* to a solid residue which, after two crystallizations from hexane–carbon tetrachloride, yielded 3.6 g. (68%) of 4-carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XVII), m.p. 89–90°.

Method B. Esterification was accomplished by conversion of the acid to the acid chloride and subsequent reaction with anhydrous methanol. Thus, 1 g. of 4-carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XII) was refluxed with 5 ml. of thionyl chloride for 5 min. The solution then was added dropwise to 10 ml. of anhydrous methanol. The mixture, after standing overnight, was evaporated to dryness on a hot plate yielding 4-carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XVII), m.p. 88–91° after recrystallization from hexane–carbon tetrachloride (not depressed by mixture with the product obtained by method A).

Alkaline hydrolysis of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone. To a solution of 15.8 g. (0.05 mole) of barium hydroxide in 160 ml. of water (*ca.* 5% by weight) contained in a 500-ml. round bottom flask was added 5.85 g. (0.025 mole) of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone (VII). After 30 min. of reflux, oily droplets began to appear in the refluxing distillate and the evolution of ammonia was evident. After 22 hr. of reflux, the oily layer was steam distilled out of the reaction mixture, the oil extracted twice from the distillate with 50 ml. portions of ether, and the combined ethereal extracts dried over anhydrous sodium sulfate. The ether solution then was filtered and the solvent removed by distillation *in vacuo* leaving 3.0 g. of acetophenone (quantitative). A 2,4-dinitrophenylhydrazone derivative was prepared, m.p. (corr.) 248.5–249° (lit.[8] m.p. 250°) after crystallization from ethyl alcohol–ethyl acetate. Mixture with the 2,4-dinitrophenylhydrazone derivative of an authentic sample of acetophenone did not depress the melting point.

The original reaction mixture was filtered to remove the precipitated barium carbonate, neutralized with dilute sulfuric acid, and again filtered to remove the precipitated barium sulfate. The filtrate was concentrated by distillation to *ca.* 25 ml., diluted with 200 ml. of absolute ethanol and refrigerated yielding 1.46 g. (66%) of alanine. A phenylureido derivative was prepared, m.p. (corr.) 167–168° (lit.[9] m.p. 168°) after two crystallizations from water. Mixture with the phenylureido derivative of an authentic sample of *dl*-alanine produced no depression in the melting point.

5-Methyl-5-(α-methoxy-α-phenethyl)hydantoin. A mixture of 55 g. (0.31 mole) of 3-phenyl-3-methoxy-2-butanone, 33 g. (0.5 mole) of potassium cyanide, 96 g. (1 mole) of ammonium carbonate, and 500 ml. of 50% ethyl alcohol was placed in a 2-liter 3-neck flask fitted with a thermometer and an air condenser. The reaction mixture was maintained at 55–60° for 5.5 hr. and then allowed to cool overnight. The resultant white precipitate was filtered off, yielding 20 g. (26%) of 5-methyl-5-(α-methoxy-α-phenethyl)hydantoin melting at 224–226° after two recrystallizations from aqueous ethanol. Concentration of the mother liquor provided further crops of product, consisting of mixtures of the two diastereoisomeric products, from which neither isomer could be obtained pure by the ordinary crystallization techniques.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.28. Found: C, 62.88; H, 6.51; N, 11.52.

Acknowledgments. The authors express their sincere thanks to Dr. C. O. Herman, Air Reduction Chemical Co., New York, and to Dr. F. E. Cislak, Reilly Tar and Chemical Co., Indianapolis, for generous gifts of acetylenic alcohols. Special thanks are due G. M. Maciak, H. L. Hunter, and G. Beckmann of the Lilly Research Laboratories, Indianapolis, for the analyses reported and to the Eli Lilly Co. for a fellowship award to F. X. O'S.

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(9) S. P. Mulliken, *Identification of Pure Organic Compounds*, II, John Wiley & Sons, New York, 1916, p. 222.

[CONTRIBUTION FROM THE MCPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Diarylacetylenes[1]

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The synthesis of a number of diarylacetylenes is recorded. A new modification of the Curtius synthesis of diarylacetylenes, involving oxidation of dihydrazones of benzils with silver trifluoroacetate and triethylamine at room temperature, is described.

In this paper are described the syntheses of a number of diarylacetylenes needed for a study of directive effects in hydration of unsymmetrical diarylacetylenes.

p-Chlorophenylphenylacetylene and *o*-chlorophenyl-*p*-chlorophenylacetylene were prepared from 4′-chloro-2-phenylacetophenone and 4′-chloro-2-*o*-chlorophenylacetophenone by treatment with phosphorus pentachloride followed by dehydrochlorination with sodium *t*-butoxide and ethoxide, respectively. However, the attempted dehydrochlorination of the reaction product of 2′-chloro-2-phenylacetophenone and phosphorus pentachloride did not yield a readily purified sample of *o*-chlorophenylphenylacetylene.

This acetylene was made by a new modification of the Curtius method[3] since the conventional procedure of heating the dihydrazone of 2-chlorobenzil with yellow mercuric oxide in refluxing benzene did not yield a very pure product. The new modification involves oxidation at room temperature with a solution of silver trifluoroacetate (other silver salts could undoubtedly be used) in triethylamine in acetonitrile or ethanol as solvent according to the following equation:

$$\underset{\|\atop NNH_2}{RC}\text{———}\underset{\|\atop NNH_2}{C}\text{—}R' + 4\ CF_3COOAg + 4(C_2H_5)_3N \longrightarrow$$

$$RC{\equiv}CR' + 4\ CF_3COOH\cdot(C_2H_5)_3N + 4Ag + 2N_2$$

The course of the oxidation was followed by measuring the nitrogen as evolved. Usually 85–100% of the theoretical nitrogen was obtained in 1–4 hr. The new method was applied to the synthesis of diphenylacetylene, di-*p*-methoxyphenylacetylene, *o*-chlorophenyl-, and *m*-chlorophenylphenylacetylenes in 80–85% yields.

The substituted benzils required for the preparation of the dihydrazones were prepared by oxidation of the corresponding aryl-substituted acetophenones with selenium dioxide[4] or alternately, and in excellent yield, by oxidation with potassium permanganate, maintaining a *p*H near 7 by passage of carbon dioxide into the reaction mixture.[5]

All of the isomeric aryl-substituted acetophenones which could result from the hydration of the chlorinated diarylacetylenes were prepared in order that suitable procedures for analysis of the hydration mixtures could be developed. These ketones had all been prepared previously[6] by the reaction of 3–4 moles of substituted benzylmagnesium halides with appropriate benzamides (40–70 hr. reaction times). We have found that the substitution of benzonitriles for benzamides allows one to use molar amounts of Grignard reagents and a reaction time of 6 hr.

EXPERIMENTAL

Synthesis of chlorinated 2-phenylacetophenones. The crude phenylacetyl chloride, prepared from 114 g. of phenylacetic acid and 160 g. of thionyl chloride in 300 ml. of benzene by refluxing for 10 hr. and removing solvent and excess thionyl chloride under vacuum, was added to a stirred slurry of 134 g. of aluminum chloride in 400 g. of chlorobenzene. The reaction mixture was held at 70° for 90 min., then cooled and poured onto ice to yield 131 g. (68%) of crude solid ketone. After three crystallizations from alcohol colorless plates of pure 4′-chloro-2-phenylacetophenone, m.p. 106.0–107.0°,[6,7] were obtained.

The remaining ketones were prepared by reaction of *o*-, *m*-, and *p*-chlorobenzylmagnesium bromides with the appropriate benzonitrile. A typical experiment involved addition of 13.8 g. of *p*-chlorobenzonitrile in 100 ml. of ether to a solution prepared by slow addition of 25 g. of *o*-chlorobenzyl bromide in 100 ml. of dry ether to a stirred suspension of 6 g. of magnesium in 150 ml. of ether. After refluxing for 6.5 hr. the mixture was worked up to yield 20 g. (75%) of 4′-chloro-2-(*o*-chlorophenyl)acetophenone, m.p. 103–107. Recrystallizations from alcohol afforded the pure ketone as colorless needles, m.p. 107.4–108.4°.[6] No attempt was made to obtain maximum yields of ketones. The yields of the other crude ketones (melting point of pure ketone in parentheses) were approximately as follows: *p*-chlorobenzylmagnesium bromide on *o*-chlorobenzonitrile, 2′-chloro-2-(*p*-chlorophenyl)acetophenone, 72%, (m.p. 63.0–65.0°); *o*-chlorobenzylmagnesium bromide on benzonitrile, 2-(*o*-chlorophenyl)acetophenone, 55%, (69.0–70.5°); benzylmagnesium chloride on *o*-chlorobenzonitrile, 2′-chloro-2-phenylacetophenone, 71%, (b.p. 144–146° at 1 mm.); benzylmagnesium

(1) Taken from the Ph.D. Thesis of D. E. Reid, The Ohio State University, 1957.

(2) Holder of the Eastman Kodak Co. Fellowship, 1955–1956.

(3) T. Curtius, *Ber.*, 22, 2161 (1889); T. Curtius and K. Thun, *J. prakt. Chem.*, **44**, 168 (1891).

(4) H. L. Riley, J. F. Morley, and N. A. C. Friend, *J. Chem. Soc.*, 1875 (1932); H. H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936).

(5) Compare to oxidation of stearolic acid, N. A. Khan and M. S. Newman, *J. Org. Chem.*, **17**, 1063 (1952).

(6) S. S. Jenkins, *J. Am. Chem. Soc.*, **55**, 703, 2896 (1933), **56**, 682 (1934); S. S. Jenkins and E. M. Richardson, *J. Am. Chem. Soc.*, **55**, 1618, 3874 (1933).

(7) All melting point determinations were taken in a Hershberg apparatus with short range thermometers calibrated by the U. S. Bureau of Standards.

chloride on *m*-chlorobenzonitrile, 3′-chloro-2-phenylacetophenone, 76%, (m.p. 60.4–61.6°); and *m*-chlorobenzylmagnesium bromide on benzonitrile, 2-(*m*-chlorophenyl)acetophenone, 47%, (m.p. 41.8–42.8°).[8]

p-Chlorophenylphenylacetylene. A mixture of 10 g. of 4′-chloro-2-phenylacetophenone and 10 g. of phosphorus pentachloride was heated at 60° for 3 hr. and distilled to yield 8.0 g. of a solid, b.p. 180–185° at 5 mm. This solid was refluxed for 4 hr. in a solution of *t*-butyl alcohol in which 6.7 g. of sodium had been dissolved. About 60% of crude acetylene was obtained which, after several recrystallizations from alcohol, had a m.p. of 81.5–82.0°.

Anal.[9] Calcd. for $C_{14}H_9Cl$: C, 79.1; H, 4.3; Cl, 16.6. Found: C, 79.1; H, 4.5; Cl, 16.4.

o-Chlorophenyl-p-chlorophenylacetylene. A mixture of 5.3 g. of 4′-chloro-2-(*o*-chlorophenyl)acetophenone, 10 g. of phosphorus pentachloride, and 50 ml. of benzene was refluxed for 4 hr. and poured into ice water. The chlorinated products formed were refluxed in a solution of 75 ml. of absolute alcohol in which 3.4 g. of sodium had been dissolved. The crude acetylene thus formed in good but not exactly determined yield was recrystallized twice from aqueous alcohol to yield pure *o*-chlorophenyl-*p*-chlorophenylacetylene, m.p. 62.5–64.5°.

Anal. Calcd. for $C_{14}H_8Cl_2$: C, 68.0; H, 3.2; Cl, 28.7. Found: C, 67.9; H, 3.3; Cl, 28.5.

o-Chlorophenylphenylacetylene. 2-(*o*-Chlorophenyl)acetophenone (20 g.), selenium dioxide (15.4 g.), and acetic anhydride were heated to reflux for 4 hr. After filtration the reaction mixture was poured into water and the crude *o*-chlorobenzil isolated.[10] Alternatively, this diketone was obtained in similar yield by stirring a solution of 10 g. of ketone, 10 g. of potassium permanganate, 70 ml. of pyridine, and 70 ml. of water at room temperature for seven hours while controlling the *p*H near 7 by addition of carbon dioxide. By heating the diketone from the former oxidation with 6.4 g. of anhydrous hydrazine and 2 ml. of acetic acid in 250 ml. of alcohol for 18 hr. there was obtained 16.3 g. (69% overall) of colorless dihydrazone. Recrystallization from acetonitrile yielded pure dihydrazone of *o*-chlorobenzil, m.p. 234–236° (dec.).

Anal. Calcd. for $C_{14}H_{13}N_4Cl$: C, 61.6; H, 4.8; N, 20.5; Cl, 13.0. Found: C, 61.6; H, 5.0; N, 20.4; Cl, 12.8.

To a stirred solution of 10 g. of dihydrazone in 200 ml. of *N*-methylpyrrolidone[11] at room temperature was added 50 g. of silver benzoate in three portions, each followed by the addition of 8 ml. of triethylamine. When the theoretical amount of nitrogen had been evolved (4 hr.) the mixture was filtered, poured into water, and worked up to yield a good but not exactly determined yield of acetylene. A pure 2.5 g. center cut of *o*-chlorophenylphenylacetylene, b.p. 146° at 3 mm. was taken for further work.

Anal. Calcd. for $C_{14}H_9Cl$: C, 79.1; H, 4.3; Cl, 16.7. Found: C, 78.9, 79.1; H, 4.4, 4.4; Cl, 16.5, 16.4.

m-Chlorophenylphenylacetylene. 3′-Chloro-2-phenylacetophenone was oxidized to *m*-chlorobenzil by the selenium dioxide and potassium permanganate methods described above. A pure sample melted at 88.8–89.8°.[12] The dihydrazone, m.p. 98–99°, was obtained in about 70% over-all yield. The pure dihydrazone, obtained by recrystallization from ethanol-water, melted at 98.4–99.0°.

To a stirred solution of 55 g. of silver trifluoroacetate in 150 ml. of alcohol was added 14.3 g. of *m*-chlorobenzil dihydrazone in 100 ml. of alcohol. During 45 min. five 5-ml. portions of triethylamine were made. After a total of 50 min., the theoretical volume of nitrogen had been evolved and the reaction mixture was poured into 150 ml. of concd. ammonium hydroxide. By ether extraction and distillation there was obtained 9.0 g. (80%) of *m*-chlorophenylphenylacetylene, b.p. 153–155° at 3 mm. A redistilled center cut was taken for the hydration studies.

Anal. Calcd. for $C_{14}H_9Cl$: C, 79.1; H, 4.3; Cl, 16.7. Found: C, 79.3; H, 4.4; Cl, 16.5.

Diphenylacetylene. To a stirred mixture of 15 g. of benzil dihydrazone,[13] m.p. 151–153°, 80 g. of silver trifluoroacetate, and 250 ml. of acetonitrile was added 70 ml. of triethylamine during 150 min. After 6 hr., 103% of the theoretical nitrogen had been evolved. After the mixture had been poured into 200 ml. of concd. ammonium hydroxide there was isolated 9.5 g. (85%) of diphenylacetylene, m.p. 58–60°.

Di-p-methoxyphenylacetylene. As in the case of diphenylacetylene di-*p*-methoxybenzil dihydrazone,[13] m.p. 115–118°, was oxidized to di-*p*-methoxyphenylacetylene,[14] m.p. 140–146°, in 85% yield. The pure acetylene melted at 145–146°, after two recrystallizations from 1:2 acetic acid–alcohol.

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(8) All of these ketones have been prepared previously; see reference 6 in this paper.

(9) Analyses by Galbraith Laboratories, Knoxville, Tenn.

(10) E. L. Shapiro and E. L. Becker, *J. Am. Chem. Soc.*, **75**, 4769 (1953).

(11) We thank the General Aniline and Film Corp. for a generous gift of *N*-methylpyrrolidone.

(12) M. T. Clarke, E. C. Hendley, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955) report a m.p. of 86°.

(13) W. Schlenk and E. Bergmann, *Ann.*, **463**, 76 (1928).

(14) H. Wiechell, *Ann.*, **279**, 338 (1894) reported a m.p. of 142°.

[CONTRIBUTION FROM THE MCPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Reactions of Dipivaloyl with Organometallic Reagents[1]

MELVIN S. NEWMAN AND GERALD R. KAHLE[2]

Received November 4, 1957

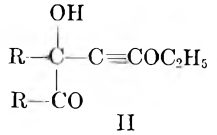
Dipivaloyl (I) reacts with ethoxyethynylmagnesium bromide and ethoxyethynyllithium to yield 3-*t*-butyl-5,5-dimethyl-1-ethoxy-3-hydroxy-4-keto-1-hexyne (II). On treatment with acid II rearranges stereospecifically to yield ethyl *cis* 3-*t*-butyl-5,5-dimethyl-4-keto-2-hexenoate (V). Reaction of I with ethyl bromoacetate yields a hydroxyester (III) which, after hydrolysis and dehydration yields IV, the acid corresponding to V. IV is shown to exist in about equal amounts in the acyclic and cyclic forms, IV and VI.

In the hope of preparing intermediates suitable for conversion into *o*-di-*t*-butylbenzene, 2,2,5,5-tetramethyl-3,4-hexanedione (I) (dipivaloyl) was treated with (*1*) ethoxyethynylmagnesium bro-

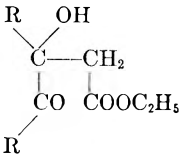
(1) Taken from the Ph.D. thesis of G. R. Kahle, Ohio State University, 1956.

(2) Holder of the Monsanto Chemical Co. Fellowship, 1954–1955.

mide, (*2*) ethoxyethynyllithium, and (*3*) ethyl bromoacetate and zinc. However, despite the use of excess reagent and long periods of heating only the condensation products 3-*t*-butyl-5,5-dimethyl-3-hydroxy-4-keto-1-ethoxy-1-hexyne (II) and ethyl 3-*t*-butyl-5,5-dimethyl-3-hydroxy-4-ketohexanoate (III) were obtained. This result was not entirely unexpected in view of the reported failure of dipivaloyl to react with *o*-phenylenediamine.[3]



II

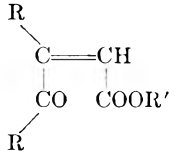


III

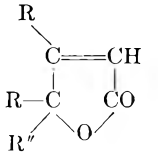
R = $(CH_3)_3C-$

Actually pure II was not isolated. The crude reaction mixtures containing II, as indicated by infrared absorption bands at 2.90 (m), 4.55 (s), and 5.86 μ (s) corresponding to hydroxyl, ethynyl, and carbonyl groups, were treated with ethanolic-hydrogen chloride to yield V ($R' = C_2H_5$) in over 50% yields.[4] The yields of V from the ethoxyethynyl carbinol reaction sequence were slightly better when the Grignard reagent was used rather than the lithium derivative. When we treated I with the solution formed by adding ethoxyacetylene to butyllithium we obtained 4-*t*-butyl-2,2-dimethyl-3-keto-4-octanol, the product to be expected by the addition of butyllithium, rather than ethoxyethynyllithium, to I.[5]

The hydroxy keto ester (III), formed in 39% yield in the Reformatsky reaction, was converted into 3-*t*-butyl-5,5-dimethyl-4-keto-2-hexenoic acid (IV) ($R' = H$) by alkaline hydrolysis followed by dehydration of the hydroxy acid with potassium acid sulfate. The structure, IV, was supported by the facts that oxidation afforded I and cyclic derivatives, VII and VIII, could be prepared from IV (see below).



IV $R' = H$
V $R' = C_2H_5$



VI $R'' = OH$
VII $R'' = Cl$
VIII $R'' = OC_2H_5$

The *cis* relationship of pivaloyl and carboxyl groups in IV and related compounds was established by the fact that normal and pseudo esters could be prepared from IV. When IV was treated with thionyl chloride the pseudo acid chloride VII was obtained in high yield. The cyclic structure for VII [and the other pseudo (cyclic) derivatives] was characterized by a single strong carbonyl absorption band at 5.65 μ. This acid chloride was recovered unchanged after refluxing for seven hours in absolute alcohol containing pyridine and thus appears to be an unusually unreactive cyclic acid chloride.[6] However, on refluxing VII with absolute ethanolic silver nitrate the pseudo ethyl ester (VIII) was obtained in high yield. On alkaline hydrolysis both V and VIII yielded the same acid, IV, and on treatment of IV with diazoethane V was formed.

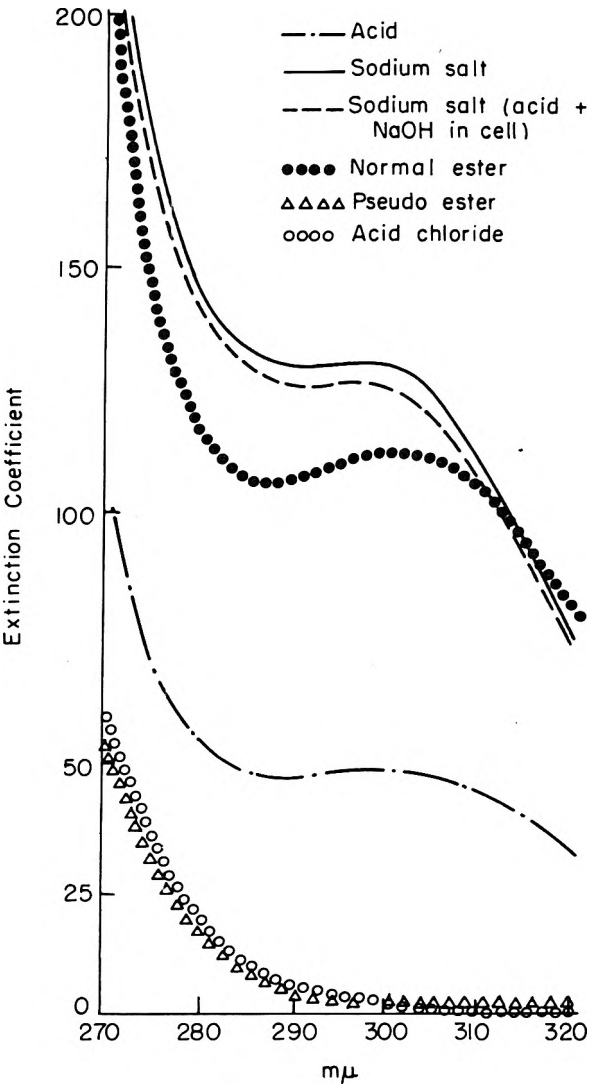


Fig. 1. Ultraviolet Absorption Spectra of IV and Derivatives of IV

By comparing the extinction coefficient at 300 mμ of a solution of IV in alcohol with those of the

(3) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).

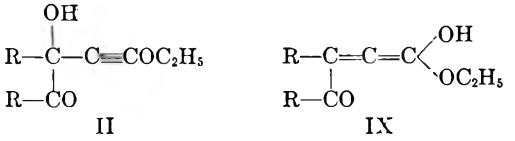
(4) I. Heilbron, E. R. H. Jones, M. Julia, and B. C. L. Weedon, *J. Chem. Soc.*, 1823 (1949), who discovered this synthesis of α,β-unsaturated esters, similarly proceeded without isolation of the ethoxyethynyl carbinols.

(5) Ethoxyethynyllithium may be formed by reaction of ethoxyacetylene with phenyllithium but not with butyllithium, private communication from Dr. D. A. van Dorp.

(6) R. E. Lutz, *J. Am. Chem. Soc.*, **52**, 3405 (1930) reports that certain pseudo acid chlorides are relatively stable towards alcoholysis. However, pseudo acid chlorides of *o*-benzoylbenzoic acids are usually reactive with alcohols, H. Meyer, *Monatsh.*, **25**, 475 (1904).

normal and pseudo ethyl esters, V and VIII, about 57% of IV was shown to be present in the cyclic form, VI.[7] The spectra are given in Fig. 1.

The fact that rearrangement of the ethynyl carbinol (II) yields V is of interest in that the hypothetical intermediate alleneol (IX) ketonizes stereospecifically to yield V. We were never able to isolate the trans isomer of V or the corresponding acid and hence assume that it was never formed. Examination of models did not indicate much difference in hindrance in *cis* and *trans* forms of IV or V. It should prove of interest to see if other analogs of II also rearrange stereospecifically.[8]



The acid-catalyzed isomerization of II to V was accompanied by another reaction which produced in small yield an acid, $C_{12}H_{20}O_3$, isomeric with IV. Since this acid did not yield I on oxidation no further work to establish its structure was done.

The ethyl ester (V) was unreactive to ethoxyethynylmagnesium bromide and to attempts at catalytic reduction over various active platinic oxide catalysts or with Raney nickel and alkali.[9] However, reduction at 50–60° over a rhodium-on-alumina catalyst afforded ethyl 3-*t*-butyl-5,5-dimethyl-4-ketohexanoate (X). X was unreactive towards ethoxyethynylmagnesium bromide, ethoxyethynyllithium, and zinc and ethyl bromoacetate. In the latter case a vigorous reaction occurred and all of the bromoester was consumed. However, isolation of unchanged X in high yield from the reaction mixture and the formation of ethyl acetate (from ethyl bromoacetate) indicated that enolization had occurred.[10]

EXPERIMENTAL[11]

2,2,5,5-Tetramethyl-3,4-hexanedione, I, (*dipivaloyl*). Crude pivaloin, m.p. 69–79°, uncorr., prepared in 80–90% yields,[12] was sufficiently pure to be oxidized to I directly. A solution of 50 g. of chromic oxide in 80 ml. of water and 220 ml. of acetic acid was added dropwise to a solution of 103 g. of crude pivaloin in 250 ml. of acetic acid, the temperature being maintained near 15°. After stirring for 24 hr. at room temperature the product, isolated by conventional methods, was vacuum-distilled to yield 59.1 g. of I as a yellow oil, b.p. 66–72° at 20 mm., which showed no hydroxyl band by infrared analysis. The residues from several such oxidations could be combined and reoxidized to give high over-all conversions to I.

On refluxing a solution of 1 g. of I in 10 ml. of alcohol containing 0.9 g. of hydrazine hydrate and a drop of hydrochloric acid until the yellow color had gone (2 days) the monohydrazone of I was obtained as a colorless solid. Recrystallization from alcohol-water yielded pure hydrazone, m.p. 46.0–46.6°.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 65.2; H, 10.9; N, 15.2. Found: C, 65.2; H, 10.9; N, 15.2.

In an attempt to react I with ethylenediamine in refluxing alcohol for 2 days no diminution of the yellow color of the solution was observed and I was recovered from the reaction mixture.

An attempt to oxidize pivaloin in acetic acid at 100° with bismuth trioxide[13] gave the diketone (I) in poor yield together with mostly unchanged pivaloin. Oxidation of pivaloin with neutral permanganate[14] was similarly unsuccessful.

Ethyl 3-t-butyl-5,5-dimethyl-4-keto-2-hexenoate (V). A solution of 18 g. of ethoxyacetylene[15] in 50 ml. of dry ether was added dropwise to 216 ml. of 1.15*M* ethylmagnesium bromide in ether cooled to 0–5°. The dark oily complex which separated dissolved on addition of 125 ml. of dry benzene. After refluxing this solution for 30 min. and cooling, a solution of 34 g. of I in 100 ml. of benzene was added dropwise. The reaction mixture was refluxed for 5 hr. (liquid temperature, 48°), then was cooled and treated with saturated ammonium chloride solution. The washed and dried solution was concentrated under reduced pressure to yield a dark oil which had strong absorption bands[11a] at 4.55 μ (C≡C) and 5.86 μ (C=O) and a medium band at 2.90 μ (OH). On adding alcohol containing hydrogen chloride a rise in temperature was noted, the extent of the rise depending on the size of the run and the amount of hydrogen chloride dissolved in the alcohol. Separation of the reaction products in a conventional way afforded 28.2 g. (58%) of colorless ester, V, b.p. 83–100° at 1 mm., n_D^{20} 1.4650, after a small forerun of I. A portion of redistilled V, b.p. 106° at 2 mm., n_D^{20} 1.4648, d^{20} 0.9672, was taken for analysis.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 70.0; H, 10.1; MR_D, 68.1. Found: C, 69.7; H, 10.3; MR_D, 68.8.

A sample of pure IV was converted into the ethyl ester (V), n_D^{20} 1.4640, with diazoethane.[16] This ester proved identical to the V originally prepared by rearrangement of II, as shown by an identical infrared spectrum.[11a]

Acidification of the alkaline extracts of the reaction

(7) Compare with results in the *o*-benzoylbenzoic acid series, M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **73**, 4627 (1951), and in the β-aroylacrylic series, R. E. Lutz *et al.*, *J. Am. Chem. Soc.*, **75**, 5039 (1953); *J. Org. Chem.*, **18**, 1638 (1953). V had a maximum at 217 mμ (ϵ = 7.45 × 10^3).

(8) Stereospecific rearrangements of ethoxyethynyl carbinols formed by addition of ethoxyethynylmagnesium bromide to ketones have been observed previously but no emphasis was placed on the stereospecificity of the reaction. In most cases the stereochemistry of the product was not mentioned. Several references to such rearrangements follow. K. Brack and H. Schinz, *Helv. Chim. Acta*, **34**, 2009 (1951); H. Kappeler *et al.*, *Helv. Chim. Acta*, **36**, 1862 (1953); D. Magrath *et al.*, *J. Chem. Soc.*, 2393 (1950); P. A. Plattner *et al.*, *Helv. Chim. Acta*, **33**, 1088 (1950); R. Helg *et al.*, *Helv. Chim. Acta*, **39**, 1269 (1956); A. Caliezi and H. Schinz, *Helv. Chim. Acta* **33**, 1129 (1950); I. M. Heilbron *et al.*, *J. Chem. Soc.*, 1823 (1949).

(9) E. Schwenk, *et al.*, *J. Org. Chem.*, **9**, 175 (1944).

(10) M. S. Newman, *J. Am. Chem. Soc.*, **64**, 2131 (1942); A. S. Hussey and M. S. Newman, *J. Am. Chem. Soc.*, **70**, 3024 (1948).

(11) All melting points corrected except as noted. Analyses by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra marked *a* in chloroform, *b* in Nujol mull, c pure liquid.

(12) J. M. Snell and S. M. McElvain, *Org. Syntheses*, **Coll. Vol. II**, 114 (1943).

(13) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(14) Compare N. A. Khan and M. S. Newman, *J. Org. Chem.*, **17**, 1063 (1952).

(15) G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *J. Chem. Soc.*, 1860 (1954).

(16) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

products produced in the above-mentioned alcoholic hydrogen chloride treatment yielded 3.0 g. of an acid, m.p. 179–184° (uncorr.), which, on several recrystallizations from alcohol-water afforded an analytical sample, m.p. 189.4–190.2°. This acid did not yield I on oxidation.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.6, 67.6; H, 9.4, 9.5.

Alternately, a solution of 5.1 g. of I in 20 ml. of benzene was added dropwise to the organolithium prepared by adding 5.6 g. of ethoxyacetylene in 30 ml. of benzene to a solution of phenyllithium made from 11.8 g. of bromobenzene and 1.12 g. of lithium in 60 ml. of ether. The mixture was stirred at room temperature for 15 hr. and was decomposed with 10 ml. of saturated ammonium chloride solution. The crude ethoxyethynyl carbinol (II) thus obtained was treated as described above for the Grignard reaction mixture to yield 3.8 g. (53%) of V.

In a similar experiment 9.0 g. of ethoxyacetylene was added to 104 ml. of a 1.16*M* solution of butyllithium[17] in ether cooled to −10°. Addition of 50 ml. of benzene failed to dissolve the white precipitate which formed. A solution of 5.1 g. of I in 25 ml. of ether-benzene (1:1) was added. After 2 hr. no reaction seemed to have occurred so 75 ml. of tetrahydrofuran was added, the ether was distilled, and the reaction mixture was refluxed (liquid temperature, 43°) for 2 hr. From the neutral fraction of the reaction mixture after basic and acidic hydrolysis there was isolated 3.6 g. of crude solids from which a moderate amount of pure 4-*t*-butyl-2,2-dimethyl-4-hydroxy-3-octanone, m.p. 81.6–82.0°, was obtained. Absorption bands[11a] at 2.80 (m) and 5.90 (s) μ were consistent with the structure which represents the addition of one equivalent of butyllithium to one carbonyl group of I.

Anal. Calcd. for $C_{14}H_{28}O_2$: C, 73.6; H, 12.3. Found: C, 73.1; H, 12.3.

3-t-Butyl-5,5-dimethyl-4-keto-2-hexenoic acid (IV). To a refluxing solution of 15 g. of ethyl bromoacetate and 5.0 g. of I in 35 ml. of dry ether and 100 ml. of benzene was added 10 g. of zinc granules. On distillation of the ether a vigorous reaction occurred. When this moderated 5 g. of bromoester and 4 g. of zinc were added and the mixture was refluxed for one hour. On distillation of the reaction products 1.2 g. of I was recovered in a forerun followed by 2.92 g. (39%) of ethyl 3-*t*-butyl-5,5-dimethyl-3-hydroxy-4-ketohexanoate (III), b.p. 89–93° at 1 mm. Redistillation afforded an analytical sample, n_D^{20} 1.4515, with absorption bands[11a] at 2.96 (s), 5.85 (s) and 5.93 μ (s, shoulder).

Anal. Calcd. for $C_{14}H_{26}O_4$: C, 65.1; H, 10.1. Found: C, 65.1; H, 9.9.

The oily acid, obtained by alkaline hydrolysis of III, could not be crystallized. It was dehydrated to IV by mixing with 0.5 g. of freshly fused powdered potassium acid sulfate in a test tube and heating at 150–160° for 10 min. and at 200° for a very short time. Pure IV, m.p. 105.8–106.5°, formed colorless elongated prisms when recrystallized from Skellysolve B (petroleum ether, b.p. 60–70°). There was no depression of the melting point when mixed with a sample of IV obtained by alkaline hydrolysis of V and the infrared absorption curves[11b] were identical.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5; N.E., 212.3 Found: C, 67.8; H, 9.4; N.E., 213.1.

Oxidation of 200 mg. of IV by shaking in 10 ml. of acetic acid and 0.5 ml. of water containing 500 mg. of chromic oxide at room temperature for 5 hr. afforded a yellow oil which on refluxing for one day with 3 ml. of absolute alcohol, 3 ml. of pyridine, and 0.2 g. of hydroxylamine hydrochloride yielded 80 mg. of the monooxime of I, m.p. 121–122°, undepressed on mixing with an authentic sample.[18] Identical x-ray powder photographs were obtained from the two oximes. Similar oxidation of the acid, $C_{12}H_{20}O_3$, m.p. 189.4–190.2°, mentioned above yielded neither yellow (adjacent dicarbonyl) oil nor oxime, hence a rearranged carbon skeleton is indicated for this acid. No further work was done with it.

Treatment of 3.0 g. of IV with 12 ml. of thionyl chloride at reflux for 90 min. afforded a solid acid chloride, m.p. 78–79° (uncorr.), in quantitative yield. Recrystallization from Skellysolve B yielded colorless cubes of the acid chloride of IV, m.p. 82.2–83.0°. The infrared absorption[11a] (one carbonyl band at 5.65 μ) indicated that this acid chloride had the cyclic structure, VII.

Anal. Calcd. for $C_{12}H_{19}O_2Cl$: C, 62.5; H, 8.3; Cl, 15.4. Found: C, 62.4, 62.3; H, 8.8, 8.7; Cl, 15.1, 14.9.

Since a solution of 1.0 g. of VII and 0.85 g. of silver nitrate in 25 ml. of absolute alcohol and 2 ml. of pyridine at room temperature gave only a slight precipitation of silver chloride in 15 min., the mixture was refluxed. After 0.5 hr. the precipitation of silver chloride was complete. Filtration yielded 0.61 g. of silver chloride (0.62 g. theory) and from the filtrate 0.92 g. (89%) of colorless crystals, m.p. 72–76° (uncorr.), was obtained. Several recrystallizations from Skellysolve B afforded large colorless cubes of pure VIII, m.p. 82.5–83.2°, depressed on mixing with VII. VIII showed strong absorption[11a] at 5.70 μ and a band at 8.80 μ, characteristic of ether linkages, not possessed by VII.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 70.0; H, 10.1. Found: C, 70.2, 70.1; H, 9.9, 10.0.

When the acid chloride (VII) was allowed to stand for 2 days in a solution of absolute alcohol and pyridine at room temperature no reaction had occurred and VII was recovered after a work-up involving treatment with aqueous potassium carbonate. The acidified aqueous extracts did not even give a haziness when treated with silver nitrate.

Ethyl 3-t-butyl-5,5-dimethyl-4-ketohexanoate (X). In the best of several experiments a solution of 14.7 g. of V in 5.0 ml. of freshly distilled alcohol containing 1.5 g. of a 5% rhodium-on-alumina[19] catalyst was shaken under 50 p.s.i. of hydrogen in a bottle held at 50–60° by heating with heating tape. The reduction required 17 hr. until the theoretical amount of hydrogen had been absorbed. An additional 1.2 g. of catalyst was added in three portions during the reduction. Distillation yielded 14.5 g. (98%) of X as a colorless oil, b.p. 83.5–86.0° at 1 mm., n_D^{20} 1.4445. A redistilled center cut, n_D^{20} 1.4440, showed strong absorption bands[11c] at 5.75 and 5.86 μ but no band near 6.13 μ (due to the unsaturation in ester V).

Anal. Calcd. for $C_{14}H_{26}O_3$: C, 69.4; H, 10.8. Found: C, 69.6; H, 11.0.

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(17) Prepared and standardized (85% yield) as described by H. Gilman and R. G. Jones, *Org. Reactions*, **6**, 352 (1951).

(18) L. Bouveault and R. Locquin, *Bull. soc. chim.*, (3) **35**, 657 (1906).

(19) Baker and Co., Newark, N. J.

[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY, LOUISIANA STATE UNIVERSITY]

Synthesis of 1-Alkenyl Alkyl Ethers

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A new method is presented for the preparation of 1-alkenyl alkyl ethers.

The synthesis of 1-alkenyl alkyl ethers has been reported by several investigators. Sigmund and Uchann[1] pyrolyzed acetals using a nickel catalyst. Voronkov[2] heated acetals with sodium bisulfate or sulfanilic acid. Deschamps, Paty, and Pineau[3] decomposed acetals by passing them over kaolin at 300°.

In this investigation it is shown that 1-alkenyl alkyl ethers may be prepared from the corresponding hemiacetals according to the following sequence of reactions.

$$RCH_2CHO + R'OH \rightleftharpoons RCH_2CH(OH)OR' \quad (1)$$

$$RCH_2CH(OH)OR' + HCl \rightleftharpoons RCH_2CH(Cl)OR' + HOH \quad (2)$$

$$RCH_2CH(Cl)OR' + NaOCOCH_3 \longrightarrow RCH_2CH(OCOCH_3)OR' + NaCl \quad (3)$$

$$RCH_2CH(OCOCH_3)OR' \rightleftharpoons RCH{=}CH{-}OR' + CH_3COOH \quad (4)$$

When equimolar quantities of an aldehyde and an alcohol are mixed, it has been shown that equilibrium (1) results.[4,5] The preparation of α-chloroalkyl alkyl ethers (Reaction 2), by saturating a cooled, equimolar mixture of an aldehyde and an alcohol with dry hydrogen chloride, was first reported by Wurtz and Frapolli[6] and the procedure was later modified and used by a number of workers.[7] Hurd and Green[8] reported the synthesis of various 1-alkoxyalkyl acetates by shaking α-chloro ethers with sodium acetate, and Bauer and Neher[9] prepared the acrylic esters of a number of hemiacetals by reacting α-halo ethers with salts of acrylic and methacrylic acid (Reaction 3).

In this work six new 1-alkoxyalkyl acetates (Ia to VIa) were synthesized and their physical constants and analyses are listed in Table I. These acetates were pyrolyzed (Reaction 4) to yield the corresponding ethers (Ib to VIb) shown in Table II. The acetates corresponding to ethers VIIb and VIIIb are not reported due to the ease of decomposition of these two acetates upon heating. Purification by distillation, therefore, was not accomplished, and the crude acetates were pyrolyzed directly.

The pyrolysis of 1-alkoxyalkyl acetates apparently has not been applied to the preparation of 1-alkenyl alkyl ethers, and it became of interest to determine the general applicability of the reaction. Consequently, there was prepared a number of ethers, of which IIb, IIIb, VIb, and VIIb have not been reported previously. This method appears to have several advantages over methods using acetals. It is necessary to use only one mole of alcohol per mole of aldehyde. The pyrolysis temperature is relatively low and decomposition is readily accomplished without the use of a catalyst. Finally, the isolation of pure intermediate products is not mandatory, and it is possible, therefore, to start with an aldehyde and an alcohol and proceed directly to the unsaturated ether.

The 1-alkoxyalkyl acetates and 1-alkenyl alkyl ethers were prepared from the following aldehyde-alcohol mixtures: I, isobutyraldehyde and ethyl alcohol; II, valeraldehyde and ethyl alcohol; III, hexanal and ethyl alcohol; IV, heptanal and ethyl alcohol; V, *n*-butyraldehyde and *n*-butyl alcohol; VI, isobutyraldehyde and isobutyl alcohol; VII, 2-ethylbutanal and 2-ethylbutanol; VIII, 2-ethylhexanal and 2-ethylhexanol.

EXPERIMENTAL

General method of preparation of 1-alkenyl alkyl ethers. *α-Chloroalkyl alkyl ethers.* These compounds were prepared by passing dry hydrogen chloride into a cooled, equimolar mixture of the aldehyde and alcohol according to known methods.[7] The chloro ethers were not distilled before using them due to large losses by decomposition. The yields of crude chloro ethers ranged from 67% to 95%.

1-Alkoxyalkyl acetates. The procedure of Hurd and Green[8] was used with the following modification. Prior to separation of the product from the solid material, the mixture of anhydrous sodium acetate and the α-chloro ether was stirred for two hours, and then heated just below the boiling point, with stirring, for two hours more to complete the reaction. Heating temperatures ranged from 70° for the lowest

(1) F. Sigmund and R. Uchann, *Monatsh.*, **51**, 234 (1929).
(2) M. G. Voronkov, *J. Gen. Chem. (U.S.S.R.)*, **20**, 2060 (1950).
(3) J. Deschamps, M. Paty, and P. Pineau, *Compt. rend.*, **238**, 2006 (1954).
(4) Anon, *Ann. Rept. Schimmel and Co.*, 71 (1933).
(5) W. Herold, *Z. Elektrochem.*, **39**, 566 (1933).
(6) A. Wurtz and A. Frapolli, *Ann.*, **108**, 226 (1858).
(7) (a) D. Gauthier, *Ann. chim. et phys.*, [8] **16**, 311 (1909); (b) B. H. Shoemaker and C. E. Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931); (c) H. R. Henze and J. T. Murchison, *J. Am. Chem. Soc.*, **53**, 4077 (1931).
(8) C. D. Hurd and F. O. Green, *J. Am. Chem. Soc.*, **63**, 2201 (1941).
(9) L. N. Bauer and H. T. Neher, U. S. Pat. Appl. 773,922.

TABLE I

1-ALKOXYALKYL ACETATES

Acetate	No.	Yield, %[a]	B.P., °C.[b]	Mm.	n_D^{25}	d_4^{25}	Analyses[c] MR$_D$ Calcd.	MR$_D$ Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1-Ethoxy-2-methyl-propyl	Ia	50.0	49.5–52	10	1.3991	0.9125	42.42	42.42	59.98	60.37	10.07	10.40
1-Ethoxypentyl	IIa	50.5	62.4–62.8	6	1.4063	0.9057	47.22	47.04	62.04	61.93	10.41	10.29
1-Ethoxyhexyl	IIIa	58.0	70.5–71.5	4	1.4108	0.9041	51.61	51.66	63.79	64.22	10.71	10.96
1-Ethoxyheptyl	IVa	53.4	84–85	4	1.4150	0.8993	56.20	56.30	65.31	64.66	10.96	10.84
1-Butoxybutyl	Va	46.81	69–72	4	1.4102	0.9016	51.68	51.66	63.79	63.61	10.71	10.68
1-Isobutoxy-2-methylpropyl	VIa	63.30	55–56.5	4	1.4058	0.8833	52.26	51.66	63.79	63.53	10.71	10.62

[a] Based on aldehyde. [b] Boiling points are uncorrected. [c] Analyses by Drs. Weiler and Strauss, Oxford, England.

TABLE II

1-ALKENYL ALKYL ETHERS

Ether	No.	Yield, %[a]	Yield, %[b]	B.P., °C.[c]	n_D^{25}	d_4^{25}	Analyses MR$_D$ Calcd.	MR$_D$ Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Methyl-1-propenyl ethyl[d]	Ib	70.5	33.0	92–94	1.4060	0.7772	31.59	31.10				
1-Pentenyl ethyl	IIb	72.5	36.7	118–119	1.4107	0.7884	35.85	35.70	73.63	73.15	12.36	12.20
1-Hexenyl ethyl	IIIb	84.4	49.0	144–147	1.4160	0.7915	40.57	40.31	74.94	74.67	12.58	12.63
1-Heptenyl ethyl[e]	IVb	65.5	35.0	165–168	1.4236	0.8033	45.07	44.93				
1-Butenyl butyl[f]	Vb	73.4	42.2	64–66 (40 mm.)	1.4151	0.7898	40.62	40.31				
2-Methyl-1-propenyl isobutyl	VIb	71.3	56.3	131–132	1.4138	0.7825	40.86	40.32	74.94	75.05	12.58	12.38
2-Ethyl-1-butenyl 2-ethylbutyl	VIIb	—[g]	51	90–90.5 (11 mm.)	1.4350	0.8150	58.90	58.79	78.19	77.77	13.13	13.34
2-Ethyl-1-hexenyl 2-ethylhexyl[h]	VIIIb	—[g]	40	135–136 (10 mm.)	1.4434	0.8199	77.65	77.26				

[a] Based on 1-alkoxyalkyl acetate. [b] Based on aldehyde. [c] Boiling points are uncorrected. [d] Lit.[2] b.p. 94°, n_D^{20} 1.4053, d_4^{20} 0.7757. [e] Lit.[10] b.p. 60–61° (12 mm.), n_D^{21} 1.4250, d_{21}^{21} 0.802. [f] Lit.[11] b.p. 35.5° (10 mm.), n_D^{20} 1.4179. [g] No corresponding pure acetate prepared. [h] Lit.[12] b.p. 137–139° (10 mm.).

molecular weight acetate to 130° for the highest molecular weight compound investigated. The infrared spectra of these acetates showed strong carbonyl absorption at 5.72 μ and strong C—O—C absorption at 8.0–8.2 μ.

1-Alkenyl alkyl ethers. The 1-alkoxylalkyl acetates were heated to temperatures sufficient for decomposition, usually 150–250°, for at least two hours and then were distilled slowly through a 30-cm. fractionating column packed with glass pearls. The distillate, a mixture of acetic acid and unsaturated ether, was washed with an excess of sodium hydroxide or sodium carbonate solution; dried over anhydrous sodium carbonate or potassium hydroxide, and distilled over potassium hydroxide. It was then fractionated to yield the 1-alkenyl alkyl ether. The yields ranged from 65.5% to 81.4%. The infrared spectra of these ethers showed strong ether absorption between 8.1–9.0 μ and strong double bond absorption at 5.9–6.1 μ.

The following examples will illustrate the general procedures employed in this synthetic process.

α-Chlorohexyl ethyl ether. Dry hydrogen chloride was passed into a cold mixture of 100 g. (1.0 mole) of freshly distilled hexanal and 46 g. (1.0 mole) of absolute ethanol until 40 g. (1.09 moles) of hydrogen chloride was absorbed. The lower (aqueous) layer was discarded and the upper layer was dried over anhydrous calcium chloride for two hours. The liquid was then kept under partial vacuum for two hours to remove any excess hydrogen chloride. Purification by distillation results in considerable losses and is unnecessary. The yield of crude α-chlorohexyl ethyl ether was 151 g. (0.915 mole, 91.5%), and it is pure enough for use in the next step of the process.

1-Ethoxyhexyl acetate (IIIa). To 82 g. (1.0 mole) of anhydrous sodium acetate in a 300-ml. three-necked flask, fitted with a mechanical stirrer and a reflux condenser protected by a drying tube, was added, all at once, 158 g. (0.915 mole) of crude α-chlorohexyl ethyl ether which had been cooled to 10°. The mixture was stirred and heat was evolved. Stirring was continued for two hours and then the mixture was warmed to 120° and stirring was continued an additional two hours. After cooling to room temperature, 50 ml. of anhydrous ethyl ether was added to the mixture. The product was then separated from the solid material by filtration, and the solid was washed with another 50 ml. of ether. The ether was removed by evaporation and the residue was distilled under reduced pressure. The distillate was fractionated to yield 109 g. (0.58 mole) of 1-ethoxyhexyl acetate, b.p. 70–71° (4 mm.), n_D^{25} 1.4108, d_4^{25} 0.9041. The yield was 58% based on hexanal and 63.7% based on α-chlorohexyl ethyl ether.

1-Hexenyl ethyl ether (IIIb). Ninety-four grams (0.5 mole) of 1-ethoxyhexyl acetate was heated at 200–230° for two

(10) J. Ficini and H. Normant, *Compt. rend.*, **237**, 731 (1953).

(11) R. H. Hall, A. R. Philpotts, and E. S. Stern, *J. Chem. Soc.*, 3341 (1951).

(12) J. K. Mertzweiler, U. S. Patent 2,578,724.

hours, and then distilled slowly to yield 90 g. of a liquid, b.p. 115–145°. This distillate was washed once with 130 ml. of 20% sodium carbonate solution and twice with 25-ml. portions of the same solution. After being dried over anhydrous sodium carbonate, the remaining 60.1 g. of liquid was distilled over solid potassium hydroxide to yield 57 g. of liquid, b.p. 138–148°, which when fractionated gave 54 g. of 1-hexenyl ethyl ether, b.p. 144–147°, n_D^{25} 1.4160, d_4^{25} 0.7915. The yield was 84.4% based on 1-ethoxyhexyl acetate and 49% based on hexanal.

The infrared spectrum of compound (IIIb) exhibited prominent absorption bands at 3.46(s), 6.02(s), 6.83(m), 7.22(s), 7.34(m), 7.67(m), 7.94(m), 8.07(m), 8.26(s), 8.49(s), 9.02(s), 10.71(m), 12.67(s) microns.

Baton Rouge 3, La.

[Contribution from the Department of Industrial Chemistry, Faculty of Engineering, Kyoto University]

Reaction of Vinyl Ethers with Acidic Imino Compounds. A New Synthesis of Some *N*-Vinyl Imides

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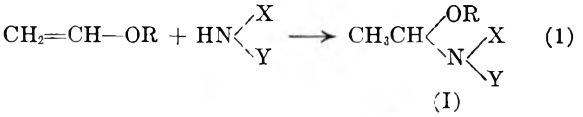
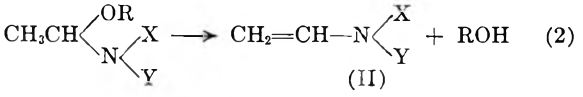
By heating vinyl ethers with dicarboxylic acid imides, there were formed addition products which were proved to be α-imidoethers. With *N*-methyl-*p*-toluenesulfonamide as a reactant, the adduct formation did not occur until an acidic catalyst was added to the reaction system. *N*-Vinylimides were prepared by elimination of alcohol, with the aid of an acidic catalyst, from the corresponding α-imidoethers. In the case of *N*-α-butoxyethyl-*N*-methyl-*p*-toluenesulfonamide, the elimination took place without any added catalyst to give *N*-methyl-*N*-vinyl-*p*-toluenesulfonamide.

In the course of our studies on organic syntheses with vinyl ethers as starting materials, these compounds were found to react readily with some acidic imides to give α-imidoethers (I), from which *N*-vinylimides (II) could be prepared by elimination of alcohol with the aid of acidic catalysts.



(1)

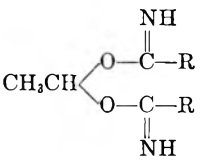


(2)

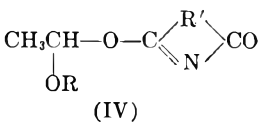
This paper examines the reactivity of these imides and certain amides in the addition reaction. Details of methods for preparing *N*-vinylimides are also reported.

The addition reaction. With dicarboxylic acid imides, the addition reaction (1) was done by heating the reaction mixture without any added catalysts. Under similar reaction conditions, benzamide[1] or *p*-toluenesulfonamide also reacted with vinyl ethers to give ethylidenediamides. *N*-Methyl-*p*-toluenesulfonamide, on the other hand, gave an imidoether (I), provided a small quantity of hydrochloric acid was added. Products, yields, and physical properties are given in Table I.

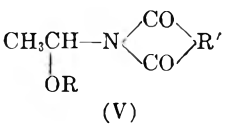
The adducts were readily hydrolyzed by 1:1 hydrochloric acid to give acetaldehyde, the corresponding alcohol, and the dicarboxylic acid, its imide, or the amide. The addition products therefore have α-imido-ether and ethylidenebisamide structures, since β-adducts would not give acetaldehyde on hydrolysis. Since Voronkov[1] reported that ethylidenediacylamides have the structure (III), the alkoxyethyl dicarboxylic imides could have a similar structure (IV). However, as will be described later, *N*-vinylphthalimide was formed by the elimination of alcohol from α-ethoxyethylphthalimide. Thus, structure (IV) can be eliminated[2] in favor of V.



(III)



(IV)



(V)

From experiments to determine the optimum condition for the preparation of *N*-α-butoxyethylsuccinimide, it was found that the optimum condition (100% conversion and 94–95% yield) is as follows: reaction temperature, 195°; reaction time, 3–5 hours; and the molar ratio of succinimide to vinyl ether, 1:2 or 3:4. Results as to the other N-α-alkoxyethyldicarboxylic acid imides are listed in Table II.

In the reaction of butyl vinyl ether with benzamide, we observed that benzamide crystals gradually disappeared on heating, and finally resulted in a clear solution; but, on prolonged heating,

(1) Voronkov reported addition reactions between vinyl ether and some acylamides. M. G. Voronkov, *J. Gen. Chem.* (*U.S.S.R.*), **21**, 1631 (1951); *Chem. Abstr.*, **46**, 8002 (1952).

(2) Ethylidenedibenzamide, $(C_6H_5CONH)_2CHCH_3$, is also reported. British Patent 710,468; *Chem. Abstr.*, **49**, 11709 (1955).

TABLE I

α-IMIDOETHERS, α-IMINOETHER AND ETHYLIDENEDIAMIDES

Compound	Yield,[a] %	M.P., °C.	Formula	Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
N-α-Ethoxyethylsuccinimide	93	124–125 (8 mm.)[b]	$C_8H_{13}O_3N$	56.12	56.26	7.65	7.50	8.18	7.91
N-α-Butoxyethylsuccinimide	95	135–138 (9 mm.)[c]	$C_{10}H_{17}O_3N$	60 28	60.51	8.60	8.78	7.03	7.04
N-α-Phenoxyethylsuccinimide	79	77.5–78.5[d]	$C_{12}H_{13}O_3N$	65 74	65.99	5.98	6.02	6.39	6.42
N-α-Ethoxyethylphthalimide	82	63–65[e]	$C_{12}H_{13}O_3N$	65 74	65.92	5.98	5.52	6.39	6.82
N-α-Phenoxyethylphthalimide	41	92.5–93.5[e]	$C_{16}H_{13}O_3N$	71 90	72.18	4.90	5.03	5.24	5.15
N-α-Butoxyethylglutarimide	91	145–146 (5 mm.)[f]	$C_{11}H_{19}O_3N$	61 94	61.18[g]	8.98	8.94	6.62	6.90
N-α-Ethoxyethylcarbazole	54	74–74.5	$C_{16}H_{17}ON$	80 30	80.08	7.16	7.01	5.85	5.57
N-α-Butoxyethyl-*N*-methyl-*p*-toluenesulfonamide	84	160–164 (4 mm.)[h]	$C_{14}H_{23}O_3NS$	58.91	58.91	8.13	7.67	4.91	5.47[i]
Ethylidenedibenzamide	63	203–205	$C_{16}H_{16}O_2N_2$	71.62	71.49	6.01	5.92	10.44	10.19
Ethylidenedi-*p*-toluenesulfonamide	11	110–114 dec.	$C_{16}H_{20}O_4N_2S_2$	52.15	52.65	5.47	5.57	7.60	7.29

[a] Based upon unrecovered imide, amide, or carbazole. [b] Boiling point of liquid adduct. [c] Boiling point of liquid adduct; n_D^{20} 1.4678, d_4^{20} 1.069. The crude product was washed three times with water, dried over sodium sulfate, and redistilled. [d] Recrystallized once from alcohol and then three times from the mixture of benzene and petroleum benzine. [e] Recrystallized from alcohol. [f] Boiling point of liquid adduct; n_D^{17} 1.4750. The crude fraction was dissolved in petroleum ether and filtered. The filtrate was redistilled under nitrogen. [g] The analysis was unsatisfactory owing to slight decomposition, but on hydrolyzing with 1:1 hydrochloric acid the adduct gave acetaldehyde in almost quantitative yield. [h] Boiling point of liquid adduct. Distillation was carried out under nitrogen. [i] The analysis was unsatisfactory owing to the slight decomposition, but the results of hydrolysis and elimination of alcohol support this structure.

TABLE II

PREPARATIONS OF SOME *N*-α-ALKOXYETHYL-DICARBOXYLIC ACID IMIDES

Product	Reactant Moles of Imide	Moles of Vinyl Ether	Temp., °C.	T, Hr.	Yield,[a] %
N-α-Ethoxyethylsuccinimide	2	5	160	7	93
N-α-Phenoxyethylsuccinimide[b]	0.1	0.15	260	4.5	79
N-α-Ethoxyethylphthalimide[c]	0.75	3.0	160	9	82
N-α-Phenoxyethylphthalimide[d]	0.1	0.15	260	2	41
N-α-Butoxyethylglutarimide[e]	0.3	1.5	220	6	91

[a] Based upon the reacted succinimide. [b] Reactants were diluted with 20 ml. of benzene. [c] Isolated after vinyl ether and acetal were removed from the reaction mixture by cooling the residue and collecting the crystals. [d] Reactants were diluted with 20 ml. of benzene. The mixture was distilled under reduced pressure, and the fraction, b.p. 170–205° (3 mm.), allowed to crystallize with cooling; the solidified fraction was pressed on a clay plate. Conversion 72%. [e] Conversion 56%.

white crystals reappeared and increased in quantity. The latter crystals were proved to be ethylidenedibenzamide. The formation of α-butoxyethylbenzamide as an intermediate may be supposed from these observations. However, an attempt to isolate the intermediate by vacuum distillation failed because of its instability.

An *N*-alkyl acylamide (*N*-methylacetamide), *N*-aryl acylamide (acetanilide, benzanilide, *p*-nitroacetanilide), ε-caprolactam and phenanthridone did not react even at temperatures as high as 200–220°.

As shown in Table I, carbazole added to ethyl vinyl ether, but indole and acridone gave only resinous substances and diphenylamine did not react under the conditions.

p-Toluenesulfonamide reacted with phenyl vinyl ether in the presence of concentrated hydrochloric acid to give ethylidenedi-*p*-toluenesulfonamide (VII). Even without the catalyst, reaction with *n*-butyl vinyl ether took place, but the product, which was obtained as white crystals, decomposed to the starting amide on further purification. Presumably, this may be the amidoether (VI). The formation of ethylidenedi-*p*-toluenesulfonamide is considered to occur in the same way as the carboxylic acid amide.

$$CH_2{=}CHOR + CH_3C_6H_4SO_2NH_2 \longrightarrow CH_3CH(OR)NHO_2SC_6H_4CH_3 \quad (3)$$

(VI)

$$CH_3CH(OR)NHO_2SC_6H_4CH_3 + CH_3C_6H_4SO_2NH_2 \longrightarrow CH_3CH(NHO_2SC_6H_4CH_3)_2 \quad (4)$$

(VII)

N-Methyl-*p*-toluenesulfonamide also reacted with *n*-butyl vinyl ether in the presence of concentrated hydrochloric acid to give an 84% yield of *N*-methyl - *N* - α - butoxyethyl - *p* - toluenesulfonamide (VIII).

TABLE III

ELIMINATION OF ALCOHOL FROM α-IMIDOETHERS

α-Imidoether	Method	Catalyst	Conversion (%)	Yield[a] (%)
N-α-Ethoxyethylsuccinimide	B	$NaHSO_4 \cdot H_2O$	100	69
N-α-Ethoxyethylsuccinimide	A	$NaHSO_4 \cdot H_2O$	Produced resins	—
N-α-Butoxyethylsuccinimide	B	$NaHSO_4 \cdot H_2O$	60–90	76
N-α-Butoxyethylsuccinimide	B	$KHSO_4$	67	61
N-α-Butoxyethylsuccinimide	B	P_2O_5	73	60
N-α-Butoxyethylsuccinimide	B	$H_2N \cdot C_6H_4 \cdot SO_3H$	0	0
N-α-Butoxyethylsuccinimide	B	H_2SO_4	79	76
N-α-Ethoxyethylphthalimide	B	$NaHSO_4 \cdot H_2O$	100	26
N-α-Ethoxyethylphthalimide	A	$NaHSO_4 \cdot H_2O$	100	65
N-α-Ethoxyethylcarbazole	B	$NaHSO_4 \cdot H_2O$	100	0
N-α-Ethoxyethylcarbazole	A	$H_2N \cdot C_6H_4 \cdot SO_3H$	88	0

[a] Based upon the reacted succinimide.

$$\begin{array}{l} CH_3CHN(CH_3)O_2SC_6H_4CH_3 \\ \quad | \\ \quad OC_4H_9 \end{array}$$

(VIII)

However, this was not so stable as products from dicarboxylic acid imides, so distillation was accompanied by slight decomposition. Even without catalyst, saccharin reacted quite readily with *n*-butyl vinyl ether, but the product was too unstable to be isolated.

From the results described above, it may be seen that -NH-group which can add to vinyl ether are loosely classified into acidic imides, amides, and imine. The sulfonyl or carbonyl group attached to the nitrogen atom seems to increase the reactivity of the amine. The pyrrole ring has also a weaker activating effect.

Preparation of N-vinylimides. The direct preparation of *N*-vinyldicarboxylic acid imides has been caried out by the reaction between acetylene and dicarboxylic acid imides in the presence of mercuric salts[3] or cadmium acetate[4] as catalyst under pressure, and by a vapor phase reaction using catalysts such as zinc oxide or cadmium oxide.[5] These methods are not satisfactory from a point of view of reaction rate or conversion. As to the indirect method, Yoshida and Hirakawa[6] reported the preparation of *N*-vinylphthalimide from vinyl acetate and phthalimide. Hanford and Stevenson[7] reported the preparation and polymerization of *N*-vinylsuccinimide and other aliphatic vinyl tertiary amides. We therefore tried to prepare *N*-vinylimides by elimination of alcohol from the α-imidoethers which were obtained through the above method.

Elimination of alcohol from the imidoether was carried out by heating a mixture of imidoether and catalyst. After the reaction, the catalyst was made inactive and the *N*-vinylimide formed was separated by chilling or distillation (Method A). This method was suitable for the preparation of *N*-vinyl imides which were relatively stable to the catalyst and heat, such as *N*-vinylphthalimide. However, in the case of unstable *N*-vinylimides such as *N*-vinylsuccinimide, the elimination reaction and the distillation were simultaneously carried out (Method B).

In Table III are listed the catalysts used and a comparison of Methods A and B.

In the elimination of butanol from *N*-α-butoxyethylsuccinimide by Method B, it is shown that sodium bisulfate and sulfuric acid are most effective catalysts. Since sodium bisulfate does not have so strong an effect, the poor reproducibility of the results may be ascribed to the heterogeneity of the reaction mixture. With sulfuric acid as catalyst, reaction was rapid and the results were reproducible, but the effect was so strong that careful control of the reaction conditions was required to avoid side reactions. Potassium bisulfate and phosphorus pentoxide were somewhat less effective catalysts.

N-Vinylsuccinimide was prepared by Method B; Method A gave only a resinous substance. Compared with *N*-vinylsuccinimide, *N*-vinylphthalimide has a higher boiling point and lower polymerizability, and so Method A gave the better result. Although attempts were also made to prepare *N*-vinylglutarimide from *N*-α-butoxyethylglutarimide by both methods, the latter compound was shown to decompose only to glutarimide, but not to *N*-vinylglutarimide under the conditions.

When *N*-methyl-*N*-α-butoxyethyl-*p*-toluenesulfonamide was distilled at 250–260° under a pressure of 22–30 mm., it was decomposed almost completely to give 1-butanol and *N*-vinyl-*N*-methyl-*p*-toluenesulfonamide in 74% yield based upon the reacted sulfonamide. Attempts to prepare *N*-vinylcarbazole from the corresponding imidoether failed

(3) R. F. Conaway, U. S. Patent **2,231,887**; *Chem. Abstr.*, **35**, 3266 (1941).

(4) A. Onishi and J. Furukawa, *J. Soc. Organic Synthetic Chem. Japan*, **9**, 69 (1951).

(5) S. Akiyoshi, T. Matsuda, and J. Murata, *J. Chem. Soc. Japan, Ind. Chem. Section*, **56**, 440 (1953).

(6) T. Yoshida and H. Hirakawa, *J. Chem. Soc. Japan, Ind. Chem. Section*, **55**, 83 (1952).

(7) W. E. Hanford and H. B. Stevenson, U. S. Patent **2,231,905**; *Chem. Abstr.*, **35**, 3267 (1941).

EXPERIMENTAL

Reaction of dicarboxylic acid imides with vinyl ethers. In a stainless steel rocking autoclave were placed dicarboxylic acid imide, an excess of vinyl ether, and 0.2–1.0 g. of hydroquinone. The autoclave was flushed with nitrogen and then heated. The temperature and the time of reaction are listed in Table II. After the reaction, the autoclave was allowed to cool to room temperature and opened. The unreacted imide was removed by filtration (followed by washing with water, if necessary, such as in the case of succinimide). Then vinyl ether and acetal were stripped off and the residue was submitted to a vacuum-distillation under nitrogen. In the case of phthalimide, recrystallizations of the residue from alcohol gave a better yield. Table I lists the yields and analytical data for these products.

Acid hydrolysis of α-imidoethers derived from dicarboxylic acid imide. A sample of 4–10 g. α-imidoether and 30–40 ml. of 1:1 hydrochloric acid were placed in a flask equipped with inlet and outlet tubes. The mixture was heated to 80° for 2–4 hr. During the period a slow current of nitrogen was passed through in order to remove the last trace of acetaldehyde formed. The acetaldehyde vapor was introduced into ethanol at 0° and converted to 2,4-dinitrophenylhydrazone according to Brady.[8] The hydrazone was recrystallized several times from ethanol, m.p. 164–166.5°, and was identified by a mixture melting point with an authentic sample. Dicarboxylic acid or its imide was obtained in good yield from the reaction mixture by filtration or by evaporating to dryness and then extracting with acetone. Melting points were not depressed by mixing with corresponding authentic samples (phthalimide, m.p. 222–224°; succinic acid, m.p. 186.5–188°; glutaric acid, m.p. 96–97°). Hydrolysis of *N*-α-butoxyethylglutarimide gave acetaldehyde (yield 99%), butanol (yield 25%) and glutaric acid (yield 80%).

N-Vinylsuccinimide[7] *from N-α-butoxyethylsuccinimide, Method B.* The apparatus consisted of a reactor, a condenser, and two receivers. The reactor was a modified Claisen distillation flask with an additional neck through which a thermometer was dipped into the reaction mixture. The second receiver, which has a coiled glass tube, was chilled with ice-salt mixture. A mixture of 199 g. (1 mole) of *N*-α-butoxyethylsuccinimide and 1.4 g. of powdered sodium bisulfate monohydrate was placed in the reactor. In the case of sulfuric acid catalyst, 0.4 ml. of the acid was placed at the beginning and 0.2 ml. more was added when the reaction rate had dropped considerably. The system was maintained at a pressure of 6–7 mm. and swept with nitrogen for 30 min. When the mixture was heated in an oil bath at 113–120°, vigorous decomposition occurred and 1-butanol and *N*-vinylsuccinimide began to distil. At the end of the reaction, the reaction temperature was elevated to 125–130°. It took 2.5–3.5 hr. to distil over the contents of the flask. The condensate in the second receiver was mainly 1-butanol (b.p. 116–118°; 3,5-dinitrobenzoate, m.p. 62–63°, identification by the mixture melting). To the condensate in the receiver I was added a small amount of hydroquinone, and it was fractionated under nitrogen. There was obtained a small amount of 1-butanol and the following fractions: (*1*) b.p. 96–111° (7.5 mm.), (*2*) b.p. 111–125° (7.5 mm.), (*3*) b.p. 125–132° (7.5 mm.). The first fraction was crystallized from ether, m.p. 48–49° (*N*-vinylsuccinimide).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.65; H, 5.52; N, 11.03.

The third fraction was a mixture of unreacted butoxyethylsuccinimide and succinimide. They were separated by filtration. The results are listed in Table III. Similar reaction conditions were employed in the case of the other catalysts.

Method A: When the above reaction mixture was heated at 113–120° for 3 hr. without simultaneous distillation of the products during the reaction, the contents were resinified and *N*-vinylsuccinimide could not be obtained on distillation.

N-Vinylsuccinimide from N-α-ethoxyethylsuccinimide, Method B. The elimination of alcohol from *N*-α-ethoxyethylsuccinimide (48.9 g., 0.29 mole) was carried out in a similar way. *N*-Vinylsuccinimide was isolated by chilling the distillate to −73° in a Dry Ice–ethanol bath. Twenty-four and seven-tenths grams of crystals were thus obtained (yield 69%), and were recrystallized from alcohol yielding white crystals, m.p. 48–49°. Yield was 18.8 g. (60%). The distillate, condensed in receiver II, was proved to be ethanol.

Acid hydrolysis of *N*-vinylsuccinimide was done in a manner similar to the α-imidoether and gave acetaldehyde in an almost quantitative yield and succinic acid in 76% yield.

N-Vinylphthalimide, Method A. A mixture of 11 g. (0.05 mole) of *N*-α-ethoxyethylphthalimide and 0.2 g. of powdered sodium bisulfate monohydrate was placed in a 100 ml., three-necked flask equipped with a thermometer, gas inlet- and outlet-tube. After the system was swept with nitrogen for 30 min., the mixture was heated at 126° (initial)–143° (final) for 15 min., cooled to room temperature and extracted with ether. Ether was stripped off and the residue was distilled under reduced pressure with a small amount of hydroquinone. A fraction (5.7 g.; 65.1%) of b.p. 119–125° (6.5 mm.), m.p. 77–82° was obtained. Recrystallization from ethanol gave white crystals, m.p. 84°.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.34; H, 4.08; N, 8.09. Found: C, 69.47; H, 4.12; N, 7.92.

Elimination of 1-butanol from N-α-butoxyethylglutarimide. Sodium bisulfate monohydrate (0.1 g.) was added to 10 g. of *N*-α-butoxyethylglutarimide and the mixture was treated according to Method B at 136–139° under reduced pressure of 8 mm. Hg. A small amount (1.5 g., 28%) of glutarimide was obtained by chilling the distillate.

Ethylidenedibenzamide. A mixture of 1 g. (0.008 mole) of benzamide and 3 g. (0.025 mole) of phenyl vinyl ether was refluxed gently for 2 hr. After cooling to room temperature, the precipitates were filtered and recrystallized from benzene, m.p. 137–157°; yield 0.7 g. (63%) of crude ethylidenedibenzamide. After four successive recrystallizations from benzene, the melting point was raised to 203–205°.

Reaction of benzamide with n-butyl vinyl ether. A mixture of 60 g. (0.5 mole) of benzamide, 200 g. (2 moles) of *n*-butyl vinyl ether and 0.5 g. of hydroquinone was heated in an oil bath at 110°. The crystals of benzamide disappeared gradually to give a clear solution. After heating for 10 hr., white crystals began to deposit. The crystals were filtered (10.8 g.) and recrystallized from benzene, m.p. 202–204°. They were identified by mixture melting with an authentic sample of ethylidenedibenzamide. Dibutyl acetal (66.8 g.) and unreacted vinyl ether were removed from the filtrate. The remaining residue (102 g.) could not be distilled without decomposition even *in vacuo* and under nitrogen. The distillate (79 g.) was composed of 1-butanol and a liquid, b.p. 165–192° (4.2 mm.), which was distilled twice at reduced pressure to yield an unknown material, b.p. 182–186° (3 mm.), having the following elementary composition.

Anal. Found: C, 71.72; H, 8.56; N, 5.43.

Reaction of p-toluenesulfonamide with n-butyl vinyl ether. When a mixture of *p*-toluenesulfonamide and *n*-butyl vinyl ether was heated at 110°, a clear solution was obtained after 5–10 min. After cooling to room temperature, the precipitates were filtered and dried. The precipitates were found not to be *p*-toluenesulfonamide by their m.p. (70–74°) and mixture melting, but the identification of their structure failed because they were too unstable to be isolated in pure state.

Ethylidenedi-p-toluenesulfonamide. A mixture of 8.5 g. (0.05 mole) of *p*-toluenesulfonamide, 12 g. (0.1 mole) of phenyl vinyl ether and two drops of concentrated hydrochloric acid was heated on a steam bath. The crystals of *p*-toluenesulfonamide disappeared after 15 min. to give an

(8) O. L. Brady, *J. Chem. Soc.*, 757 (1931).

orange solution. Heating was stopped after 20 min., the mixture was cooled to room temperature, and the precipitates were filtered. The precipitates were heated with 20 ml. of benzene and filtered hot with suction. Insoluble matter was washed with benzene and dried, m.p. 115–117°, yield, 1 g. (11%). After five successive crystallizations from benzene, white needles melting with decomposition at 110–114° were obtained.

The acid hydrolysis of ethylenedi-*p*-toluenesulfonamide was worked up as described previously. Acetaldehyde 2,4-dinitrophenylhydrazone and *p*-toluenesulfonamide (85.8%) were obtained.

N-α-Butoxyethyl-N-methyl-p-toluenesulfonamide (IX). A mixture of 111 g. (0.6 mole) of *N*-methyl-*p*-toluenesulfonamide, 240 g. (2.4 moles) of *n*-butyl vinyl ether and 0.6 ml. of concentrated hydrochloric acid was heated at 60° for 2.5 hr., allowed to cool, washed successively with 5% sodium hydroxide solution and water, and dried over sodium sulfate overnight. Vacuum distillation under nitrogen yielded 144.2 g. (84%) of product, b.p. 162–184° (5.5 mm.). During the distillation, slight decomposition was observed. An analytical sample was prepared by redistillation, b.p. 160–164° (4 mm.).

The same procedure was used for the acid hydrolysis of (IX) as described previously. Acetaldehyde 2,4-dinitrophenylhydrazone (91%) and *N*-methyl-*p*-toluenesulfonamide (77%) were identified.

N-Vinyl-N-methyl-p-toluenesulfonamide. A sample of 144 g. (0.505 mole) of *N*-α-butoxyethyl-*N*-methyl-*p*-toluenesulfonamide was heated in a Claisen flask under a pressure of 22–30 mm. The bath temperature was maintained at 250–260°. The imidoether distilled with decomposition to give 1-butanol and a yellow, oily fraction, b.p. 196–198° (22–30 mm.). Redistillation of the oil yielded 93 g. (87%) of crude product, b.p. 150–157° (4 mm.), which was recrystallized from petroleum ether-benzene to give white crystals, m.p. 56–57.7°.

Anal. Calcd. for $C_{10}H_{13}O_2NS$: C, 56.84; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.31; N, 6.57.

Polymerization. N-Vinyl-*N*-methyl-*p*-toluenesulfonamide was heated with 2% benzoylperoxide for 7 hr. on a boiling water bath, but failed to polymerize. On the other hand, when a few drops of an ether solution of boron trifluoride etherate were added to an ether solution of the vinyl sulfonamide, a white polymer deposited, which was insoluble in ether, acetone, and benzene.

N-α-Ethoxyethylcarbazole. A 13.4 g. (0.08 mole) sample of carbazole was treated with 34.6 g. (0.48 mole) of ethyl vinyl ether for 5 hr. at 180° by the same procedure as in the case of dicarboxylic acid imide. There was obtained 8.8 g. (54%) of crude product, b.p. 163–169° (3 mm.). After recrystallization from ethanol, it melted at 74–74.5°.

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Pyrolysis of Organic Carbonates

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A study of the pyrolysis of organic carbonates in a flow system has been carried out to determine the utility of the reaction for the introduction of unsaturation into aliphatic chains.

A comparison of the ease of decomposition of ethyl carbonates and acetates of α-phenethyl alcohol and β-phenethyl alcohol has indicated that the four esters can be arranged into the following order of pyrolytic instability: 300°: β-acetate ≃ β-carbonate ≃ α-acetate ≃ α-carbonate; 400°: β-acetate < β-carbonate < α-acetate < α-carbonate; 500°: β-acetate < β-carbonate < α-acetate = α-carbonate. Pyrolysis of aliphatic bis(ethyl carbonates) led to the formation of dienes as well as a number of intermediate products.

In another study,[1] the disproportionation of unsymmetrical carbonates to form symmetrical carbonates was studied. Formation of the symmetrical carbonates depended on the nature of the group, Ar, and the catalyst.

$$2ArOCO_2C_2H_5 \xrightarrow[\text{catalyst}]{} ArOCO_2Ar + (C_2H_5O)_2CO$$

Ethyl β-phenethyl carbonate underwent a side reaction to form considerable amounts of styrene, rather than the symmetrical carbonate. The catalyzed disproportionations were carried out at 250°, a temperature approaching the range in which esters pyrolyze to form olefins and acids. It was decided to investigate to what extent the formation of styrene was due to the noncatalyzed pyrolysis reaction.

$$C_6H_5CH_2CH_2O\overset{\overset{O}{\|}}{C}OC_2H_5 \longrightarrow C_6H_5CH{=}CH_2 + C_2H_5OH + CO_2$$

This route is apparently favored over formation of ethylene and β-phenethyl alcohol, since no β-phenethyl alcohol was isolated from the pyrolyses mixtures.

A comparison of acetate and carbonate pyrolyses has been included in this work. It is hoped that carbonic ester pyrolysis will serve as an acid-free pyrolysis system, for use in the preparation of unsaturates bearing acid sensitive functional groups.

A. Pyrolyses of phenethyl alcohol esters. Pyrolyses of the acetates and ethyl carbonates of α-phenethyl alcohol and β-phenethyl alcohol indicate that the carbonate structure undergoes pyrolytic rupture under conditions similar to those used for the acetate unit. Both the α- and β-esters of the two al-

(1) J. L. R. Williams, D. D. Reynolds, K. R. Dunham, and J. F. Tinker, unpublished results.

cohols pyrolyze only very slowly in the vicinity of 300° while the pyrolysis rates of both the acetates and the carbonates of the α-alcohol increase more rapidly with increase in temperature than do the β-alcohol esters. The four esters can be arranged into the following order of pyrolytic instability:

300° β-acetate ≈ β-carbonate ≈ α-acetate ≈ α-carbonate
400° β-acetate < β-carbonate < α-acetate < α-carbonate
500° β-acetate < β-carbonate < α-acetate = α-carbonate

These relationships indicate that at 300° there is very little difference in pyrolytic stability between the carbonates and the acetates of α-phenethyl alcohol and β-phenethyl alcohol since all four esters decompose to the extent of less than one per cent. In the presence of catalysts, considerable decomposition has been shown to occur[1] at 250°. At 400°, however, the esters decompose at different rates as a result of two structural features: (*1*) acetate *vs.* carbonate structure, and (*2*) primary alcohol ester *vs.* a secondary alcohol ester. The 400° pyrolyses indicate that although the primary esters are more stable than the secondary esters, there is, nevertheless, a difference between the stability of the carbonate structure and the acetate structure in both the α- and the β-series. At 500°, the secondary ester structure contributes much more to the instability than does the difference between carbonate and acetate structures. However, in the primary ester system at 500°, the carbonate structure causes greater instability than does the acetate.

The pyrolyses work was extended to other carbonic esters to investigate the effect of structure and the general synthetic utility.

B. Pyrolysis of 1,5-bis(ethoxycarbonyloxy)pentane. Following are the products isolated from the pyrolysis of 1,5-bis(ethoxycarbonyloxy)pentane:

$C_2H_5OCO_2(CH_2)_5OCO_2C_2H_5 \longrightarrow$

$CH_2{=}CH{-}CH_2{-}CH{=}CH_2$	8.6%
$CH_2{=}CH_2$	no recorded yield
C_2H_5OH	23.5%
$CH_2{=}CH{-}CH_2{-}CH_2{-}CH_2{-}OH$	30.2%
$HO{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}OH$	7.6%
CO_2	no yield

During the pyrolysis of 1,5-bis(ethoxycarbonyloxy)pentane, there is competition between the two reaction sequences which can introduce double bonds into either the five-carbon chain or the two-carbon chain. Formation of ethylene will lead to the formation of the alcohol or diol in the five-carbon chain.

$$2CH_2{=}CH_2 + HOCH_2(CH_2)_3CH_2OH$$
$$C_2H_5OCO_2CH_2(CH_2)_3CH_2OCO_2C_2H_5 \quad + CO_2$$
$$2C_2H_5OH + CH_2{=}CHCH_2CH{=}CH_2$$

extreme cases

Formation of ethanol requires introduction of double bonds into the five-carbon chain. In practice, however, both reaction sequences proceed simultaneously, leading to the products just outlined. It would be expected that, under different flow rates and temperatures, the ratios of the various products would be shifted.

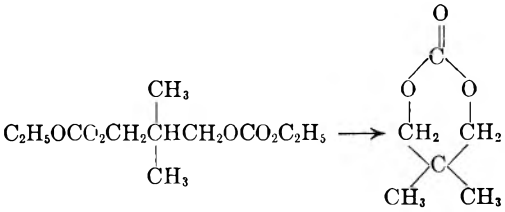
C. Pyrolysis of 1,10-bis(ethoxycarbonyloxy)decane. Pyrolysis of 1,10-bis(ethoxycarbonyloxy)decane under conditions identical with those used for 1,5-bis(ethoxycarbonyloxy)pentane led to the formation of two additional types of products, the mono-olefin-monocarbonate and the carbonate-carbinol.

$C_2H_5OCO_2(CH_2)_{10}OCO_2C_2H_5 \longrightarrow$

$C_2H_5OCO_2(CH_2)_8CH{=}CH_2$	3.4%
$C_2H_5OCO_2(CH_2)_{10}OH$	7.8%
$CH_2{=}CH(CH_2)_5CH{=}CH_2$	10.6%
$CH_2{=}CH(CH_2)_8OH$	27.4%
$HO(CH_2)_{10}OH$	18%
Ethylene	no recorded yield
Ethanol	4.7%

As in the case of 1,5-bis(ethoxycarbonyloxy)-pentane, the major product (highest conversion) was the olefinic carbinol. The isolation of the mono-olefin-monocarbonate and the carbonate-carbinol would indicate a somewhat slower decomposition in the case of the ten-carbon system.

D. Pyrolysis of 1,3-bis(ethoxycarbonyloxy)-2,2-dimethylpropane. Pyrolysis of 1,3-bis(ethoxycarbonyloxy)-2,2-dimethylpropane caused cyclization of the carbonate structure with elimination of ethyl carbonate or its equivalents, to form 2,6-dioxa-4,4-dimethylcyclohexanone in 51.5% yield.



Ethylene—no recorded yield
Ethanol—no recorded yield

E. Pyrolysis of allyl ethyl carbonate. The reaction mixture produced by the pyrolysis of allyl ethyl carbonate failed to yield any clean-cut fractions upon distillation. The fractions were shown, by infrared spectroscopy and mass spectrometry, to consist of the following components:

$CH_2{=}CHCH_2OCO_2C_2H_5 \longrightarrow$

C_2H_5OH	5.5%
$CH_2{=}CHCH_2OH$	44.5%
$C_2H_5OCO_2C_2H_5$	2.2%
$CH_2{=}CHCH_2OCO_2C_2H_5$	45.5% recovery

TABLE I

STARTING MATERIALS

Compound	B.P. or M.P., °C. Found	B.P. or M.P., °C. Lit.	Refractive Index and Density Found	Refractive Index and Density Lit.	Analysis Calcd.	Analysis Found
α-Phenethyl acetate[a]	213–216		d_{17} 1.050			
β-Phenethyl acetate[b]	224		n_D^{25} 1.5108 d_{26} 1.029			
Ethyl α-phenethyl carbonate	72/0.5 mm.		n_D^{25} 1.4859 d_{26} 1.051		C—68.0 H— 7.3	67.8 7.4
Ethyl β-phenethyl carbonate[c]	99 (1.0 mm.)	140–141 (1.7 mm.)	n_D^{25} 1.4904 d_{26} 1.023	n_D^{22} 1.4889 d_{22} 1.063	C—69.9 H— 6.9	70.0 7.0
1,5-Bis(ethoxycarbonyloxy)-pentane[d]	138/2.5 mm.		n_D^{25} 1.4253			
1,10-Bis(ethoxycarbonyloxy)-decane[d]	176–178/1.3 mm. m.p. 17					
1,3-Bis(ethoxycarbonyloxy)-2,2-dimethylpropane	83–84/0.8 mm.				C—53.3 H— 8.0	53.1 7.7
Allyl ethyl carbonate[e]	148–149		n_D^{25} 1.4069 d_{26} 0.985	n_D^{25} 1.4095 d_{25} 0.98		

[a] Beilstein, **6,** 476 (1923). [b] Beilstein, **6,** 479 (1923). [c] P. Schviny and S. Sabetay, *Bull. soc. chim. France,* **43,** 859 (1928). [d] D. D. Reynolds and J. Van Den Berghe (Eastman Kodak Co.), U. S. Patent **2,789,968** (1957). [e] D. E. Adelson and H. Dannenberg, U. S. Patent **2,595,214** (1952).

TABLE II

PYROLYSIS PRODUCTS

Compound	B.P. or M.P., °C. Found	B.P. or M.P., °C. Lit.	Refractive Index and Density Found	Refractive Index and Density Lit.	Analysis Calcd.	Analysis Found
1,4-Pentadiene[a]	25.5	25.8–26.2	n_D^{25} 1.3890	n_D^{20} 1.3883		
5-Hydroxy-1-pentene[b]	53 (17 mm.)	53 (17 mm.)	n_D^{25} 1.4320	n_D^{15} 1.4305		
5-Ethoxycarbonyloxy-1-pentene	42 (0.2 mm.)		n_D^{25} 1.4198		C—60.7 H— 8.8	61.1 9.2
1,5-Pentanediol[c]	238–239		n_D^{25} 1.4470			
Ethylene dibromide[d]	131.5	131.6	n_D^{25} 1.5337	n_D^{25} 1.5379	Br—85.2	85.2
1,9-Decadiene[e]	60 (15 mm.)	165	n_D^{25} 1.4297	n_D^{20} 1.4300		
10-Hydroxy-1-decene[f]	85–86 (2 mm.)	234–238	n_D^{25} 1.4454	n_D^{25} 1.4480		
10-Phenylureido-1-decene	49–50 m.p.	49–50 m.p.				
10-Ethoxycarbonyloxy-1-decene	106 (0.5 mm.)		n_D^{25} 1.4362 $d_{20/4}$ 0.937		C—69.0 H—10.5	68.5 10.8
1-Hydroxy-10-ethoxycarbonyloxydecane	170–175 (0.5 mm.)		n_D^{25} 1.4410 $d_{25/4}$ 0.997		C—63.5 H—10.6	63.8 10.5
1-Phenylureido-10-ethoxycarbonyloxydecane	65–67 m.p.				C—65.8 H— 8.8 N— 3.8	65.3 8.8 3.8
1,10-Decanediol[g]	70–71 m.p.	70.5				
1,10-Bis(phenylureido)decane	166–167 m.p.				C—70.0 H— 7.8 N— 6.8	70.1 7.5 6.7
2,6-Dioxa-4,4-dimethylcyclohexanone	109–110 m.p.				C—55.3 H— 7.7	54.9 7.9
Allyl alcohol[h]		96–97		n_D^{25} 1.4135		
Diethyl carbonate[i]	128–129	127–129 (760 mm.)	n_D^{25} 1.3850	n_D^{20} 1.3852		

[a] P. Krogerman, *J. Am. Chem. Soc.,* **52,** 5060 (1930). [b] *Org. Syntheses,* **25,** 84 (1945). [c] N. Demjanow and M. Dojarenko, *Ber.,* **40,** 2589 1907). [d] V. Meyer and P. Petrenko-Kritschenko, *Ber.,* **25,** 3304 (1892). [e] J. L. Everett and G. A. R. Kon, *J. Chem. Soc.,* 3131 (1950). [f] J. W. Hill and W. A. Carothers, *J. Am. Chem. Soc.,* **55,** 5031 (1933). [g] L. Bouveault and G. Blanc, *Comp. rend.,* **137,** 328 (1903). [h] L. Henry, *Comp. rend.,* **145,** 1247 (1907). [i] W. H. Perkin, *J. Chem. Soc.,* **65,** 402 (1894).

Pyrolytic decomposition of allyl ethyl carbonate apparently proceeds more easily through the route involving formation of ethylene and allyl alcohol than that of ethyl alcohol and allene since no allene was found to be present in the pyrolyzate. Formation of diethyl carbonate in small amounts can only be explained by the possibility of the interchange of ethanol with allyl ethyl carbonate. Such an equilibrium would not be favored on the basis of volatility at the temperature of pyrolysis, but may possibly have occurred during the distillation of the products. The

isolation of ethanol would indicate that allene may be formed in very small amounts or, more probably, that diethyl carbonate was decomposed.

EXPERIMENTAL

Apparatus and procedure. Pyrolysis of the carbonates was carried out by passing the compound through a 25-mm. o.d. Pyrex tube packed for a distance of 30 inches with Pyrex helices and heated to the desired temperature by means of an electrically controlled furnace. The reactants were pumped into the reaction zone by means of a Corsen-Ceverni bellows pump. The pyrolyzates were collected in traps cooled by Dry Ice and distilled through either a 12-inch Vigreux-type column or a 12-inch helices-packed column, depending on the boiling points of the products. Ethylene was detected by means of a gas trap containing a carbon tetrachloride solution of bromine. Carbon dioxide was detected using a lime-water trap. The percentage figures represent the composition of the pyrolyzates.

Intermediates. The physical constants of the starting materials are listed in Table I, and those of the products in Table II. Literature values for both groups of known materials are listed therein, for convenience of comparison.

Pyrolyses

A. Pyrolysis of α-phenethyl acetate, β-phenethyl acetate, ethyl α-phenethyl carbonate, and ethyl β-phenethyl carbonate. Pyrolysis of the compounds was carried out at 300°, 400°, and 500° in the system described in the preceding paragraphs at the flow rates shown in Table III.

TABLE III

FLOW RATES FOR ESTER PYROLYSIS (MOLES PER HOUR)

Ester	Temperatures and Flow Rates		
	300°C.	400°C.	500°C.
α-Phenethyl acetate	0.50	0.50	0.50
β-Phenethyl acetate	0.50	0.43	0.54
Ethyl α-phenethyl carbonate	0.49	0.50	0.50
Ethyl β-phenethyl carbonate	0.42	0.47	0.38

Table IV lists the conversions to styrene per pass, determined by iodometric titration.

TABLE IV

PYROLYSIS OF ESTERS OF PHENETHYL ALCOHOLS

Ester	Temperature % Conversion to Styrene		
	300°C.	400°C.	500°C.
α-Phenethyl acetate	0.5	12.2	61.8
β-Phenethyl acetate	0.3	2.02	37.7
Ethyl α-phenethyl carbonate	0.6	26.9	62.2
Ethyl β-phenethyl carbonate	0.2	5.7	46.4

B. Pyrolysis of 1,5-bis(ethoxycarbonyloxy)pentane. Pyrolysis temperature, 500°; flow rate, 0.28 mole/hr.

Products: (1) 1,4-pentadiene, b.p. 25.5°, n_D^{25} 1.3890, 8.6%; (2) ethylene detected as the dibromide; (3) ethanol, b.p. 78.2°, n_D^{25} 1.3625, 23.5%; (4) 5-hydroxy-1-pentene, b.p. 37–39° (0.45 mm.), n_D^{25} 1.4230, 30.2%; (5) 1,5-dihydroxypentane, b.p. 86–91° (0.4 mm.), n_D^{25} 1.4470, 7.6%; (6) carbon dioxide.

C. Pyrolysis of 1,10-bis(ethoxycarbonyloxy)decane. Pyrolysis temperature, 500°; flow rate, 0.28 mole/hr.

Products: (1) ethylene, detected as the dibromide; (2) ethanol, b.p. 78.7°, n_D^{25} 1.3648, 4.7%; (3) 1,9-decadiene, b.p. 60° (15 mm.), n_D^{25} 1.4297, 10.6%; (4) 10-hydroxy-1-decane, b.p. 80–82° (0.8 mm.), n_D^{25} 1.4454, 27.4%; (5) 1,10-dihydroxydecane, m.p. 70–71°, 18% phenyl urethane, m.p. 166–167.5°; (6) 10-ethoxycarbonyloxy-1-decane, b.p. 106–117° (0.5 mm.); n_D^{25} 1.4365; 3.4%; (7) 10-ethoxycarbonyloxy-1-hydroxydecane, b.p. 155–175° (0.5 mm.); n_D^{25} 1.4412; 7.8%; phenylurethane, m.p. 48.5–49.5°; (8) 1,10-dihydroxydecane, m.p. 70–71°.

D. Pyrolysis of 1,3-bis(ethoxycarbonyloxy)-2,2-dimethylpropane. Pyrolysis temperature, 500°; flow rate, 0.27 mole/hr.

Products: (1) 2,6-dioxa-4,4-dimethylcyclohexanone, m.p. 109–110°, 51.5%; (2) ethanol, b.p. 78°, n_D^{25} 1.3647; (3) ethylene, detected as the dibromide.

E. Pyrolysis of allyl ethyl carbonate. Pyrolysis temperature, 500°; flow rate, 0.52 mole/hr.

Products: After distillation into 3 fractions: b.p. 72–88.5°, 88.5°, and 68–86° (105 mm.); the following components were determined by infrared and mass spectrometry: (1) ethanol, 5.5%; (2) allyl alcohol, 44.5%; (3) diethyl carbonate, 2.2%; (4) allyl ethyl carbonate, 47.8% recovery.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. IV. Raney Nickel–Hydrazine Hydrate Reduction of Various Mono- and Dinitrofluorene Derivatives; Some New 9-Substituted Fluorenes[1]

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A Raney nickel–hydrazine hydrate method for reducing aromatic nitro groups has been extended to fluorene derivatives including those having >C=O, >C=C<, $NHCOCF_3$ and other functional groups, and dinitro compounds. For the less soluble substances, certain specific directions must be followed, but most yields were 90% or higher and the first crop out of the reaction mixture was of good quality. A nitro compound with an azomethine linkage gave a product with both functions reduced. Some new substances are described.

The convenient steam bath reduction, in excellent yields, of some aromatic nitro compounds to amines with Raney nickel and hydrazine hydrate in ethanol was reported by Balcom and Furst.[2] Since then, a few reports[3,4] have appeared in which this method has been tried on one or two nitro compounds with good results, after failure or poor results with other methods.

This work is presented because there have been several recent reports of reduction of nitrated derivatives of fluorene in poor yield or by methods more tedious than this, because we have found this reaction, with few exceptions, thoroughly satisfactory, and because in certain of the procedures, notably with dinitro compounds and fluorenone derivatives, simple but necessary precautions must be observed.

It was found,[5] and confirmed,[2] that without a catalyst nitro compounds did not undergo reduction at room temperature. Some can be reduced to the amine in refluxing alcohol by hydrazine hydrate alone[5,6] but yields are often low and the reaction is slow. Higher temperatures often lead to side reactions. Recently, reduction with palladized charcoal and hydrazine hydrate was reported.[7] Yields, with one exception, ranged from 60 to 68%, whereas yields with Raney nickel, at a comparable state of purity, are from 80 to 95% (mostly 90% and above). Furthermore, it is stated that the reduction with palladized charcoal is successful only with "activated" nitro groups. We have found no such limitation with Raney nickel.

Mono- and dinitrofluorenes and ring-substituted derivatives of these (with amino, dimethylamino, acetamido, trifluoroacetamido, iodo and *p*-tosylamido groups) have been readily reduced in this laboratory with 3 to 4 or more molar equivalents per nitro group of 100% hydrazine hydrate[8] (64% N_2H_4) and catalytic amounts of Raney nickel.[9]

The factor limiting batch size with many of the nitro compounds was solubility[10] and we found that toluene, with sufficient ethanol to insure initial complete miscibility of the hydrazine hydrate, gives fully as satisfactory reductions as ethanol alone.

Balcom and Furst[2] reported that the carbonyl groups of the compounds they used were not affected. This is essentially correct in our experience, but we have found that reduction of 2-nitrofluorenone gives us a very small but consistent (3%) yield of 2-amino-9-fluorenol. Prolongation of the reaction time does not raise this yield and there is no 2-nitro-9-fluorenol in the starting material. In the case of the compound cited, even this small amount of 9-ol was sufficient to give us 2-aminofluorenone of apparent poor quality until, its presence realized, we learned how to separate the 9-ol and allow recovery of 90–94% yields of pure 2-aminofluorenone. In this reduction we have also

(1) This investigation was supported in part by research grant C-1744 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service. For preceding publications in this series see: (a) M. E. Taylor and T. L. Fletcher, *J. Org. Chem.*, **21**, 523 (1956); (b) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

(2) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953). These investigators reported that reduction also takes place at room temperature, but with most of our substances low solubility made steam bath temperatures necessary. See A. Furst and R. E. Moore, *J. Am. Chem. Soc.*, **79**, 5492 (1957) for further observations.

(3) D. S. Tarbell, R. F. Smith, and V. Boekelheide, *J. Am. Chem. Soc.*, **76**, 2470 (1954).

(4) R. K. Brown and N. A. Nelson, *J. Am. Chem. Soc.*, **76**, 5149 (1954).

(5) L. P. Kuhn, *J. Am. Chem. Soc.*, **73**, 1510 (1951).

(6) R. Möhlau, H. Beyschlag, and H. Köhres, *Ber.*, **45**, 133 (1912).

(7) M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 2556 (1956).

(8) Obtained from the Mathieson Chemical Corp., Baltimore, Md. This company generously donated some of this material at the beginning of our work.

(9) See C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956) and footnotes, for reference to alkylation of primary aromatic amines with alcohols and (relatively) large amounts of Raney nickel. In this connection see also G. N. Kao, B. D. Tilak, and K. Venkataraman, *J. Sci. Ind. Research (India)*, **14B**, 624 (1955).

(10) We have successfully reduced 2-nitrofluorene in an amount of alcohol insufficient to effect complete solution. This variation is not successful with less soluble compounds.

TABLE I

RANEY NICKEL–HYDRAZINE HYDRATE REDUCTION OF SOME AROMATIC NITRO COMPOUNDS

Nitro Compounds[a]	Mole	Products	Yield, %	M.P., °C.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
				Fluorenes						
2-Tosylamido-3-nitro-(T,A)[b]	0.01	2-Tosylamido-3-amino-	90–95	200–201					8.00	8.00
2-Amino-3-nitro-(A)[c]	0.01	2,3-Diamino-	90	191–193 (193)[c]						
2-Acetamido-3-nitro-(T,A)[b]	0.01	2-Acetamido-3-amino	90	235–237 (225–227)[l]	75.60	75.89	5.92	6.19	11.76	11.74
2-Amino-7-nitro-(T,A)[b]	0.05	2,7-Diamino-	90	164–165 (165)[g]					14.28	14.42
2-Acetamido-7-nitro-(A)[b]	0.05	2-Acetamido-7-amino	90–95	200–202 (198–199)[m]						
2-Trifluoroacetamido-7-nitro-(T,A)[d]	0.05	2-Trifluoroacetamido-7-amino-	90	201–202	61.64	61.63	3.77	3.87	9.58	9.65
2-Dimethylamino-3-nitro-(A)[b]	0.1	2-Dimethylamino-3-amino-	85–90	155–156	80.32	80.41	7.19	7.14	12.49	12.43
2-Dimethylamino-7-nitro-(A)[e]	0.01	2-Dimethylamino-7-amino-	80	147–148	80.32	80.55	7.19	7.37	12.49	12.66
2-Iodo-7-nitro-(A)[f]	0.01	2-Iodo-7-amino-	85	159–161 (158–160)[f]						
2,7-Dinitro-(T,A)[g]	0.01	2,7-Diamino-	95–97	164–165 (165)[g]						
2,5-Dinitro-9-oxo-(T,A)[g]	0.01	2,5-Diamino-9-oxo	85–90	200.5–203 (200)[n]	74.27	74.14	4.79	4.99	13.33	13.48
2-Nitro-9-morpholino-(A)	0.05	2-Amino-9-morpholino-	95–97	229–230					10.52	10.58
2-Nitro-9-benzylidene-(T,A)[h]	0.01	2-Amino-9-benzylidene-	80–85	105–121 (105–130)[h]	89.18	89.18	5.61	5.73	5.20	5.25
2-Nitro-9-biphenylylimino-(T,A)[i]	0.01	2-Amino-9-biphenylylamino-	95	164–165					8.04	8.16
				Quinolines						
6-Nitro-(A)[j]	0.01	6-Amino-	90–95	115–115.5 (114)[j]						
8-Nitro(A)[k]	0.01	8-Amino-	90–95	63–64 (64–65)[k]						

[a] T (toluene), A (ethanol) following the compound name signifies the reaction solvent used. [b] F. Bell and D. B. Mulholland, *J. Chem. Soc.*, 2020 (1949), 2-Tosylamido-3-nitrofluorene was synthesized by Mr. M. E. Taylor and Mr. W. H. Wetzel of this laboratory in another connection. [c] O. Diels *et al.*, *Ber.*, **35**, 3286 (1902). [d] From 2-amino-7-nitrofluorene and trifluoroacetic anhydride in benzene, m.p. 201–201.5°. *Anal.* Calcd. for $C_{15}H_9F_3N_2O_3$: C, 55.91; H, 2.82; N, 8.69. Found: C, 56.03; H, 3.05; N, 8.58. [e] From 2-amino-7-nitrofluorene and trimethyl phosphate in the presence of an equivalent of lithium bromide (see[1b]), m.p. 229–230°. *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.75; H, 5.70; N, 10.80. [f] E. K. Weisburger, *J. Am. Chem. Soc.*, **72**, 1758 (1950). [g] G. T. Morgan and R. W. Thomason, *J. Chem. Soc.*, 2691 (1926). [h] See[1a]. [i] See[11]. [j] F. Linsker and R. L. Evans, *J. Am. Chem. Soc.*, **68**, 874 (1946). [k] L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 1644 (1940). [l] H. R. Gutmann and S. W. Fenton, *J. Am. Chem. Soc.*, **77**, 4422 (1955). [m] S. Schulman, *J. Org. Chem.*, **14**, 382 (1949). [n] C. Courtot, *Compt. rend.*, **217**, 453 (1943).

recovered 1–2% of 2,2′-azoxyfluorenone. Slight alteration of the procedure described below (such as too high a concentration of the nitro compound, use of Raney nickel prepared more than a few weeks previously, insufficient hydrazine hydrate or nickel, or insufficient initial heating) has given us a much higher yield of the azoxy compound together with a mixture of other high melting substances. With all of the nitrofluorenone derivatives, the presence of some Raney nickel at the time the hydrazine hydrate is added seems essential (perhaps to prevent hydrazone and/or ketazine formation) for a high yield of good amine. In addition, for dinitro compounds and, in general, for substances with low solubility, initial application of sufficient heat is mandatory (see Experimental).

We have also tried this reduction on several different types of 9-substituted fluorenes. With 2-nitro-9-morpholinofluorene, obtained by interaction of 2-nitro-9-bromofluorene with morpholine, poor results were obtained until the amount of hydrazine hydrate was increased to at least 5 equivalents. The product was identical with that from hydrolysis of 2-trifluoroacetamido-9-morpholinofluorene.

The *cis-trans* mixture of 2-nitro-9-benzylidene-

fluorenes described by Bergmann *et al.*[11] was reduced with 8 molar equivalents of hydrazine hydrate to the corresponding mixture of 2-amino-9-benzylidenefluorenes[11] in good yield, but with three equivalents of the hydrazine hydrate a mixture of two substances resulted: one compound, with high melting point, had correct analyses for 2,2′-azoxy-9,9′-benzylidenefluorene; the other, lower melting, was thought at first to be a stereoisomer but analyses were not compatible with this structure.

It has been reported[12] that the aryl —C≡N group is partially reduced under these conditions (upon hydrolysis of the product, the corresponding aldehyde is obtained), and that a nitropyrimidine was not successfully reduced.[13] As an extension, to substances containing a formal unsaturated carbon to nitrogen linkage, we found that 6-nitro and 8-nitroquinoline each gave a high yield of the corresponding amine. However, when we tried this reaction with a 9-aryliminofluorene, 2-nitro-9-*p*-biphenylyliminofluorene[1a], and five equivalents of hydrazine hydrate, we observed a sluggish reaction and, after 10 minutes, added another five equivalents. A brisk foaming took place and after the customary time on the steam bath we obtained a good yield of 2-amino-9-*p*-biphenylylaminofluorene.

New data on the preparation and purification of 2,5-dinitrofluorene is presented in the experimental section. This substance has been reported as melting at 207°[14] and is commonly used melting at 205–206°. In this stage the compound is contaminated with 2,7-dinitrofluorene and at least one other substance. We observed discoloration upon melting 2,5-dinitrofluorene of the usual purity, and inconsistent or poor reductions with Raney nickel and hydrazine hydrate. Attempts to purify the compound by repeated crystallization from acetic acid or toluene raised the melting point to 210–211° but the product still contained a small amount of high-melting material. The procedure described below gave us the dinitro compound melting at 214.5–215.5.° After storage in the dark for one year, the melting point was the same.[15]

EXPERIMENTAL[16]

Description of two typical reductions follows, and procedures leading to some new compounds.

2-Aminofluorene. A solution of 105.5 g. (0.5 mole) of 2-nitrofluorene[17] in 1500 ml. of toluene and 500 ml. of 95% ethanol was heated almost to boiling in a 6-l. Erlenmeyer flask. We used a 4-l. flask, but this requires considerable care at the beginning to prevent loss by foaming. The flask was then transferred to the steam bath and 70 ml. (~3 moles) of 100% hydrazine hydrate[8] were carefully added with thorough mixing. Immediately thereafter, Raney nickel[18] was cautiously added with mixing. Heating was continued for 40 min. with addition of a small amount of catalyst 15–20 min. after the start of the reaction.[19] The mixture was then boiled down in the presence of a small amount of fresh Raney nickel (and boiling chips) and when alkaline vapors no longer came off, the solution was filtered and the filtrate boiled down to about 300 ml. After slight cooling, 100 ml. of ethanol was carefully added with mixing. A mass of white crystals came out. Cooling, filtration, and drying gave 86 g. (95%) of amine, m.p. 127–128°. A second crop of about 3.5 g. was recovered (~4%), m.p. 125–127°. The material in the first crop is sufficiently pure for most work. One crystallization from ethanol (82 g. from 86 g.) raised the m.p. to 128–129°. Smaller amounts of 2-nitrofluorene can be reduced conveniently in alcohol alone.

2-Aminofluorenone. To a solution of 15 g. (0.066 mole) of 2-nitrofluorenone (from toluene[1b]) in 1 l. of toluene and 300 ml. of ethanol in a 3-l. Erlenmeyer flask, a small amount of Raney nickel was added and, with the solution just under boiling, 12 ml. of hydrazine hydrate, with thorough mixing, followed by more catalyst. The mixture was then brought to a vigorous boil and lowered into the steam bath under an Allihn condenser fitted with a cork. After 15–20 min. catalyst was added and after 30 min., the solution having become a clear red, boiling chips and more catalyst were added and the mixture boiled down until the vapors were no longer alkaline. Decomposition of all the hydrazine is necessary before filtering, otherwise by-products are formed. After filtration and washing of the filter with hot toluene, the solution was boiled almost to dryness and allowed to stand for 1 hr. The solid was then taken up in 400 ml. of 95% ethanol (alternatively, from this point on, 6 to 12 reductions were combined and worked up identically), and warmed on the steam bath to effect solution. Filtration removed a small amount of highly insoluble orange-colored azoxyfluorenone; the amount (from 15 g. of the nitro compound) varied from none detectable to ~0.3 g. The filter was washed with warm alcohol and the solution boiled down to 160 ml. and allowed to stand until crystallization was complete. The first crop amounted to 9.6 g. (74%), m.p. 159–161°. Upon reducing the filtrate to 60–70 ml., a further 1.8 g. was removed (14%), m.p. 157–160°. Both crops were recrystallized from

(11) E. D. Bergmann, B. Pullman, and Y. Sprinzak, *Bull. soc. chim. biol.*, **34**, 586 (1952).

(12) S. Pietra and C. Trinchera, *Gazz. chim. ital.*, **85**, 1705 (1955).

(13) P. E. Fanta and E. A. Hedman, *J. Am. Chem. Soc.*, **78**, 1424 (1956).

(14) E. D. Hughes, C. G. LeFèvre, and R. J. W. LeFèvre, *J. Chem. Soc.*, 202 (1937).

(15) See footnote 16 in J. H. Weisburger, E. K. Weisburger, and H. P. Morris, *J. Am. Chem. Soc.*, **74**, 4540 (1952), regarding stability of 2,5-dinitrofluorene as generally used.

(16) Melting points are corrected. Analyses were made by W. Manser, Zurich, Switzerland; Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and (some of the nitrogens) by Mr. M. E. Taylor of this laboratory.

(17) Prepared in the usual way (see W. E. Kuhn in *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 447), but much more conveniently in a large beaker in 250-g. batches. The product is filtered, washed, crystallized from acetic acid and, to remove traces of acetic acid, recrystallized from toluene.

(18) This amount (0.5–0.6 g. dried) was three times that conveniently transferred (from ethanol) on the end of a spatula having a blade 65 mm. wide. The nickel was prepared as described in the chapter by R. Schröter in *Newer Methods of Preparative Organic Chemistry*, Interscience, New York, N. Y., 1948, p. 65. It appears to lose its efficiency after a few weeks especially with 2-nitrofluorenone and 2,5-dinitrofluorene.

(19) Occassionally a yellow color has persisted in the mixture as long as 0.5 hr. and, if allowed to remain, the product (in slightly lower yield) is yellow. In such cases we have added another 15 ml. of hydrazine hydrate with some Raney nickel and kept the mixture on the steam bath another 15–20 min.

a small amount of toluene with almost quantitative recovery, m.p. 160.5–162° (analytically pure). A third crop was boiled with hydrochloric acid (1 part acid plus 10 parts water) in a ratio of 500 ml. acid to 10 g., and filtered hot. The filtrate deposited yellow needles of the hydrochloride of 2-aminofluorenone[20] (a further 3–4% of good quality amine). The acid solution, after separation of the preceding, was made alkaline and the precipitate dried and recrystallized from alcohol giving ~3% of 2-amino-9-fluorenol, m.p. 200.5–201° (lit.[21] m.p. 200°; mixture melting point with authentic sample undepressed).

2,2′-Azoxyfluorenone.[22] The orange compound resulting above was extremely insoluble in all solvents tried. It was purified by extraction with hot toluene followed by acetone, m.p. > 330° dec.

Anal. Calcd. for $C_{26}H_{14}N_2O_3$; C, 77.60; H, 3.51; N, 6.96. Found: C, 77.84; H, 3.66; N, 7.10.

2,5-Diaminofluorene. Fluorene (100 g.) was dinitrated in the usual way (see Table[9]). The crude product was washed with cold acetic acid, cold alcohol and water, dried, and extracted by boiling with 750 ml. of acetic acid, filtering hot, and then with a further 500 ml., again filtering hot. The combined filtrates were boiled down and the first crop was recrystallized from acetic acid (m.p. 206–208°, with slight residue and discoloration). At this stage several runs were combined and taken up in nitrobenzene[23] (500 ml. to 75 g.) warmed to 120° to effect solution, allowed to cool, and the precipitated crystals filtered off and washed with cold alcohol. Recrystallization from toluene (Darco) and then chloroform served to raise the m.p. to 212–213.5° with no residue and no discoloration. This material was analytically pure and used for further work. However, recrystallization from acetic acid then toluene gave m.p. 214.5–215.5° (lit. 207°[14]).

The dinitro compound (8.6 g., 0.033 mole) was dissolved in a mixture of 1200 ml. of toluene and 400 ml. of ethanol and reduced with 30 ml. (~10 equivalents per nitro group) of hydrazine hydrate in the usual way, but with the initial boiling period lengthened to 5 min. beginning at the time of addition. Reflux was not necessary. After 0.5 hr. the solution was boiled down (fresh catalyst), filtered, and further taken to small volume; yield 6.2 g. (95%), m.p. 175.5–176.5°. Recrystallization from toluene gave 6.0 g., m.p. 176.5–177° (lit.[24] m.p. 177–178.5°). A small second crop was also recovered.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.57; H, 6.04; N, 14.37.

Acetylation gave 2,5-diacetamidofluorene which after two crystallizations from acetic acid melted at 301–302° corr. (lit.[25] m.p. 296°).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. Found: C, 73.07; H, 5.70.

9-Morpholino-2-nitrofluorene. Equivalent quantities of 9-bromo-2-nitrofluorene and morpholine were heated together under reflux in a small amount of methanol for 30 min. and the reaction mixture filtered from a small amount of reddish-orange material (probably 2,2′-dinitrobifluorenylidene) stirring into dilute potassium carbonate solution. Filtration and drying gave 95–98% yields. Recrystallization from methanol (Darco) gave cream-colored needles, m.p. 150–151.5°.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: N, 9.45. Found: N, 9.52.

9-Morpholino-2-trifluoroacetamidofluorene. Morpholine (2 equivalents) and 9-bromo-2-trifluoroacetamidofluorene[26] were heated under reflux in ethanol and stirred into cold dilute potassium carbonate. The dried product was treated in benzene with Darco, filtered, and boiled down to small volume. The resulting crystals were dried and recrystallized from methanol giving 85% yields. One more crystallization from alcohol gave a pure sample, m.p. 209–209.5°.

Anal. Calcd. for $C_{19}H_{17}F_3N_2O_2$: C, 62.98; H, 4.73; N, 7.73. Found: C, 62.91; H, 4.75; N, 7.82.

2-Amino-9-morpholinofluorene. A portion of the stirred suspension of the above reaction mixture (dilute potassium carbonate) was boiled gently in a covered beaker for 2 hr., replacing the water occasionally, and filtered. The dried material yielded (methanol) white crystals identical with the product from reduction of 2-nitro-9-morpholinofluorene (melting point and mixture melting point, see Table I).

2-Acetamido-9-morpholinofluorene. Acetylation of the latter compound gave a quantitative yield, m.p. 234–235°. One crystallization from methanol (Darco), m.p. 236–236.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.96; H, 6.79; N, 9.14.

2,2′-Azoxy-9,9′-dibenzylidenefluorene(?). When three equivalents of hydrazine hydrate were used in the reduction of the 2-nitro-9-benzylidinefluorene (*cis* and *trans* mixture, Table I), the product consisted of two substances. One, obtained by extraction with alcohol and recrystallization from benzene (light yellow needles), melted at 182.5–184° and has not been identified. The other, a residue from the above extraction was recrystallized three times from benzene (yellow needles), m.p. 244.5–247.5°.

Anal. Calcd. for $C_{40}H_{26}N_2O$: C, 87.25; H, 4.76; N, 5.09. Found: C, 87.60; H, 4.69; N, 5.11.

2-Acetamido-9-(N-acetyl)-p-biphenylylaminofluorene. Attempted acid hydrolysis of the reduction product from 2-nitro-9-biphenylylimmofluorene (Table I) returned the starting material quantitatively. Acetylation gave a diacetylated product, m.p. 132–133°, from alcohol-water.

Anal. Calcd. for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59. For the monoacetyl compound: C, 83.43; H, 5.19. Found: C, 80.94; H, 5.78.

SEATTLE 5, WASH.

(20) This method of separation had been worked out in another connection by Mr. M. E. Taylor of this laboratory.

(21) O. Diels, *Ber.* **34**, 1758 (1901).

(22) Use of impure 2-nitrofluorene or insufficient hydrazine hydrate gave the known 2,2′-azoxyfluorene in good yield.

(23) We obtained a clearer product if, instead of using commercial nitrobenzene, we first treated it with dilute sodium carbonate solution, then dilute sulfuric acid followed by water washing and drying.

(24) J. H. Weisburger and E. K. Weisburger, *J. Org. Chem.*, **21**, 514 (1956).

(25) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

(26) From 16 g. (0.09 mole) of *N*-bromosuccinimide and 22 g. (0.08 mole) of 2-trifluoroacetamidofluorene in 850 ml. of refluxing benzene with ultraviolet illumination for 4 hr. The solution was cooled to 50–60°, extracted with several portions of water, dried over sodium sulfate, and the benzene distilled off. The residue was then dried on the steam bath (air current), and the product recrystallized with filtration from carbon tetrachloride 75–80% yields, m.p. 181–183°. One more crystallization gave an analytical sample, m.p. 182–183°.

Anal. Calcd. for $C_{15}H_9BrF_3NO$: C, 50.59; H, 2.55. Found: C, 50.68; H, 2.52. This preparation was first carried out by Mr. H. L. Pan of this laboratory in another connection.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Studies in the Bicyclo[2.2.1]heptane Series. V. Reactions of Bicyclo[2.2.1]heptadiene[1]

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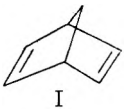
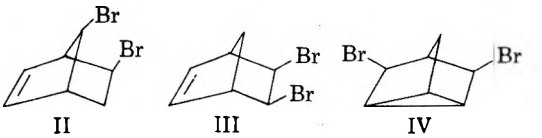
The course of the reaction of bicyclo[2.2.1]heptadiene (norbornadiene) with water, methanol, performic acid, hydrobromic acid, and nitrosyl chloride is described and the preparation of a sample of 3,5-dibromonortricyclene free of olefinic isomers is reported.

In connection with previous investigations in this Laboratory of the preparation and properties of compounds containing the bicyclo [2.2.1] heptyl ring system, it seemed of interest to study the addition of certain common reagents to bicyclo [2.2.1] heptadiene (norbornadiene) (I), the preparation of which has been reported by Hyman,[3] by Parham and his co-workers,[4] and by Hine and his co-workers.[5] The addition of ionic reagents to the



I

diene has been shown in some instances to proceed with rearrangement to the nortricyclenic system and in others to give unrearranged addition products. Bromination of I at low temperature has been reported by Schmerling and his co-workers[6] to give a complex mixture of isomeric dibromides; namely, 5,7-dibromo-2-norbornene (II), 5,6-dibromo-2-norbornene (III), and 3,5-dibromonortricyclene (IV). The bromination of I has also been reported by Winstein and Shatavsky.[7] Addition of formic acid resulted in the formation of 3-formylnortricyclene (V), and hydrogen chloride and hydrogen bromide gave a mixture of unsaturated and nortricyclenic halides.[6] On reaction with *p*-methylthiophenol,[8] the diene again afforded two products, a nortricyclenic (VI) and an isomeric olefinic addition product (VII). A series of nortircyclenic halides,[9] esters,[10] and ethers[11] has also been reported recently in the patent literature. The present paper describes the addition to norbornadiene of water, methanol, performic acid, nitrosyl chloride, and hydrobromic acid and the



II III IV

V, X = —O—C—H (O) VII

VI, X = —S—$C_6H_4CH_3$—*p*

preparation of a sample of 3,5-dibromonortricyclene (IV) free of olefinic impurity.[6]

The low temperature bromination of bicycloheptadiene was repeated and the results of Schmerling and his co-workers were duplicated.[6] The complex mixture of dibromides was treated with a slight excess of performic acid to remove olefinic dibromides II and III in order to furnish a sample of pure 3,5-dibromonortricyclene (IV). This latter dibromide was found to be stable toward performic acid, bromine in carbon tetrachloride solution, and hydrogen over Adams' oxide. In the presence of sodium amide in liquid ammonia IV gave an intractable material from which no pure compound could be isolated.

When bicycloheptadiene was heated under reflux with hydrobromic acid a dibromo compound was obtained along with a small amount of 3-bromonortricyclene (IX) and some carbinol impurity.[12] This new dibromo-heptane gave no

(1) (a) For previous paper in this series, see A. Winston, G. Youngblood, and P. Wilder, Jr., *J. Org. Chem.*, 22, 876 (1957). (b) Taken in part from a thesis submitted by G. T. Youngblood to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree, October, 1956.

(2) American Cyanamid Pre-doctoral Fellow, 1955–1956.

(3) J. Hyman, Belgian Patent 498,178 (1951).

(4) W. E. Parham, W. T. Hunter, R. Hanson, and T. Lahr, *J. Am. Chem. Soc.*, 74, 5646 (1952).

(5) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner, and M. Hine, *J. Am. Chem. Soc.*, 77, 594 (1955).

(6) L. Schmerling, J. R. Luvisi, and R. W. Welch, *J. Am. Chem. Soc.*, 78, 2819 (1956).

(7) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, 77, 4183 (1955); S. Winstein and M. Shatavsky, *Chem. & Ind. (London)*, 56 (1956).

(8) S. J. Cristol and G. D. Brindell, Abstracts of Papers presented at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, April, 1955, page 35N.

(9) H. Bluestone, S. B. Soloway, J. Hyman, and R. E. Lidov, U. S. Patent 2,730,548 (1956).

(10) S. B. Soloway, R. E. Lidov, H. Bluestone, and J. Hyman, U. S. Patent 2,738,356 (1956).

(11) H. Bluestone, S. B. Soloway, J. Hyman, and R. E. Lidov, U. S. Patent 2,782,238 (1957).

(12) The formation of 3-bromonortricyclene under conditions approximating those used in this investigation has been reported (*cf.* ref. 9), but no mention was made of a dibromo derivative.

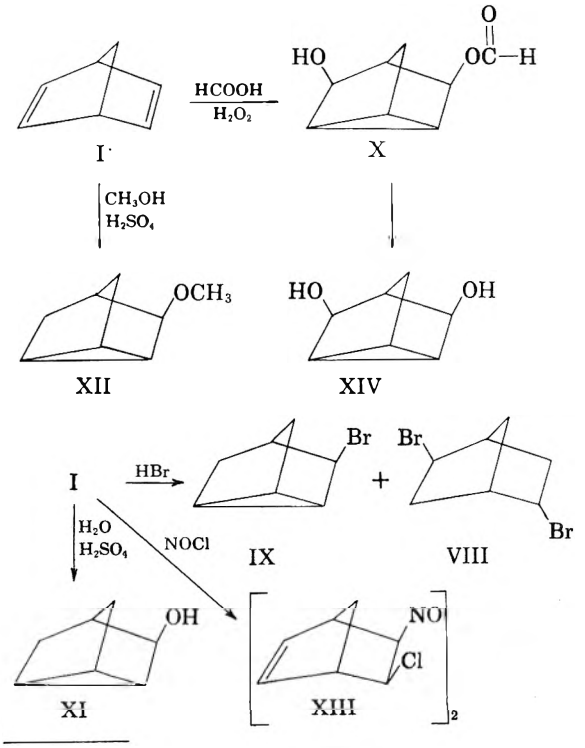
spectroscopic evidence of a three-membered ring and was smoothly reconverted into I by sodium amide in liquid ammonia, chemical evidence that the two bromine atoms were attached to different ethylene bridges in the molecule. While the stereochemistry of the dibromide has not been definitively established the structure VIII is assigned in the assumption that the initial bromine atom will exert an anchimeric effect and influence the avenue of approach of the second bromine.[13]

Hydroxylation with performic acid yielded a mixture of products consisting of the hydroxyformate (X) and a product or products formed possibly by addition of two moles of peracid per mole of diene. These latter products were not investigated. The structure X was assigned to the hydroxyformate on the basis of a band at 12.3 μ in the infrared[6,14,15] and by analogy with the dibromide IV. Compound X was related by hydrolysis to the 3,5-dihydroxynortricyclene of Roberts,[9,16] which was in turn prepared by the hydrolysis of *trans*-2,3-dichlorobicyclo [2.2.1] heptene-5.

Hydration of norbornadiene in the presence of sulfuric acid gave the carbinol, 3-hydroxynortricyclene (XI), which had been previously prepared and characterized by Roberts.[15] In a similar reaction in methanol solution the product was the methyl ether XV, which was contaminated with some olefinic and hydroxylic material and by the addition of a second molecule of methanol to one of the initial reaction products.[11] Only after this material was passed through an alumina column at room temperature were all traces of carbonyl and olefin removed by adsorption.

Similar to other compounds containing the norbornylene ring, norbornadiene gave with nitrosyl chloride an addition product to which is assigned the dimeric structure XIII by analogy with dicyclopentadiene.[17] The elemental analysis of the adduct is consistent with a 1 : 1 addition product. Infrared spectroscopy indicated that the product contained an olefinic linkage[18] (6.36 μ), but no evidence for the presence of the nortricyclenic ring system was obtained. Further evidence that rearrangement did not occur in this instance was the conversion of the dimeric nitroso chloride XIII by the method of Wieland and Bergel[19] into the monomeric oxime which in an exchange reaction with 2,4-dinitrophenylhydrazine gave the known dinitrophenylhydrazone of 2-ketobicyclo[2.2.1]-5-heptene[4] and not that of 3-keto-nortricyclene.[15] The adduct of I and phenyl azide was prepared without difficulty, but limited solubility in organic solvents made purification virtually impossible.[4]

On the basis of the limited data available, it would be difficult to make any generalizations concerning the several competitive avenues of reaction for bicycloheptadiene, although the temperature of the reaction and the nature of the reactant seem to affect the course of the reaction. Work along these lines is continuing in this Laboratory.



(13) It should be pointed out here that VIII may indeed be the 2,6-dibromide.

(14) A. Winston and P. Wilder, *J. Am. Chem. Soc.*, **76**, 3045 (1954).

(15) J. D. Roberts, E. P. Trumbull, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(16) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Am. Chem. Soc.*, **76**, 5692 (1954).

EXPERIMENTAL[20]

Bromination of bicyclo[2.2.1]heptadiene[21] (I). A solution of 46 g. (0.50 mole) of the diene dissolved in 300 ml. of carbon tetrachloride was treated dropwise with a solution of 84 g. (0.55 mole) of bromine in 300 ml. of the same solvent at −70°, according to the directions of Schmerling.[6] A yield of 106 g. (84%) of a mixture of dibromides II, III, and IV was obtained, b.p. 100–102° (2 mm.); n_D^{25} 1.5771 [reported[6] 99–102° (5 mm.); n_D^{25} 1.5795].

A mechanically stirred solution of 73 g. of the combined dibromides in 200 ml. of 88% formic acid was treated dropwise with 30 g. of 30% hydrogen peroxide. Stirring was continued for 15 hr. at room temperature. The reaction mixture was poured into a liter of water and was extracted twice with ether. The ether extract was washed first with a saturated

(17) Unpublished work of P. Wilder and G. T. Youngblood; G. T. Youngblood, Ph.D. thesis, Duke University, October, 1956.

(18) P. R. Schleyer and M. M. Donaldson, *J. Am. Chem. Soc.*, **78**, 5702 (1956).

(19) H. Wieland and F. Bergel, *Ann.*, **446**, 13 (1926).

(20) All melting points and boiling points are uncorrected. Infrared spectra were obtained by the use of a Perkin-Elmer, Model 21, double beam recording spectrophotometer with sodium chloride prism, using a solution of the substance in a suitable solvent in a 1-mm. sodium chloride cell or pressed KBr pellets. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(21) A sample of this material was kindly furnished by the Shell Chemical Corp., Houston, Tex.

aqueous solution of sodium bicarbonate and then with water and was dried over anhydrous magnesium sulfate. The ether was removed by evaporation, and the residue was distilled to yield 50.4 g. of IV, b.p. 105–107° (4 mm.). On redistillation an analytical sample was obtained, b.p. 95–96° (2 mm.); d_4^{20} 1.8686; n_D^{25} 1.5779.

Anal. Calcd. for $C_7H_8Br_2$: C, 33.37; H, 3.20. Found: C, 33.50; H, 3.32.

The infrared spectrum gave no evidence of an olefinic linkage. The dibromide failed to discolor a solution of bromine in carbon tetrachloride. Catalytic hydrogenation in ethyl acetate over Adams' catalyst at room temperature did not alter the compound.

To a solution of sodium amide prepared by dissolving 6.5 g. (0.29 mole) of sodium in 400 ml. of liquid ammonia was added in one portion 35 g. (0.14 mole) of the dibromide. After the addition of 300 ml. of anhydrous ether the mixture was stirred for 3 hr. and was then treated with wet ether to decompose excess amide ion. The ether layer was separated, washed with water, and dried over anhydrous magnesium sulfate. After removal of the ether, there was isolated a dark brown rubbery mass which could not be redissolved in any of the usual organic solvents.

The experiment was repeated using 61.0 g. (0.24 mole) of the dibromide and 5.8 g. (0.25 mole) of sodium. Only 18.8 g. (31%) of unchanged dibromide and the same rubbery intractable mass were isolated.

Addition of hydrobromic acid. A mixture of 46 g. (0.5 mole) of the diene and 100 g. of 48% hydrobromic acid was heated at 70–80° for 5 hr. The mixture was then diluted with water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the ether on a steam bath, distillation of the residue yielded 5 g. (6%) of the rearranged bromide IX, b.p. 74–75° (20 mm.); d_4^{20} 1.4651; n_D^{25} 1.5241 [reported[16] 86–88° (32 mm.); d_4^{25} 1.4609; n_D^{25} 1.5269].

There was also obtained 36.1 g. (29%) of the dibromo compound (VIII). After being dissolved in 250 ml. of anhydrous ether, the dibromo compound was passed through an alumina column to remove carbinol impurities. The ether was removed and the residue was distilled under reduced pressure, b.p. 75° (0.5 mm.).

Anal. Calcd. for $C_7H_{10}Br_2$: C, 33.05; H, 3.98. Found: C, 33.21; H, 3.95.

To a solution of 5.75 g. (0.25 mole) of sodium in 400 ml. of liquid ammonia was added 25.7 g. (0.11 mole) of dibromide. After the addition of 100 ml. of anhydrous ether the mixture was stirred for 3 hr. Wet ether was added to decompose excess amide ion, and then 100 ml. of water was added. The ether layer was separated, washed with ether, and dried over anhydrous magnesium sulfate. The ether was removed and distillation of the residue yielded 4.1 g. (40%) of norbornadiene, b.p. 89–91° (758 mm.). The diene gave a negative Beilstein test for halogen.

Addition of performic acid. A mixture of 46 g. (0.50 mole) of norbornadiene, 150 g. of 88% formic acid, and 115 g. of 30% hydrogen peroxide was stirred rapidly in an ice bath. After the ice melted, the system was allowed to come to room temperature. After being stirred for 10 hr., the solution was poured into 1 liter of water and extracted with ether. The ether extract was washed first with sodium bicarbonate solution, then with ferrous sulfate solution, and finally with water and was dried over anhydrous magnesium sulfate. The ether was removed, and the residue on distillation yielded 7.0 g. (9%) of hydroxyformate X, b.p. 127° (9 mm.); n_D^{25} 1.4858.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.49. Found: C, 62.55; H, 6.38.

An infrared spectrum of X gave evidence of an O—H band at 2.80 μ, an ester carbonyl group at 5.77 μ, and a nortricyclenic ring system at 12.3 μ.

Hydrolysis of hydroxyformate. To 1.0 g. of hydroxyformate was added one gram of potassium hydroxide and 4 ml. of absolute ethanol. The mixture was shaken at intervals for 5.5 hr. The reaction mixture was diluted with 50 ml. ether and the precipitate, which formed during reaction, was removed by filtration. To the ether solution was added 25 ml. of hexane. The ether was removed by evaporation and the hexane-ethanol solution was boiled until all ethanol was removed. At this point the diol was precipitated. The solid was separated by filtration and washed with hexane. A quantitative yield was obtained, m.p. (after sublimation) 160–161° (reported[16] 161–163°).

Addition of methanol. To a solution of 10 g. of concentrated sulfuric acid in 100 g. of absolute methanol was added 23 g. (0.25 mole) of diene. The mixture was heated under slow reflux for 1 hr. Methanol was removed by evaporation on a steam bath under reduced pressure, and the residue was taken up in water and ether. The ether layer was separated and dried over anhydrous magnesium sulfate. Removal of the ether and distillation of the residue yielded 3.2 g. (9.5%) of material, b.p. 125–126° (40 mm.) and 185–186° (758 mm.); n_D^{25} 1.4586. Hydroxyl and unsaturated impurities were removed by passage of the crude yield in anhydrous ether over an alumina column.

Anal. Calcd. for $C_8H_{12}O$: C, 77.42; H, 9.67. Found: C, 77.23; H, 9.79.

An infrared spectrum of XII gave evidence for the nortricyclenic structure at 12.35 μ and the methoxy group by the intense band at 8.90–9.25 μ.

Addition of water to norbornadiene. To a flask fitted with reflux condenser, stirrer, and dropping funnel was added 100 ml. of 50% (by volume) sulfuric acid. The solution was cooled to 0° in an ice bath, and 46 g. (0.50 mole) of norbornadiene was added dropwise (caution!) over a period of 2 hr. After addition was complete, the mixture was stirred for an additional hour. To the reaction mixture, cooled in an ice bath, was added rapidly 200 ml. of water. The reaction mixture was saturated with sodium chloride and was extracted with ether. The ether layer was washed with water and was then saturated with sodium bicarbonate solution. The ether solution was dried over magnesium sulfate. The yield of 3-hydroxynortricyclene (XI) was 8.7 g. (16%), m.p. 95–100° after three sublimations (reported[15] m.p. 107–108.8°). The phenylurethane derivative was prepared, m.p. 146° (reported[15] 146–147.5°).

The addition of nitrosyl chloride. To a rapidly stirred solution of 10 g. (0.12 mole) of norbornadiene, 20 ml. of glacial acetic acid, 20 ml. of 95% ethanol, and 20 g. (0.17 mole) of isoamyl nitrite, cooled in an ice bath, was added during 20 min. a solution of 25 ml. (0.25 mole) of 36% hydrochloric acid in 50 ml. of 95% ethanol. The color of the mixture turned green immediately, and after about 5 min. precipitation of a white solid occurred. The solid, which was removed by filtration, was washed with ethanol (95%) and collected. The yield was 12 g. (71%). An analytical sample was purified by two recrystallizations from toluene, m.p. 164° (darkened at 162°).

Anal. Calcd. for C_7H_8NOCl: C, 53.33; H, 5.08. Found: C, 53.74; H, 5.09.

A band at 6.36 μ in the infrared clearly indicated the presence of a norbornene[18] ring; there was no evidence at 12.3 μ for a nortricyclene ring. A sample of the dimeric nitroso chloride was converted by the method of Wieland and Bergel[19] into the monomeric oxime which in an exchange reaction with 2,4-dinitrophenylhydrazine gave a product, m.p. 134–136° (reported[4] for the 2,4-dinitrophenylhydrazone of 2-ketobicyclo[2.2.1]-5-heptene, m.p. 133–137°; reported[15] for the 2,4-dinitrophenylhydrazone of 3-ketonortricyclene, m.p. 188.2–189.6°).

Acknowledgment. This investigation was supported in part by a grant from the Research Corp.

DURHAM, N. C.

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

Observations on the Nature of McAlpine's "Stable" and "Unstable" Xanthates

HAROLD R. NACE, DONALD G. MANLY, AND SERAFINO FUSCO

Received October 23, 1957

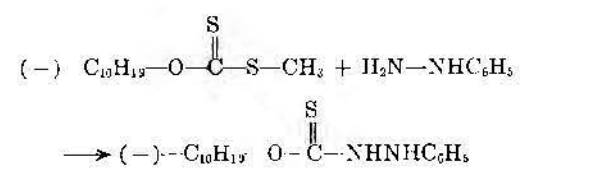
Evidence is presented which shows that the "stable" form of (−)-menthyl methyl xanthate, first reported by McAlpine,[1] is formed by the removal of peroxide impurities from the "unstable" form. The stable form can be converted back to the unstable form by the addition of benzoyl peroxide. The two forms are identical structurally.

In studies on the pyrolysis of various xanthates, McAlpine[1] reported the curious behavior of the methyl xanthates of (−)-menthol and (−)-borneol, which under certain conditions were stable to vacuum distillation. This behavior is contrary to that usually exhibited by xanthates, which on heating readily decompose to give olefins in high yield in the well known Chugaev reaction.[2]

McAlpine[1] found that the "stable" methyl xanthate of (−)-menthol could be obtained in several ways. Distillation under reduced pressure of (−)-menthyl methyl xanthate prepared according to Chugaev[3] resulted in 50% decomposition to a menthene mixture, and the remainder of the distillate was the stable xanthate, which could be distilled repeatedly without further decomposition. When the "unstable" xanthate was heated in 1-butanol it was also converted to the stable form.

McAlpine[1] was unable to detect any difference in physical properties between the stable and unstable xanthates. The two compounds had identical melting points, which showed no depression on admixture, had identical optical rotations, and gave the same results on analysis.

McAlpine's work has been repeated and confirmed in this laboratory. Further evidence that the two compounds are identical has also been obtained. The stable and unstable xanthate were converted to the phenylhydrazine derivatives, according to the procedure of Mann.[4] The derivatives had identical melting points and no depression was observed on admixture, indicating that the xanthate linkage was intact in both compounds.



The infrared spectra of the stable and unstable xanthates were superposable. Finally, both xanthates had identical rates of decomposition when pyrolyzed at 150° at *atmospheric pressure*. The menthene mixtures obtained from large scale pyrolyses of both xanthates were analyzed by the racemization technique of Barton, Head, and Williams.[5] The unstable xanthate gave 24% Δ^2-menthene, and the stable gave 27% Δ^2-menthene. Hückel, Tappe, and Legutke[6] obtained a value of 28% Δ^2-menthene in the mixture obtained by reduced pressure distillation.[7] Within experimental error, these values are identical, and thus the two forms of the xanthate give the same ratio of Δ^2- to Δ^3-menthene on pyrolysis.

The evidence points to the conclusion that the two compounds have identical structures, and that the stable xanthate was produced by the removal from the unstable xanthate of an impurity, present in quantities too small to be detected by the above tests.

The methods used by McAlpine[1] to produce the stable xanthate suggested that a peroxide was the most likely impurity. Tarbell and Harnish[8] suggested that the xanthate was decomposing by a chain process, and that the stable form was produced when the chain initiator was removed by sufficient purification.

To test the peroxide hypothesis, a solution of the unstable xanthate in benzene was shaken with an aqueous solution of ferrous ammonium sulfate. Subsequent distillation under reduced pressure gave an 84% yield of the stable xanthate.

Further evidence that the difference in behavior was due to the presence of peroxides was obtained by adding a trace of benzoyl peroxide to a benzene solution of the stable xanthate. Subsequent distillation under reduced pressure resulted in complete decomposition of the xanthate. Substitution of benzoic acid for the benzoyl peroxide had no effect on the stability of the xanthate.

When a sample of the stable xanthate was irradiated with ultraviolet light for several days, the sample slowly liquefied, lost weight, darkened in color, and the odor of methyl mercaptan was evi-

(1) I. M. McAlpine, *J. Chem. Soc.*, 1114 (1931); 906 (1932).

(2) *Cf.* G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **74**, 5454 (1952) for discussion and further references.

(3) L. Chugaev, *Ber.*, **32**, 3332 (1899).

(4) F. G. Mann, *J. Chem. Soc.*, 666 (1945).

(5) D. H. R. Barton, A. J. Head, and R. J. Williams, *J. Chem. Soc.*, 453 (1952).

(6) W. Hückel, W. Tappe, and G. Legutke, *Ann.* **543**, 191 (1940).

(7) Their menthyl methyl xanthate was prepared in the same manner as Chugaev's and McAlpine's, and would thus correspond to the unstable form.

(8) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, 49, 61 (1951).

dent. No attempt was made to identify the other products of the decomposition.

The results reported here, together with those obtained by McAlpine,[1] indicate that (−)-menthyl methyl xanthate (and probably (−)-bornyl methyl xanthate[1]) is rendered unstable towards heat by the presence of traces of peroxides. It therefore appears likely that an additional mode of decomposition, probably proceeding by a free radical path, is possible in the pyrolysis of xanthates. Although both forms gave products indicating preference for *cis*-elimination, this need not imply that the free-radical decomposition proceeds through a cyclic intermediate[2] involving a *cis*-hydrogen. The 4-hydrogen of the menthane ring is tertiary while the 2-hydrogen is secondary, and it is well known that tertiary hydrogens are attacked more readily than secondary ones by free radicals.[9]

It is interesting to note that treatment of β-cholestanyl methyl xanthate with ferrous ammonium sulfate had no effect on the rate of pyrolysis.[2] Elucidation of the generality and mechanism of the peroxide-induced instability awaits further investigation.

EXPERIMENTAL

(−)-Menthyl methyl xanthate. The procedure of Chugaev[3,10] was used. The (−)-menthol had m.p. 43–43.5°; $[\alpha]_D$ −45° (1% in $CHCl_3$), −51° (1% in 95% EtOH). Reported[11] m.p. 43°, $[\alpha]_D$ −49°. The (−)-menthyl methyl xanthate had m.p. 39–39.5°, 39.9–40.3° (corr.); $[\alpha]_D$ −80° (1% in $CHCl_3$) after 1 recrystallization from dilute ethanol. Reported[3,10] for unstable xanthate, m.p. 39°; $[\alpha]_D$ −81.7° (4.5% in $CHCl_3$).

Conversion of the unstable xanthate to the stable xanthate. A. by treatment with ferrous ammonium sulfate. A solution of 2.5 g. of unstable xanthate in 35 ml. of benzene (Merck & Co., Inc., thiophene-free grade) was washed with six 25-ml. portions of freshly prepared ferrous ammonium sulfate solution, then with water, and finally dried over anhydrous magnesium sulfate. The benzene was removed by distillation under reduced pressure (bath temperature 25°), and the residue was distilled in a modified Claisen flask with a 3-in. Vigreux side arm to give 2.1 g. (84%) of the stable xanthate, b.p. 110–121° (11 mm.); m.p. 38.5–39°. Several repetitions of the experiment gave comparable results.

B. by distillation under reduced pressure. The results obtained by McAlpine[1] were confirmed. The stable xanthate obtained from the initial distillation had b.p. 130–140° (10 mm.) on redistillation; m.p. 39–39.5°; mixture melting point with unstable xanthate, 38.5–39.5°; yield 40–50%.

C. by heating in 1-butanol. A solution of 15 g. of unstable xanthate in 100 ml. of 1-butanol was heated under reflux for 14 hr. Then the solvent was removed under reduced pressure and the residue was distilled from a Claisen flask to give 10.4 g. (71%) of stable xanthate, b.p. 92–101° (0.5 mm.); m.p. 39.5–40.5°; m.p. of unstable xanthate taken at same time, 39.5–40.5°; mixture m.p. 39.5–40.5°; $[\alpha]_D$ − 78° (1% in $CHCl_3$).

Pyrolysis of unstable xanthate. A 10-g. (0.041 mole) sample of unstable xanthate was heated at 145–155° for 6 hr. under reflux. Distillation of the residue through an efficient semimicro column[12] gave a 57% yield of menthenes, b.p. 64.5–65° (22 mm.); n_D^{25} 1.4500; $[\alpha]_D$ + 117° (1% in $CHCl_3$). A sample was racemized[6] and then had $[\alpha]_D$ + 32° (1% in $CHCl_3$) which corresponds to 24% of Δ^2-menthene in the original mixture.

Pyrolysis of stable xanthate. An 8.0-g. (0.0325 mole) sample of the stable xanthate was pyrolyzed in the same fashion, and 2.30 g. (51% yield) of menthenes was obtained, b.p. 61–64° (20–22 mm.); n_D^{25} 1.4500; $[\alpha]_D$ + 36° (1% in $CHCl_3$); after racemization, +35°, which corresponds to 26.5% of Δ^2-menthene in the original mixture.

Phenylhydrazine derivatives of stable and unstable xanthates. The same procedure was used for the stable and unstable xanthate. A solution of 2.0 g. of the xanthate and 0.72 g. of phenylhydrazine in 40 ml. of ethanol was heated under reflux for 6 hr. The solvent was evaporated and the residue allowed to stand in a refrigerator until (10 days) it solidified. The crystals were triturated with cold ligroin and recrystallized from 95% ethanol. The derivative of the stable xanthate had m.p. 150–151°; of the unstable xanthate, 148.5–149.5°; mixture m.p. 147–149°.

Comparison of infrared spectra of stable and unstable xanthate. The spectra of 2% solutions in carbon tetrachloride of unstable and stable (prepared by the butanol method) were superimposable (20 identical peaks between 3.30 and 11.15μ). Samples of the two in Nujol mulls also gave identical spectra (16 identical peaks between 3.28 and 12.0μ). The spectra were determined with a sodium chloride prism.

Rate of decomposition of the stable and unstable xanthates. The rate of decomposition was measured by placing weighed samples of the xanthates in test tubes in a bath held at 149.5–150°. Periodically the tubes were removed, the reaction quenched by cooling in cold benzene, and the tubes weighed. From the weight loss the per cent decomposition was calculated. Plots of log per cent decomposed *versus* time gave straight lines with slope = 2.75, 2.12 for the unstable; 2.47, 2.24 for the stable (prepared by the butyl alcohol method).

Treatment of the stable xanthate with benzoyl peroxide. To a solution of 3.0 g. (0.012 mole) of stable xanthate (prepared by the butyl alcohol method) in 15 ml. of anhydrous benzene (Merck & Co., Inc., thiophene-free grade) was added a few crystals of benzoyl peroxide. The resulting solution was allowed to stand overnight in a refrigerator and then the solvent was removed under reduced pressure at 25°. The residue was distilled through a Claisen flask with a 3-in. Vigreux side arm and 1.32 g. (79%) of menthene was obtained, b.p. 68–70° (50 mm.); n_D^{25} 1.4516.

The above experiment was repeated but the solution was distilled immediately after the addition of the benzoyl peroxide. An 85% yield of menthenes was obtained, b.p. 68–70° (50 mm.); n_D^{25} 1.4497.

The experiment was then repeated but with a few crystals of benzoic acid in place of the benzoyl peroxide. The stable xanthate was recovered in 91% yield, b.p. 110–116° (11 mm.); m.p. 39–39.5°.

Chromatography on alumina of the unstable xanthate. A solution of 2 g. of the unstable xanthate in heptane was passed over a column of alumina (Merck & Co., Inc., suitable for chromatographic absorption) and 1.82 g. was recovered on removal of the solvent. The residue distilled completely at 17 mm. pressure and the distillate solidified, m.p. 38.5–39°; mixture melting point with unstable xanthate, 38.5–39°.

Acknowledgment. The authors thank Dr. G. L. O'Connor and Dr. C. J. Pederson for helpful discussions.

PROVIDENCE 12, R. I.

(9) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., N. Y., N. Y., 1956, Chap. 22.

(10) L. Chugaev, *Ber.*, **42**, 4631 (1909).

(11) J. L. Simonsen, *The Terpenes*, 2nd ed., Cambridge University Press, Cambridge, England, 1947, pg. 243.

(12) C. W. Gould, Jr., G. Holzman, and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

[CONTRIBUTION FROM THE TRUBEK LABORATORIES]

Structure of Hydroxycitronellal

WILLIAM J. HOULIHAN[1]

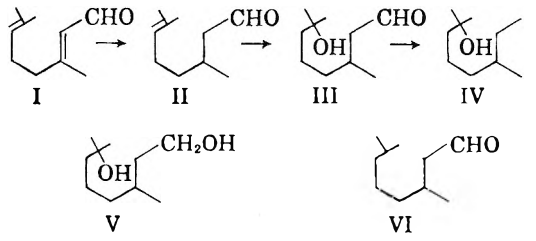
Received October 29, 1957

The structure of hydroxycitronellal has been shown to be 3,7-dimethyl-7-hydroxyoctanal by relating it to the known 2,6-dimethyl-2-octanol. The synthesis of DL-hydroxycitronellal is also reported.

The acidic or basic decomposition of the bisulfite adduct of citronellal (II) is reported[2] to give hydroxycitronellal which has been assigned structure III. The evidence for this structure[3] is due mainly to the work of Palfray *et al.*[4] These workers reduced hydroxycitronellal to a hydroxycitronellol and studied the behavior of this diol to formylation, acetylation, and tritylation. From their results they concluded that the diol contained a primary and a tertiary hydroxyl group and was best represented as V. They also concluded that III was the structure of hydroxycitronellal.

In the present work it was desired to establish a direct relationship between the known 2,6-dimethyl-2-octanol (IV) and hydroxycitronellal, thereby fixing the position of the hydroxy group.

The partial low pressure hydrogenation of citral (I) with a 5% palladium-carbon catalyst[5] gives DL-citronellal (II) together with *ca.* 6–7% DL-dihydrocitronellal (VI). The infrared spectrum of this material showed no hydroxyl bands, indicating that only the carbon-carbon double bonds had been affected. The conversion of II to its sodium bisulfite addition product followed by acid hydrolysis gave a 30% yield of DL-hydroxycitronellal (III). The Wolff-Kishner reduction of III gave a 75%



yield of a tertiary alcohol that was shown by its infrared spectrum and derivatives to be identical with the known DL-2,6-dimethyl-2-octanol[6] (IV).

(1) Present address: Dept. of Chemistry, Seton Hall University, South Orange, N. J.

(2) A. Verley, *Bull. soc. chim.*, [IV] **43**, 849 (1928).

(3) Several other structures have been postulated for hydroxycitronellal. For a discussion of these see P. Z. Bedoukian, *Perfumery Synthetics and Isolates*, D. Van Nostrand Co., Inc., New York, 1951, pp. 231–237.

(4) L. Palfray, S. Sabetay, and A. Rangel, *Compt. rend.*, **212**, 911 (1941).

(5) The reduction of citral has been studied under a wide variety of conditions and catalysts. For a summary see J. L. Simonsen, *The Terpenes*, Cambridge Press, 1947, Vol. I, pp. 90–1.

EXPERIMENTAL[7,8]

DL-*Citronellal.* Citral (247 g., 1.62 moles) in absolute ethanol (100 ml.) was treated with 5% palladium-carbon (3.0 g.) and hydrogenated at room temperature at an initial pressure of 51.0 p.s.i. The theoretical amount of hydrogen for one double bond was absorbed in 8 hr. The catalyst was removed by filtration. The filtrate was added to 2% sodium carbonate (200 ml.) and the mixture was refluxed for 2.5 hr. The organic layer was separated and distilled through a 10-in. packed column. The main fractions (202 g.) consisted largely of DL-citronellal,[9,10] b.p. 78–78.5° (6.0 mm.), n_D^{20} 1.4434–1.4443, d_{20}^{20} 0.8505. The presence of dihydrocitronellal in *ca.* 6–7% was confirmed during the preparation of hydroxycitronellal.

The product yielded an orange 2,4-dinitrophenylhydrazone, m.p. 82° (ethanol), (lit.[11] m.p. 89–90°).

Anal. Calcd. for $C_{16}H_{23}N_4O_4$: C, 57.47; H, 6.63; N, 16.74. Found: C, 57.52; H, 6.12; N, 16.94.

DL-*Hydroxycitronellal.* The procedure of Verley[2] was followed.

From DL-citronellal (165 g., 1.08 moles) there was obtained 56 g. (30%) of DL-hydroxycitronellal, b.p. 106–107.5° (4.0 mm.), n_D^{20} 1.4482, d_{20}^{20} 0.9220, M_{obs}^R 49.78, M_{calcd}^R 49.90. This showed characteristic aldehyde bands at 3.65 μ and 5.80 μ. A tertiary C—O stretching band[12] was observed at 8.70 μ. The literature[13] reports n_D^{20} 1.4494, d_{20} 0.9220 for the (+)-isomer.

An insoluble bisulfite fraction was obtained while working up the product. The treatment of this material with saturated sodium carbonate followed by steam distillation gave 10 g. of liquid. Distillation gave 9.1 g. of material boiling at 60–61° (4.0 mm.) n_D^{20} 1.4310, d_{20}^{20} 0.8584. The infrared showed an unconjugated aldehyde carbonyl at 5.78 μ.

Anal. Calcd. for $C_{10}H_{20}O$: C, 77.56; H, 12.82, for $C_{10}H_{16}O$: C, 80.00; H, 10.52. Found: C, 78.37; H, 11.89.

(6) The synthesis of DL-2,6-dimethyl-2-octanol will be reported in a forthcoming publication by W. J. Houlihan, J. Levy, and J. Meyer.

(7) All melting points are uncorrected.

(8) The microanalyses were performed by the Schwarzkoff Microanalytical Laboratory, 56–19 37th Avenue, Woodside 77, N. Y.

(9) The citronellal obtained by this procedure contained some unreduced citral or other α,β-unsaturated aldehyde (as indicated by the ultraviolet spectrum) and dihydrocitronellal. If it is assumed that the ultraviolet maximum is caused by citral alone then there is 1.1% of this material present—calculated on the starting citral with λ_{max}^{EtOH} 240 mμ, ϵ 14,288.

(10) The physical constants reported in the literature for (+)-, (−)-, and DL-citronellal vary widely. For some more recent constants see: A. Tauchenauer and H. Schinz, *Helv. Chim. Acta*, **32**, 1269 (1949); C. Grundmann, *Ann.*, **524**, 31 (1936); and ref. 2.

(11) Y. R. Naves, L. Desalbres, and P. Ardizio, *Bull. soc. chim. France*, **1956**, 1768.

(12) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **75**, 897 (1953).

(13) A. Muller, *Ber.*, **74**, 1745 (1941).

This material gave a yellow 2,4-dinitrophenylhydrazone, m.p. 89–89.5° (ethanol) and a semicarbazone, m.p. 91–92° (ethanol).

From the above constants and derivatives it is believed that the above material is DL-dihydrocitronellal (VI) contaminated with some citral.

The literature[11] reports for VI, b.p. 81° (12 mm.), n_D^{20} 1.4257, d_4^{20} 0.8253, 2,4-dinitrophenylhydrazone, m.p. 93.5°, semicarbazone, m.p. 91–92°.

Wolff-Kishner reduction of DL-*hydroxycitronellal.* Hydrazine hydrate (85%; 44 g., 0.76 mole) was added in 1 hr. to a solution of DL-hydroxycitronellal (43 g., 0.25 mole) in diethylene glycol (200 ml.). The temperature rose to 52° during the addition. Potassium hydroxide (15 g., 0.27 mole) was added and the temperature slowly raised so that 45 g. of azeotrope (33 g. of water) b.p. 105–115° was collected over 2 hr. Water (200 ml.) was added to the residue in the flask. The organic layer was separated and the water layer was washed with benzene (75 ml., twice). The combined organic layers (including that from the azeotrope) were distilled through a 6-in. packed column. There was obtained 29.7 g. (75.2%) of DL-2,6-dimethyl-2-octanol (IV), b.p. 69.0–69.5° (4.0 mm.), n_D^{20} 1.4338, d_{20}^{20} 0.8275. Authentic[6] IV has a b.p. 75–76° (7.0 mm.), n_D^{20} 1.4336, d_{20}^{20} 0.8273.

The infrared spectrum of the above alcohol was identical with the known 2,6-dimethyl-2-octanol.

This gave a phenylurethane, m.p. 84.8–85.2° which failed to depress the melting point of the phenylurethane obtained from an authentic sample[6] of DL-2,6-dimethyl-2-octanol.

Acknowledgment. The author wishes to express his appreciation to Prof. Harry Wasserman of Yale University and Mr. Irwin Sommer of our analytical department for valuable assistance during this work.

EAST RUTHERFORD, N. J.

[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

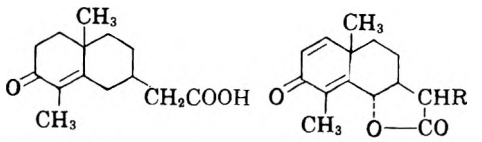
Santonin and Related Compounds. XV.[1] Preparation of *trans*- and *cis*-4,9-Dimethyl-Δ^4-3-octalon-6-acetic Acids[2]

MASAITI YANAGITA, SEIITI INAYAMA, MINORU HIRAKURA, AND FUJIO SEKI

Received November 19, 1957

The Michael addition of diethyl malonate to 3-keto-4,9-dimethyl-$\Delta^{4,5}$-hexahydronaphthalene (III) with sodium *tert*-butoxide gave two stereoisomers of the adduct (IV). The relative yield of these isomers depended on the conditions employed. One isomer, which was predominantly obtained on prolonged reaction at room temperature, may be assigned the *trans*-structure (IVA) with the malonate side chain at an axial position. Another isomer, formed chiefly under more severe conditions, must possess the *cis*-structure (IVB). Hydrolysis and decarboxylation of each isomer of the substituted malonate (IV) gave, respectively, the corresponding monoacid (IA or IB) through the diacid (V). The formation of two isomers on Michael addition does not conform to the earlier belief. From this view, the Michael reactions in the same or closely related systems reported previously were examined. It was reported that addition of diethyl methylmalonate to III under similar conditions gave exclusively the stable *cis*-adduct even at room temperature. An alternative route to the monoacid (I) involved the Robinson reaction of 4-methylcyclohexan-3-one-1-acetate (VIII, R=CH_3) with the Mannich base (VII), giving chiefly the ester of the *trans*-acid (IA). This aspect of the stereochemistry agrees with the earlier postulates. A possible mechanism is offered for explanation of the steric course of Robinson reactions of this type.

From the viewpoint of stereochemical research on the α-propionic acid side chain of the lactone ring in the santonin molecule (II, R = CH_3), it was desirable to prepare, as a model compound, 4,9-dimethyl-Δ^4-3-octalon-6-acetic acid (I) in a state of stereochemical purity. This acid, moreover, will represent a useful intermediate for the synthesis of a simple santonin analog such as II



I II

(R = H). Since this work was initiated, certain papers[3–6] have appeared in which the same ground is covered. Abe, *et al.*[7] announced the total synthesis of natural santonins and of their stereoisomers, which provided the basis for discussion of configuration at the asymmetric centers in santonin (II, R = CH_3).

A route to the acid (I) involving the reaction sequence III → IV → V was first disclosed by Matsui, *et al.*[3] The Michael addition of diethyl malonate to the $\Delta^{4,5}$-dienone (III) was effected at relatively low temperature, and a semisolid product (IV) on hydrolysis was said to give two acids (V), a solid and a liquid, which were each decarboxylated

(1) Paper XIV, R. Futaki, *J. Org. Chem.*, **23**, 451 (1958).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Japan*, **27**, 7 (1954).

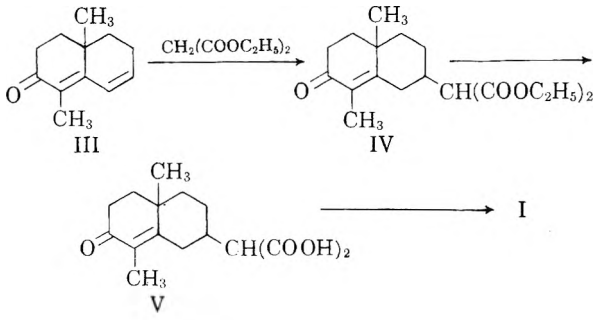
(4) F. J. McQuillin, *Chem. & Ind. (London)*, 311 (1954).

(5) T. Miki, *J. Pharm. Soc. Japan*, **75**, 395 (1955).

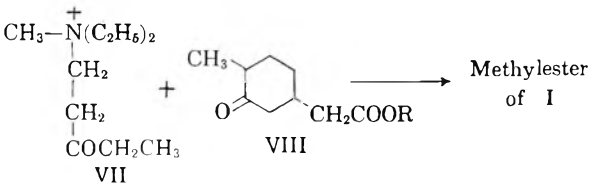
(6) F. D. Gunstone and A. P. Tulloch, *J. Chem. Soc.*, 1130 (1955).

(7) (a) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953). (b) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1416 (1956). (c) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956). *Cf.*, reference 3 and J. K. Chakrabarti, P. Dutt, and P. C. Dutta, *J. Chem. Soc.*, 4978 (1956).

to the corresponding monoacid (I). Almost at the same time, McQuillin[4] mentioned that the same



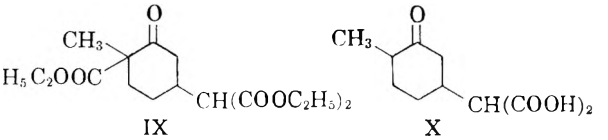
reaction at a relatively high temperature furnished an oily adduct (IV), which was characterized as its 2,4-dinitrophenylhydrazone. Soon after, Miki[5] reported the isolation of one isomer of the adduct (IV) in crystalline form on prolonged reaction at ordinary temperature. A diacid (V) and monoacid (I), derived from the solid adduct, show melting points different from those of the corresponding compounds reported by Matsui, *et al.*[3] (Table I). Simultaneously, Gunstone and Tulloch[6] published an alternative route to the acid (I) through the Robinson condensation of 1-diethylaminopentan-3-one methiodide (VII) with the cyclohexanone-acetate (VIII, R = CH_3), followed by hydrolysis of the resulting monoester. The melting point of the acid so obtained is the same as that of one of the acids of Matsui, *et al.*[3] (Table I).



The compounds reported in the previous papers have as yet not been correlated. No information has been recorded concerning the configuration of these compounds, except an equatorial assignment by Miki[5] to the malonate side chain in his solid adduct (IV). The present paper deals with the preparation of isomeric pairs of the products in pure state by the above two different courses, and the establishment of the spatial arrangement of these compounds. Furthermore, based on our data, the interpretation for the stereochemistry of santonin suggested previously, is discussed.

When the paper of Gunstone and Tulloch[6] appeared describing the preparation of I by the Robinson reaction, our studies along the same lines had already been completed. For comparison purposes, it seems worth while to mention our results, which include certain new findings. The starting acid (VIII, R = H), as described previously,[6,8,9] was prepared by Michael addition of diethyl malonate to ethyl 1-methyl-3-cyclohexen-2-one-1-carboxylate, followed by hydrolysis and decarboxylation of the resulting triester (IX). In this Michael reaction, the intermediates, a monoester (VIII, R = C_2H_5) and a diacid (X), both formed in minute amounts, were isolated and characterized.

Gunstone and Tulloch[6] reported that the Robinson reaction of VIII (R = CH_3) and the Mannich base (VII) with sodium methoxide in methanol led to a rather low yield (11.5%) of methyl ester of I. We used absolute ethanol instead of methanol. There was obtained, besides the predominant neutral product in better yield, a small amount (12%) of an octalone–acetic acid (IA), m.p. 135–136°. Hydrolysis of the neutral product with alkali gave in 34% yield the same acid (IA), which was the sole product isolated previously.[6] However, from



the mother liquor of IA, another isomer (IB), m.p. 144–145°, was consistently isolated, though in a small amount.

As an alternative route to I, the above cited Michael reaction of the $\Delta^{4,5}$-dienone (III) with diethyl malonate was explored. As first reported by Gunstone and Heggie,[10] the dienone (III) was prepared by bromination of the monoenone (XI) and subsequent dehydrobromination of the resulting monobromide (XII) with pyridine. Careful examination of the oily product showed that the dienone fraction (III) was contaminated, together with starting ketone (XI), with a small amount of the known cross-conjugated dienone (XIII),[10,11] characterized as its 2,4-dinitrophenylhydrazone. The latter, which was hitherto accessible only with difficulty, was readily prepared by oxidation of the monoenone (XI) with selenium dioxide in refluxing *tert*-butanol. It has been stated[10,11b,12] that the dienone-phenol rearrangement of XIII with acetic anhydride and concentrated sulfuric acid, which are the most common reagents for this reaction, led frequently to an unidentifiable oily mixture. It is found now that this rearrangement to the *ar*-2-tetralol can be readily effected by warming the dienone (XIII) with dilute sulfuric acid. Similarly, rearrangement of 2,4,4-trimethylcyclohexa-$\Delta^{2,5}$-di-

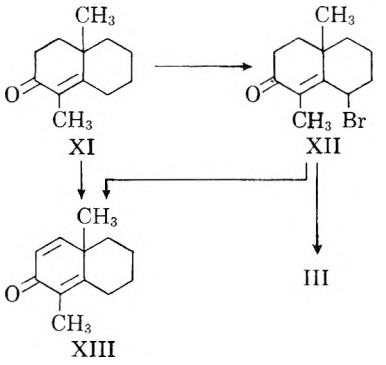
(8) S. M. Mukherjie, *J. Ind. Chem. Soc.*, **25**, 155 (1948); *Chem. Abstr.*, **43**, 2605 (1949).

(9) M. Yanagita, S. Inayama, and R. Kitagawa, *J. Org. Chem.*, **21**, 612 (1956).

(10) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.* 1437 (1952).

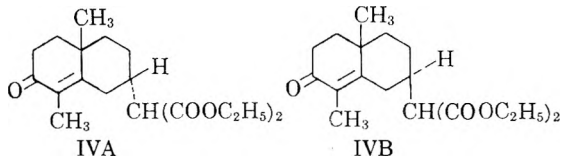
(11) (a) P. R. Hill and F. J. McQuillin, *J. Chem. Soc.*, 4060 (1953). (b) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956). (c) M. Sumi, *Pharm. Bull. Japan*, **4**, 147 (1956). T. Miki claimed the preparation of XIII from XI with selenium dioxide in glacial acetic acid, but no details of experimentation had been described [*J. Pharm. Soc. Japan*, **75**, 403 (1955)].

(12) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954).



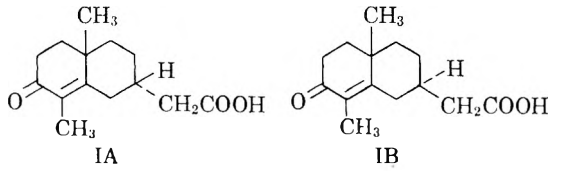
enone to pseudocumenol proceeded much more readily with dilute sulfuric acid than with acetic anhydride–sulfuric acid as reported previously.[12] It has been reported from our laboratory[13] that the reaction of 5-bromo-9-methyl-Δ^4-3-octalone with anhydrous sodium acetate furnished, along with the predominant $\Delta^{4,5}$-dienone (XVII), the rearranged $\Delta^{1,4}$-dienone in a minute amount. The formation of XIII from XII represented an additional instance of such rearrangement during dehydrobromination with a base.

The Miachel reaction of the dienone (III) with diethyl malonate in the presence of potassium *tert*-butanol was extensively examined under a variety of the reaction conditions. When the mixture was allowed to react at room temperature for 2 days and then at 80–90° for 2 hours, one adduct (IVA), m.p. 70–71°, was obtained in 32% yield as the chief product. In addition, a small amount of crystals (IVB), m.p. 75–76°, showing melting point depression with IVA, was isolated from the mother



liquor of IVA. This result is somewhat surprising, since the Michael reaction of such type had been claimed[7] to give only the more stable isomer of the possible two adducts, independent of the conditions employed. On prolongation of the reaction at refluxing temperature, the higher-melting isomer (IVB) was chiefly obtained in 28% yield. Based on these results, the lower-melting adduct may be possibly assigned the *trans*-configuration (IVA) with the malonate side chain in an axial conformation, and the higher-melting isomer the *cis*-configuration (IVB) with an equatorial side chain. It may be predicted that each isomer of the malonate adducts (IVA and IVB) would be selectively produced under control of the reaction conditions. This prediction was confirmed. Thus, when the reaction was conducted at room temperature for 10 days, the yield of the *trans*-isomer (IVA) was raised to 51%, while refluxing of the mixture for 10 hours led in a 39% yield to the *cis*-isomer (IVB).

The *trans*-diester (IVA) was hydrolyzed to a diacid (VA), which on pyrolysis gave the substituted acetic acid (IA), m.p. 135–136.° The latter was



identified with the aforementioned acid obtained from the chief product of the Robinson condensation. Similarly, the *cis*-diester was converted through a diacid (VB) into the *cis*-monoacid (IB), m.p. 143–145°, identical with the acid from the minor product of the Robinson reaction. It is clear that the Robinson reaction of the 4-substituted 2-methylcyclohexanone with the Mannich base favors the formation of the octalone with the C_6-substituent in an axial position.

The melting points of the compounds noted in this and earlier papers of this series are compared in Table I. The close agreement of the melting points leaves no doubt that the Michael reaction adduct (IV) and the derived diacid (V) of Miki[5] have the C_6-side chain in an axial position, contrary to the previous assignment by this worker. That the substituted acetic acid (I) reported by Miki[5] possesses a melting point higher than those of IA of others is hard to understand. It is clear that Matsui, *et al.*[3] had in hand the two pure isomers of the monoacid (IA and IB) from the Michael adduct (IV), and that the compounds of McQuillin[4] and of Gunstone and Tulloch[6] are in the *trans*-series.

In the total synthesis of santonin (II, R = CH_3), Abe, *et al.*[7] reported the preparation of the C_{11}-methyl homologs (XV) of IV, as an intermediate, by the Michael reaction of diethyl methylmalonate to the dienone (III) at room temperature. It has been inferred by certain workers[7a,14] that, by analogy with previous work,[15] this mode of reaction permits an equatorial assignment to the introduced side chain in XV, suggesting stereospecificity of the Michael reactions. Hydrolysis and decarboxylation of the diester (XV) gave rise to two epimers of the monoacid (XVIB), each of which was respectively transformed to α- or β-santonin in few steps. This result was considered[7a,14] to give strong support for an equatorial position of the α-propionic group of the lactone ring in santonin. The two monoacids (XVIA), prepared previously by the Robinson reaction of methyl 4-methylcyclohexan-3-one-1-α-propionate and the Mannich base (VII), are isomeric at the 6-position with XVIB, and would be assigned the *trans*-structure.[7a]

(13) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955).

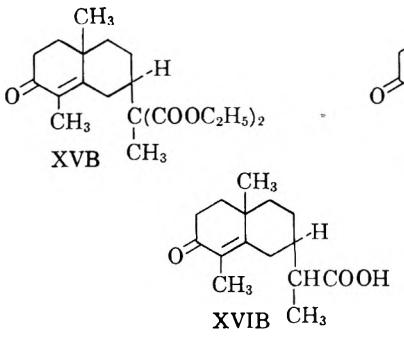
(14) (a) R. B. Woodward and P. Yates, *Chem. & Ind. (London)*, 1391 (1954). (b) E. J. Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955).

(15) J. W. Ralls, *J. Am. Chem. Soc.*, **75**, 2123 (1953).

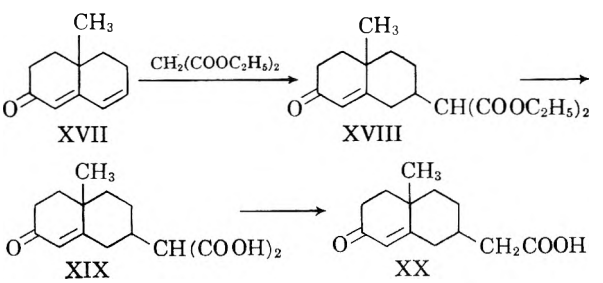
TABLE I

	Present Work	Matsui,[3] *et al.*	McQuillin[4]	Miki[5]	Gunstone[6] *et al.*
trans-Monoacid (IA)	135–136°	135°		139°	135°
cis-Monoacid (IB)	143–145°	143–145°			
trans-Diacid (VA)	174–176°	oil		173°	
cis-Diacid (VB)	185–186°	185°			
trans-Diester (IVA)	70–71°			71°	
2,4-Dinitrophenylhydrazone of IVA	174–176°		170°	177°	
cis-Diester (VB)	75–76°				
2,4-Dinitrophenylhydrazone of VB	129–130°				

However, the above cited basis for the *cis*-assignment of the stereoformula (XVIB) does not seem valid, in view of the present observation that the Michael addition reaction in most closely related systems is not wholly stereospecific, but forms the isomeric adducts in varying relative yields. Particularly, the foregoing fact that, like the *trans*-substituted malonate (IVA), the methylmalonate adduct (XV) was preferentially formed by the Michael reaction at ordinary temperatures, would favor the *trans*-configuration (XVA) for this adduct. Nevertheless, an equatorial character of the α-propionic acid side chain in santonin had been well established by other means,[16,17] and hence, the formulas (XV, XVIA, and XVIB) should be correct. These formulas were strongly supported by our finding that the *cis*-malonate adduct (IVB) was transformed into XVB by methylation with methyl iodide and sodium *tert*-butoxide. It is remarkable that the Michael additions of diethyl malonate and methylmalonate to the dienone (III) proceed through different steric courses under similar reaction conditions. On the other hand, it can be seen that the Robinson reactions showed stereospecificity to yield predominantly the *trans*-product. This agrees with the earlier work.[18]



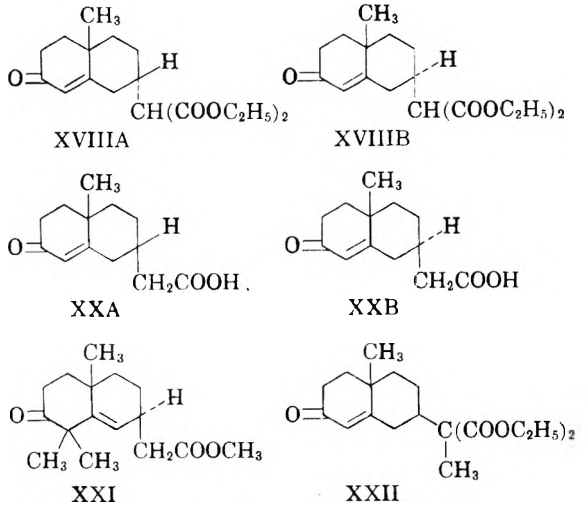
The marked influence of the methyl group in the malonate anion on the stereochemical pattern in the Michael reaction prompted us to investigate the same malonate addition reaction to the $\Delta^{4,5}$-dienone (XVII), the lower homolog of III. It has been reported by Gunstone and Tulloch[6] that the Michael reaction of the dienone (XVII) with diethyl malonate and sodium ethoxide in refluxing ethanol gave rise to a liquid adduct (XVIII), characterized as a 2,4-dinitrophenylhydrazone, m.p. 146–150°. The diester (XVIII) was converted through a diacid (XIX) to the substituted acetic acid (XXB), m.p. 85–88°, which was reported to be not obtained in an analytically pure state.[6] On repetition of this reaction sequence, it was found that the malonate adduct of the reported boiling point was not sterically pure, and formed a mixture of 2,4-dinitrophenylhydrazones, from which one form, m.p. 143–145°, was isolated, accompanied by a small amount of a second form, m.p. 145–150°. Hydrolysis of the diester mixture (XVIII) gave the diacid (XIX), possessing the melting point (dec.) identical with that reported previously.[6] On decarboxylation of the diacid (XIX), the monoacid (XXB), m.p. 90–94°, was chiefly obtained, along with a small amount of the isomer (XXA), m.p. 113–115°. The lower-melting acid, which gave satisfactory analyses, is probably identical with the acid, m.p. 85–88°, of Gunstone and Tulloch.[6] When the addition reaction was carried out with sodium *tert*-butoxide in *tert*-butanol at room temperature for 7 days, there was chiefly obtained a solid adduct



(XVIIIA), forming the 2,4-dinitrophenylhydrazone of the higher melting point. In addition, a minute amount of the liquid isomer (XVIIIB) was detected as its 2,4-dinitrophenylhydrazone after chromatography. This steric result completely parallels that of the same reaction with III, clearly indicating that the solid adduct (XVIIIA) and its liquid isomer (XVIIIB) possess, respectively, the malonate side chain in axial and equatorial positions. It is to be noted that when the above Michael addition was performed in refluxing *tert*-butyl alcohol, the *trans*-isomer (XXA), contrary to the

(16) A. Tahara, *J. Org. Chem.*, 21, 442 (1956).
(17) W. Cocker and T. B. H. McMurry, *Chem. & Ind. (London)*, 1954, 1199: M. Yanagita and A. Tahara, *J. Org. Chem.*, 20, 959 (1955).
(18) E. J. McQuillin, *J. Chem. Soc.*, 528 (1955).

reaction in refluxing ethanol, was chiefly obtained, but in much lower yield than that of the reaction at ordinary temperature. The solid diester (XVIIIA) was converted through a diacid (XIXA) to the higher-melting monoacid (XXA). This acid



showed the same melting point as that of the acid derived previously from the Robinson condensation product of VIII and diethylaminobutan-3-one methiodide.[6] To prove unequivocally the configuration of the side chain in XXA, an effort was made to convert the *trans*-monoacid into IA by monomethylation at the 4-position. After model experiments, which will be reported in the following paper, the methyl ester of XXA was reacted with methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol. Chromatographic separation of the oily product furnished, together with the predominant 4,4,9-trimethyl compound (XXI), a minute amount of the methyl ester of IA which was identified as its 2,4-dinitrophenylhydrazone.

The Michael addition of methylmalonate to the dienone (XVII) in the presence of sodium ethoxide in ethanol has been reported by Harukawa.[19] It proceeded at ordinary temperature with ease comparable to that observed in its addition to III. The only product (XXII), which may be assigned the *cis*-structure, was converted to an isomer of the two possible monoacids. This acid was shown to be different from the acid prepared by the Robinson condensation of methyl 4-methylcyclohexan-3-one-1-α-propionate and diethylaminobutan-3-one methiodide, followed by hydrolysis.[19] It is not clear whether this discrepancy is due to a different configuration at two asymmetric centers or at only one. However, as proposed previously, the *trans*-assignment to the acid from the Robinson condensation product seems correct.

We should like to offer a possible explanation for the steric course of the Robinson reaction described in the present work. It has been stated by Johnson[20] that in the formation of a tricyclic ketone by the Robinson method, alkylation of carbanion of the bicyclic methyl ketone involves preferential attack so that the incoming alkyl group assumes an axial conformation. This is in line with the steric consideration for bromination of cyclic ketones suggested by Corey.[21] On application of this rule to the Robinson reaction cited above, it may be assumed that the carbanion (XXIII) of VIII (R = CH_3) may be attacked selectively by the Mannich base from the axial side to form XXIV. The latter can be inverted to XXV which is less favored by one more skew interaction than XXIV. The diketone (XXIV) may be intramolecularly cyclized to the *cis*-decalol (XXVI). Isolation of a cyclic ketol of similar type has been reported by McQuillin[18] in the synthesis of cyperones by the Robinson procedure. Transformation of XXVI to the observed octalones (as IA) with inversion of the side chain would be expected to proceed through a hypothetical unsaturated intermediate (XXVII) where the angular methyl group is equatorial to the ring with the side chain. Such an octalone, as shown by molecular models, requires a boat form for the unsaturated ring. It is more plausible to infer that the elimination would take place in the inverted form (XXVIII) of XXVI, which gives directly the observed octalone (as IA). Similar cyclization of the diketone (XXV) may lead to *cis*- and *trans*-decalonols (XXVIII and XXIX), the latter forming the same octalone (as IA). On the other hand, an equatorial attack of the alkylating reagent at the carbanion (XXIII) may give rise to the *cis*-monoacid (as IB) through a *trans*-decalonol bearing the acetate side chain equatorial.[22]

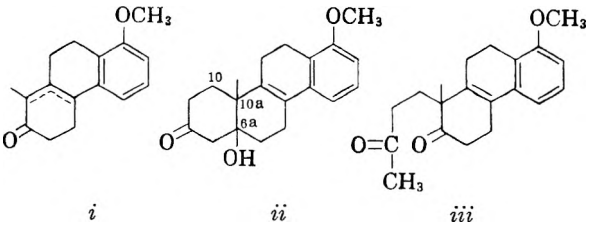
Based on the results of his cyperone studies, McQuillin[18] declared that in the Robinson reaction of 5-substituted 2-methylcyclohexanone, the formation of each isomer of the intermediate decalonol, corresponding to XXVI, is in proportion to the

(19) T. Harukawa, *J. Pharm. Soc. Japan.*, **75**, 521 (1955).

(20) W. S. Johnson, *Chem. & Ind. (London)*, 167 (1956).

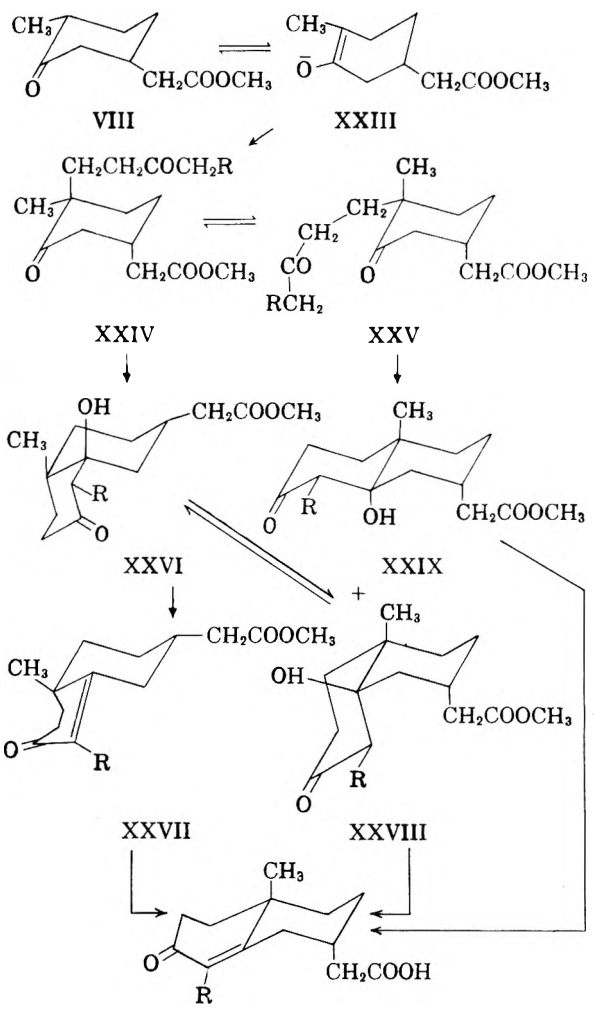
(21) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954).

(22) Johnson *et al.* [*J. Am. Chem. Soc.*, **78**, 6302 (1956)] reported that the base-catalyzed condensation of methyl vinyl ketone with the tricyclic ketone (*i*) gave a mixture of isomers of the tetracyclic ketol (*ii*) which are different in configuration at C_{6a}. This result clearly indicated the equatorial attachment of the bond 10–10a at the angular carbon in *ii*. It is reasonable to consider that according to the above generality,[20] an attack of methyl vinyl ketone at the anionic ketone at the anionic center of *i* would occur preferentially from the axial side, and the resulting intermediate (*iii*), possessing only one asymmetric carbon, may be immediately inverted to the stable form under migration of the axial ketone side chain into the equatorial position, and then cyclized to *ii*.



i *ii* *iii*

population of the two conformations of the cyclohexanone used. A survey of the literature[23] indicates that in polycyclic systems, a cyclohexanone ring in which ring inversion is impossible because of rigid fixation by other rings, also reacted with the alkylating reagent to give an epimeric mixture, as in the case described above. Obviously, this suggests the occurrence of an alkylation from either side of a cyclic ketone in only one conformation. Therefore, the postulation of McQuillin[18] for the steric course of the Robinson reaction seems unlikely.



EXPERIMENTAL[24]

All temperatures are uncorrected.

Diethyl 4-methyl-4-ethoxycarbonyl-3-cyclohexanone-1-malonate (IX). This was prepared by a slight modification of the procedure reported by Mukherjie. To a stirred mixture of sodium metal (4 g.) and diethyl malonate (40 g.) in 150 cc. of absolute ethanol was added, dropwise, ethyl 1-methyl-3-cyclohexen-2-one-1-carboxylate[9] (30 g.) with ice-salt cooling and the stirring was kept up for 2 hr. Working up of the reaction mixture as usual gave the adduct (IX, 44 g., 78%) as a colorless viscous oil, b.p. 185–189° at 3 mm. (Reported,[8] b.p. 192° at 5 mm.).

On prolonged standing with semicarbazide in dilute acetic acid, the semicarbazone was obtained in 54% yield. Recrystallization from dilute ethanol furnished colorless prisms, m.p. 128–129°. Reported,[8] m.p. 126°.

4-Methyl-3-cyclohexanone-1-acetic acid (VIII, R = H). According to the procedure reported previously,[6] the above substituted malonate (IX, 50 g.) was heated with concentrated hydrochloric acid on a boiling water bath for 26 hr. The oily product, which solidified mostly, was treated with cold ethyl acetate to give 10.1 g. (40.7%) of crude monoacid (VIII, R = H), m.p. 89–93°. Recrystallization from benzene-hexane furnished colorless prisms, m.p. 96–98° (reported, m.p. 95–99°[6] and 91–94°[9]).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.39. Found: C, 63.70; H, 8.82.

The semicarbazone, formed almost quantitatively, was recrystallized from ethanol to colorless prisms, m.p. 198–200° (reported,[6] m.p. 193–195°).

Anal. Calcd. for $C_{10}H_{17}N_3O_3$: N, 18.49. Found: N, 18.62.

The acid formed almost quantitatively the 2,4-dinitrophenylhydrazone, m.p. 106–110°, which was recrystallized from ethanol to orange needles, m.p. 118–119°.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.90; H, 5.01; N, 15.62.

The mother liquor of the monoacid (VIII, R = H) gave a dark red oil (19.2 g.), which was dissolved in ether and shaken with aqueous sodium carbonate. Acidification of the carbonate solution furnished an additional 4.7 g. (total 60%) of the crude monoacid (VIII, R = H). The neutral fraction, a pale yellow oil (4.2 g.), was distilled to give 3.7 g. (13%) of a colorless oil, b.p. 117–120° at 25 mm. It formed in 88% yield a 2,4-dinitrophenylhydrazone, m.p. 104–108°. Recrystallization from ethanol furnished orange silky needles, m.p. 117–119°, undepressed on admixture with the same derivative of ethyl ester (VIII, R = C_2H_5) of the monoacid, described below.

In another run, a mixture of the diester (IX, 30 g.) and concentrated hydrochloric acid (240 cc.) was heated for 4 hr. The product, a brown oil, was treated with ether to give a diacid (X, 0.5 g.), as sparingly soluble crystals, m.p. 153–156°. Washing with warm ether gave analytically pure sample, m.p. 165–168°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.07; H, 6.94.

The mother liquor of the diacid gave the crude monoacid (VIII, R = H) (10.4 g., 69%), m.p. 82–90°.

A *methyl ester* (VIII, R = CH_3) was prepared by methylation of the acid with diazomethane in ether solution. A colorless oil, b.p. 126–129° at 5 mm., was obtained in 96% yield. A sample, prepared from the acid with sulfuric acid and methanol, was reported to have the b.p. 136–137° at 13 mm.[6]

The ester formed almost quantitatively a *semicarbazone*, m.p. 138–142°, which was recrystallized from ethanol to white fine scales, m.p. 148–150°. On drying under reduced pressure at 100° for 6 hr., it showed m.p. 141–143°.

Anal. Calcd. for $C_{11}H_{19}N_3O_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.58; H, 7.72; N. 17.24.

The methyl ester formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 108–112°, which was recrystallized from ethanol to orange needles, m.p. 127–129°.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.69; H, 5.02; N, 15.69.

An *ethyl ester* (VIII, R = C_2H_5) was prepared by refluxing the monoacid (0.1 g.) with concentrated sulfuric acid (1 drop) in absolute ethanol (0.5 cc.) for 6 hr. The neutral product, a pale yellow oil, was fractionated to a colorless oil (0.05 g.), b.p. 119° at 4 mm. (bath temperature).

(23) For example see L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth, *J. Am. Chem. Soc.*, **75**, 2112 (1953).

(24) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurement by Miss M. Suzuki.

It formed almost quantitatively a *semicarbazone*, m.p. 162–166°, which was recrystallized from ethanol to prisms, m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{21}N_3O_3$: N, 16.46. Found: N, 16.93.

The ethyl ester formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 99–104°, which was once recrystallized from ethanol to silky orange needles, m.p. 117–119°.

Anal. Calcd. for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81. Found: C, 53.73; H, 5.95; N, 14.56.

Preparation of 4,9-dimethyl-Δ^4-3-octalon-6-acetic acid (IA) *by the Robinson reaction.* This was carried out by an improvement of the procedure reported previously.[6] Diethylaminopentan-3-one (6.3 g., VII) was treated with methyl iodide (5.8 g.) under cooling, and the above cyclohexanoneacetate (VIII, R = CH_3) (3.7 g.) was added dropwise, followed by a solution of sodium methoxide (from 0.95 g. sodium) in absolute methanol (30 cc.). The mixture was allowed to stand at room temperature overnight, and refluxed for 40 min. with stirring. After cooling, the reaction was acidified with acetic acid, then evaporated under reduced pressure, the residue was diluted with water and extracted with ether. The ether solution was shaken successively with aqueous sodium bicarbonate, sodium carbonate, and water.

(*a*) *Acid product.* Acidification of the carbonate solution gave a pale yellow oil (1.2 g.), which mostly solidified. Treatment with ethyl acetate–petroleum ether furnished 0.56 g. (12%) of the *trans*-acetic acid compound (IA), m.p. 127–130°, which was recrystallized from the same solvent mixture to white prisms, m.p. 135°: λ_{max}^{EtOH} 248 mμ (log ε 4.18). Reported,[6] m.p. 135°.

It formed almost quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 225–228° (dec.), which was recrystallized from ethyl acetate and then acetic acid to red fine scales, m.p. 234–236°: $\lambda_{max}^{CHCl_3}$ 260 mμ (log ε 4.31), 290 mμ (log ε 4.11) (infl.), and 392 mμ (log ε 4.51).

Anal. Calcd. for $C_{20}H_{24}N_4O_6$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.41; H, 5.70; N, 13.00.

A *semicarbazone*, m.p. 229–232°, obtained almost quantitatively, was recrystallized from ethanol to white prisms, m.p. 235–236°.

Anal. Calcd. for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.33. Found: C, 61.23; H, 7.70; N, 14.16.

(*b*) *Neutral product.* The above ether solution, washed with aqueous sodium carbonate, was dried and evaporated to leave a pale yellow oil (3.25 g.), which was fractionated. A forerun of the starting material (1.2 g., 46%), b.p. 111–125° at 4 mm., was followed by the octalone–acetic ester (I, R = CH_3) (1.7 g.), b.p. 170–195° at 5 mm. Refractionation gave 1.45 g. (29%) of a pale yellow viscous oil, b.p. 170–191° at 5 mm. This oil formed, in 85% yield, a 2,4-dinitrophenylhydrazone, melting in the range of 130° and 155°. Repeated recrystallizations from ethyl acetate furnished deep red fine needles, m.p. 178–180°: $\lambda_{max}^{CHCl_3}$ 260 mμ (log ε 4.26), 295 mμ (log ε 4.03) (infl.), and 392 mμ (log ε 4.46). It melted at 182–183° on admixture with the same derivative of the methyl ester of the *trans*-monoacid (IA), described below (reported,[6] m.p. 176–177°).

The above ester fraction (1.0 g.) was heated to reflux with potassium hydroxide (1.0 g.) in methanol (10 cc.) for 2 hr. The crude acid (I) was obtained as a pale yellow viscous oil, which soon solidified partly. Crystallization from ether–petroleum ether gave 0.44 g. (47%) of the *trans*-monoacid (IA) as yellowish crystals, m.p. 122–129°. Recrystallization from ethyl acetate furnished colorless prisms, m.p. and mixed m.p. 133–135°.

The mother liquor of crystallization of IA gave the *cis*-isomer (IB) (0.14 g.), melting in the range of 108–119°. Recrystallization from ethyl acetate to colorless prisms, m.p. 144–145°, undepressed with the authentic sample described below.

Bromination-dehydrobromination of 4,9-dimethyl-Δ^4-3-octalone (XI). This reaction was previously performed by two procedures[10] to yield the $\Delta^{4,5}$-dienone (III). The one involves bromination of the monoenone (XI) with *N*-bromosuccinimide and subsequent elimination of the bromide (XII) with hot pyridine, and the other consists of the bromine treatment of the monoenone (XI) and distillation of the resulting bromide (XII) after standing at room temperature. On repetition, it was found that the latter procedure was unfavorable, since distillation of the bromide was always accompanied with evolution of white smoke, giving a distillate which soon colored deeply.

By combination of these procedures, a convenient method for the $\Delta^{4,6}$-dienone (III) was developed.

The monobromide (XII), prepared from the monoenone (XI, 15.0 g.) with bromine (14.1 g.) in carbon tetrachloride (50 cc.), was heated to reflux with dried pyridine (30 cc.) for 4 hr. The product, a red brown oil (13.9 g.), was fractionated to a pale yellow oil (9.3 g., 63%), b.p. 110–111° at 3 mm., and a yellowish oil (2.4 g., 16%), b.p. 113–127° at 3 mm.; both had λ_{max}^{EtOH} 288 mμ (log ε 4.29). These fractions, consisting mainly of the $\Delta^{4,5}$-dienone (III), formed the same 2,4-dinitrophenylhydrazone, m.p. 200–205°. Recrystallization from ethyl acetate–ethanol furnished dark red plates, m.p. and mixed m.p. 212–214°: $\lambda_{max}^{CHCl_3}$ 266 mμ (log ε 4.20), 312 mμ (log ε 4.15), and 402.5 mμ (log 4.54) (reported,[10] m.p. 216°).

The higher-boiling fraction formed in about 70% yield the semicarbazone of the $\Delta^{4,5}$-dienone (III), m.p. 220–222°, after recrystallization from ethanol. It had λ_{max}^{EtOH} 300 mμ (log ε 4.55) [reported,[10] m.p. 216–217°; λ_{max}^{EtOH} 300 mμ (log ε 4.55)].

To the mother liquor of crystallization of the semicarbazone was added Brady's reagent (an ethanolic solution of 2,4-dinitrophenylhydrazone and concentrated sulfuric acid), and the red crystals, m.p. 198–205°, which separated, were recrystallized from ethyl acetate–ethanol to dark red plates, m.p. 218–220°; $\lambda_{max}^{CHCl_3}$ 263 mμ (log ε 4.22), 315 mμ (log ε 3.87), and 406 mμ (log ε 4.52). The sample showed no depression of the melting point on admixture with the same derivative, m.p. 226–227°, of the $\Delta^{1,4}$-dienone (XIII).[11b]

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.49; H, 5.50; N, 15.38.

Oxidation of 4,9-dimethyl-Δ^4-3-octalone (XI) *with selenium dioxide.* The monoenone (XI, 1.78 g.) was heated to reflux in a stream of nitrogen with 1.2 g. of freshly sublimed selenium dioxide in 100 cc. of *tert*-butyl alcohol and 1 cc. of glacial acetic acid for 48 hr. After filtration of the selenium, the reaction mixture was evaporated under reduced pressure, the residual oil was mixed with ether, and again filtered to remove the remaining selenium. The ether solution was washed with aqueous sodium hydroxide and then with water. Evaporation of the dried ether solution left a brown oil (2.05 g.), which was fractionated to 1.1 g. (62.5%) of the $\Delta^{1,4}$-dienone (XIII) as a pale yellow oil, b.p. 108–112° at 2 mm. Refractionation gave an almost colorless oil (1.0 g.), b.p. 109–111° at 2 mm.; n_D^{20} 1.5449; λ_{max}^{EtOH} 241 mμ (log ε 3.95) and 265 mμ (log ε 3.79) (infl.); $\lambda_{C=O}^{CCl_4}$ 6.0 μ ($\alpha,\beta,\alpha',\beta'$-diunsaturated ketone), $\lambda_{C=C}^{CCl_4}$ 6.11 μ, 6.195 μ (reported[11a] b.p. 108–110° at 1 mm.; n_D^{20} 1.5322).

The oil formed quantitatively the 2,4-dinitrophenylhydrazone, m.p. 225–228°, which is higher than the melting point of the pure sample of one form reported from our laboratory.[11b] Recrystallization from ethyl acetate–ethanol and then ethyl acetate alone gave deep red scales, m.p. 232–234°. It had $\lambda_{max}^{CHCl_3}$ 260 mμ (log ε 4.39), 312 mμ (log ε 3.98), and 407 mμ (log ε 4.67), which is practically identical with the reported value,[10] but somewhat different from the value of the lower-melting form described above.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.94; H, 5.40; N, 15.50.

Dienone-phenol rearrangement of 3-keto-4,9-dimethyl-$\Delta^{1,4}$-hexahydronaphthalene (XIII) *and related compound.* A mixture of the above dienone (XIII, 0.10 g.) and dilute sulfuric acid (5 cc. each of concentrated sulfuric acid and water) was warmed at 50–60° on a water bath for 9 hr. with stirring. After cooling, the reaction mixture, which precipitated a

brown oil, was poured onto water and extracted with ether. Evaporation of the dried ether solution left 0.04 g. of 1,4-dimethyl-*ar*-2-tetralol, m.p. 103–104°, after recrystallization from petroleum ether. It showed no depression of the melting point on admixture with the authentic sample reported previously.[11b] This material had λ_{max}^{EtOH} 217 mμ (10 g. ε 3.90) and 285.5 mμ (log ε 3.29).

Similarly, 2,4,4-trimethylcyclohexa-$\Delta^{2,5}$-dienone (0.1 g.)[12] was warmed with dilute sulfuric acid for 13 hr. The reaction mixture was diluted with water, extracted with ether, and the ether solution was shaken with 10% aqueous sodium hydroxide. Acidification of the alkaline solution gave pseudocumenol as a brown oil (0.07 g.) which soon solidified almost completely, m.p. 50–54°. Recrystallization from petroleum ether furnished white silky prisms, m.p. and mixed m.p. 70.5–72.5°.

Michael addition of diethyl malonate to 3-keto-4,9-dimethyl $\Delta^{4,5}$*-hexahydronaphthalene* (III). (*a*) *at room temperature for 2 days and then at 80–90° for 2 hr.* To a stirred potassium *tert*-butoxide paste, prepared from 0.22 g. of potassium metal and 5 cc. of absolute *tert*-butyl alcohol, 3.65 g. of diethyl malonate and then 2.0 g. of the $\Delta^{4,5}$-dienone (III) were added dropwise with ice cooling. The mixture was allowed to react with occasional stirring at room temperature for 48 hr. and then heated at 80–90° (water bath temperature) for 2 hr. The deep brown solution was neutralized with acetic acid, evaporated to a small volume, acidified with hydrochloric acid, and extracted with ether. The ether solution was washed with aqueous sodium hydroxide and with water. Evaporation of the dried ether solution left a brown oil (5.25 g.), which was fractionated. With a forerun of the starting materials, the adduct (IV) was obtained as a pale yellow viscous oil (2.01 g.), b.p. 188–201° at 3 mm., which almost completely solidified. On washing ether–petroleum ether 1.22 g. (32%) of the *trans*-adduct (IVA) was obtained as crystals, m.p. 55–61°, which was recrystallized from ethyl acetate–petroleum ether as colorless large prisms, m.p. 70–71°; λ_{max}^{EtOH} 246 mμ (log ε 4.25). Miki[5] reported m.p. 71° and λ_{max}^{EtOH} 246 (log ε 4.15) for his adduct which was considered to be *cis*.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 67.83; H, 8.39. Found: C, 67.70; H, 8.07.

The 2,4-*dinitrophenylhydrazone* had the m.p. 174–176° (red-orange prisms), after recrystallization from ethyl acetate: $\lambda_{max}^{CHCl_3}$ 261 mμ (log ε 4.25), 295 mμ (log ε 4.03) (infl.), and 392 mμ (log ε 4.47) (reported,[5] m.p. 177°).

IVA quantitatively formed a *semicarbazone*, m.p. 152–156°, which was recrystallized from dilute ethanol to fine prisms, m.p. 160–162°.

Anal. Calcd. for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.11; H, 7.98; N, 10.56.

The mother liquor of IVA gave a pale yellow, viscous oil (0.7 g.), which was distilled to 2 fractions, a pale yellow oil (0.12 g.), b.p. 190–220° (bath temperature), and a yellowish oil (0.45 g.), b.p. 195–205°, both at 3 mm. After standing for about 1 month, the former fraction furnished an additional 0.05 g. of the crude *trans*-adduct (IVA), and the latter fraction gave 0.1 g. of the *cis*-isomer (IVB), m.p. 61–67°. Recrystallization from ethyl acetate–petroleum ether furnished crystals, m.p. and mixed m.p. 75–76° with the authentic sample described below (*c*).

(*b*) *at room temperature for 3 days and then refluxing for 48 hr.* A mixture of potassiomalonate (from 1.38 g. of potassium, 15 cc. of *tert*-butyl alcohol, and 21.9 g. of diethyl malonate) and 12.0 g. of the $\Delta^{4,5}$-dienone (III) was reacted at room temperature for 3 days, and then was heated to reflux for 48 hr. Worked up as described in (*a*), a red brown oily product (25 g.) was fractionated to a pale yellow viscous oil (14.9 g.), b.p. 170–220° at 5 mm., which slowly solidified. Treatment with petroleum ether gave the *cis*-adduct (IVB, 11.5 g.), melting in the range of 56–70°. On one recrystallization from ethyl acetate, 6.5 g. (28.4%) of white prisms, m.p. 71–74°, was obtained, which was further recrystallized from the same solvent to raise the m.p. to 75–76°; λ_{max}^{EtOH} 246 mμ (log ε 4.23). It showed obvious depression (15–20°) of the melting point on admixture with the *trans*-adduct (IVA).

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.42; H, 8.38.

A *semicarbazone*, m.p. 172–177°, prepared quantitatively, was recrystallized from dilute ethanol to fine prisms, m.p. 176–178°.

Anal. Calcd. for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.35; H, 7.78; N, 10.46.

A 2,4-*dinitrophenylhydrazone*, m.p. 123–125°, prepared quantitatively, was recrystallized from ethyl acetate–ethanol to reddish-orange plates, m.p. 129–130°; λ_{max}^{EtOH} 260 mμ (log ε 4.24), 295 mμ (log ε 4.03), and 392 mμ (log ε 4.46).

Anal. Calcd. for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.24; N, 10.85. Found: C, 58.26; H, 6.59; N, 10.97.

(*c*) *at room temperature for 10 days.* A mixture of potassiomalonate (from 1.0 g. of potassium, 25 cc. of *tert*-butyl alcohol, and 16.4 g. of diethyl malonate) and 8.9 g. of the $\Delta^{4,5}$-dienone (III) was stirred at room temperature for 10 days. The solid slowly dissolved to form a yellowish-brown fluorescent solution. The oily reaction mixture was fractionated to a pale yellow oil (11.65 g.), b.p. 192–196° at 1.2 mm., which mostly solidified. Washing with petroleum ether and recrystallization from ethyl acetate by addition of petroleum ether furnished (6.52 g., 33%) the *trans*-adduct (IVA) as colorless large prisms, m.p. 70–71°. The mother liquor of crystallization of IVA gave an additional 2.24 g. (total 51%) of the crude IVA.

(*d*) *at reflux temperature for 10 hr.* A mixture of potassiomalonate (from 1.25 g. of potassium metal, 30 cc. of *tert*-butyl alcohol, and 20 g. of diethyl malonate) and 11.0 g. of the $\Delta^{4,5}$-dienone (III) was refluxed for 10 hr. and worked up as above. The reaction mixture was fractionated to a pale yellow viscous oil (12.7 g.), b.p. 180–190° at 0.025 mm., which slowly crystallized on addition of a little hexane. Washing with hexane and recrystallization from ethyl acetate furnished 8.12 g. (39%) of the *cis*-adduct (IVB), m.p. and mixed m.p. 74–76°. Hydrolysis and decarboxylation of the mother liquid of IVB, as will be described in the following paragraph, furnished only the *trans*-monoacid (IA, 1.01 g.), m.p. and mixed m.p. 133–135°, after recrystallization from ethyl acetate.

Hydrolysis and decarboxylation of diethyl-trans-4,9-dimethyl-Δ^4*-3-octalone-6-malonate* (IVA). This reaction was carried out by improvement of a reported procedure[5] to raise the yield of the products.

To a solution of 8.0 g. of the *trans*-malonate adduct (IVA) in 30 cc. of methanol was added a solution of 8.0 g. of potassium hydroxide in 10 cc. of water and 40 cc. of methanol with cooling. After standing overnight at room temperature, the solution was heated to reflux for 40 min. The chilled reaction mixture was neutralized with acetic acid and evaporated under reduced pressure. The residue was dissolved in water and acidification with 20% hydrochloric acid separated a dirty green oil. On standing, the *trans*-diacid (VA) (6.5 g., 97%) deposited as needles, m.p. 166–169° (dec.). Recrystallization from dilute methanol and then ethyl acetate raised the melting point to 174–176° (dec.); λ_{max}^{EtOH} 247.5 mμ (log ε 4.24).

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.22.

Pyrolysis of the diacid (VA, 6.25 g.) at 170–180° (oil bath temperature) for 10 min. in a stream of nitrogen gave a red brown oil (sublim.), which solidified on cooling. Recrystallization from ethyl acetate with active carbon gave the *trans*-monoacid (IA, 4.63 g., 89%), m.p. 132–134°. Recrystallization from ethanol furnished colorless prisms, m.p. 135–136°; λ_{max}^{EtOH} 248 mμ (log ε 4.20). It showed no depression of the melting point on admixture with the above sample, prepared by the Robinson reaction.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.91; H, 8.17.

This acid was methylated with diazomethane in ether solution. A *methyl ester* had the b.p. 153–155° at 2 mm.; λ_{max}^{EtOH} 247 mμ (log ε 4.21).

It formed almost quantitatively a *2,4-dinitrophenylhydrazone* as deep red fine needles, m.p. 171–178°. Recrystallization from ethyl acetate–ethanol and then glacial acetic acid raised the m.p. to 182–184°.

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.87; H, 5.97; N, 12.98.

Hydrolysis and decarboxylation of diethyl cis-4,9-dimethyl-Δ⁴-3-octalone-6-malonate (IVB). These reactions were carried out exactly as described above for the *trans*-isomer (IVA). The crude *cis*-diacid, m.p. 185° (dec.), was obtained in 98% yield. Recrystallization from ethyl acetate gave white prisms, m.p. 185–186° (dec.); λ_{max}^{EtOH} 247.5 mμ (log ε 4.23). Matsui *et al.*[3] gave the m.p. 185° for one isomer of the diacid (V).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.88; H, 7.52.

Pyrolysis of the diacid gave in 91% yield the *cis*-monoacid, melting in the range of 128–137°. Recrystallization from ethyl acetate gave colorless prisms, m.p. 143–145°; λ_{max}^{EtOH} 248 mμ (log ε 4.19).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.92; H, 8.23.

It formed almost quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 231–234°, which was recrystallized from ethyl acetate and then from glacial acetic acid to red silky needles, m.p. 243–245°: λ_{max}^{EtOH} 261.5 mμ (log ε 4.30), 295 mμ (log ε 4.08) (infl.), and 392 mμ (log ε 4.51).

Anal. Calcd. for $C_{20}H_{24}N_4O_6$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.86; H, 5.44; N, 13.23.

The *semicarbazone*, m.p. 243–248°, obtained almost quantitatively, was recrystallized from ethanol to white scales, m.p. 249–250°.

Anal. Calcd. for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.33. Found: C, 61.44; H, 7.49; N, 13.89.

This acid was methylated with diazomethane in ether solution. A *methyl ester* had b.p. 147–149° at 2 mm.; λ_{max}^{EtOH} 247 mμ (log ε 4.20). It formed quantitatively a *2,4-dinitrophenylhydrazone*, deep red fine needles, m.p. 180–183°. Recrystallization from ethyl acetate raised the m.p. to 185–187°; $\lambda_{max}^{CHCl_3}$ 260.5 mμ (log ε 4.26), 295 mμ (log ε 4.05) (infl.), and 392 mμ (log ε 4.48).

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.52; H, 6.09; N, 12.72.

Methylation of diethyl cis-4,9-dimethyl-Δ⁴-3-ocialone-6-malonate (IVB) *with methyl iodide.* To a stirred potassium *tert*-butoxide paste, prepared from 0.12 g. of potassium metal and 10 cc. of *tert*-butyl alcohol, 1.0 g. of the *cis*-malonate adduct (IVA) was added dropwise, followed by 4 cc. of methyl iodide. After refluxing for 1 hr., another 1 cc. of methyl iodide was added, and the refluxing was continued further for 3 hr. The neutral reaction mixture was evaporated under reduced pressure, the residue was dissolved in water, and extracted with ether. The ether solution was washed with sodium bicarbonate solution, dried, and evaporated to leave a pale yellow oil (0.59 g.). Fractionation furnished almost colorless oil (0.4 g.), b.p. 160–162° at 0.02 mm., which was chromatographed on alumina (12 g.) as a petroleum ether solution. Elution with petroleum ether–benzene gave 0.08 g. of crystals, m.p. 53–56°, which was recrystallized from petroleum ether to white prisms, m.p. 59–60°. It showed no depression of the melting point on admixture with the *cis*-methylmalonate adduct (XV), m.p. 61–62°, kindly furnished by Dr. Abe.[7b] The *2,4-dinitrophenylhydrazone* had m.p. 125° (after recrystallization from ethanol), undepressed on admixture with the same derivative, m.p. 125°, of the diester (XV) of Abe, who gave the m.p. as 123°.

Michael addition of diethyl malonate to 3-keto-9-methyl-Δ⁴·⁵-hexahydronaphthalene (XVII). The Δ⁴·⁵-dienone (XVII) was prepared by bromination-dehydrobromination of 9-methyl-Δ⁴-3-decalone, as reported previously.[6] The product contained 20–25% of the unchanged starting ketone, which was used for the Michael reaction without further purification. Its *2,4-dinitrophenylhydrazone* was recrystallized from benzene-methanol to deep red plates, m.p. 194–195°; λ_{max}^{EtOH} 268 mμ (log ε 4.20), 308.5 mμ (log ε 4.14), and 402 mμ (log ε 4.53). Reported, m.p. 187–190°[6] and m.p. 177°.[26]

(*a*) *at reflux temperature in ethanol.* The Michael reaction of XVII was first carried out by a modification of the procedure reported previously.[6] To a sodium ethoxide solution, prepared from 0.12 g. of sodium metal and 5 cc. of ethanol, 7.0 g. of diethylmalonate was added, followed by 1.80 g. of the ketone (XVII). The mixture was heated to reflux for 90 min. The chilled mixture was acidified with acetic acid (0.5 cc.) and evaporated under reduced pressure. The residue was mixed with water, extracted with ether, and the ether solution was washed with sodium bicarbonate solution and water. Evaporation of the dried ether solution left an oil which was fractionated to a colorless oil (0.37 g.), b.p. 96–100° at 3 mm., and a pale yellow oil (2.04 g.), b.p. 175–180° at 0.05 mm.; n_D^{20} 1.5020 (reported,[6] b.p. 174–180° at 0.05 mm., and n_D^{20} 1.5105).

The former fraction mainly consisted of 9-methyl-Δ⁴-3-octalone, which was characterized as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 168–169°.[26] The latter fraction (0.09 g.) formed 0.12 g. (85%) of 2,4-dinitrophenylhydrazone, melting in the range of 95 and 110°, which was chromatographed on alumina (acid-washed, 5 g.), and eluted with carbon tetrachloride–chloroform (9:1). The more readily eluted fraction gave 0.065 g. of the hydrazone of the *cis*-adduct (XVIIIB) as orange red plates, m.p. 143–145° (after recrystallization from benzene–petroleum ether). The less readily eluted fraction gave orange-yellow fine needles (10 mg.), m.p. 149–150° (after recrystallization from ethyl acetate–ethanol), undepressed on admixture with the same derivative of the *trans*-adduct (XVIIIA), described below. Reported,[6] m.p. 146–150° (from ethanol).

(*b*) *at room temperature in tert-butyl alcohol.* To a paste of potassiomalonate, prepared from 0.35 g. of potassium metal, 20 cc. of *tert*-butyl alcohol, and 10.5 g. of diethyl malonate, 2.92 g. of the ketone (XVII) was added and stirred at room temperature for 7 days. The brown solution was worked up as described above (*a*). The oily mixture was fractionated to give the starting monoenone (0.79 g.), 118–122° at 7 mm., and a pale yellow viscous oil (3.06 g.), b.p. 165–172° at 0.02 mm.; n_D^{20} 1.4990. The latter fraction mostly solidified on standing in a refrigerator. Filtration by suction and washing with petroleum ether gave 2.4 g. (57%, based on unrecovered monoenone) of the *trans*-adduct (XVIIIA) as colorless prisms, m.p. 37–39°.

The *trans*-adduct formed in 90% yielded a *2,4-dinitrophenylhydrazone*, melting in the range of 135–144°, which was recrystallized from ethyl acetate–ethanol to orange-yellow needles, m.p. 149–150°. It showed obvious depression (5–10°) of the melting point on admixture with the same derivative of the above *cis*-isomer (XVIIIB).

Anal. Calcd. for $C_{24}H_{30}N_4O_8$: C, 57.36; H, 6.02; N, 11.15. Found: C, 57.65; H, 6.23; N, 11.07.

The mother liquid (0.10 g.) of XVIIIA formed 2,4-dinitrophenylhydrazone (0.125 g.), m.p. 102–105°, which was subjected to chromatographic separation on alumina (5 g.) as described above. There were obtained the hydrazone of the *cis*-adduct (XVIIIB) (55 mg.), m.p. and mixed m.p. 143–145°, and the hydrazone of the *trans*-adduct (XVIIIA) (10 mg.), m.p. and mixed m.p. 149–150°.

(*c*) *at reflux temperature in tert-butyl alcohol.* A mixture of potassium metal (0.24 g.), *tert*-butyl alcohol (15 cc.), diethyl malonate (8 g.), and the ketone (XVII, 2.00 g.) was heated to reflux on a water bath for 90 min. Worked up as described above, the crude product was fractionated to the starting monoenone (0.52 g.) and a pale yellow viscous oil (1.76 g.),

(25) T. Harukawa, *J. Pharm. Soc. Japan*, 75, 421 (1955).

(26) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

b.p. 172–182° at 0.2 mm.: n_D^{20} 1.5050. The latter fraction was seeded with the *trans*-adduct (XVIIIA) and kept in a refrigerator for about 40 days. The partly solidified oil was filtered by suction and washed with petroleum ether to give 0.42 g. (14%) of the *trans*-adduct (XVIIIA), m.p. and mixed m.p. 37–39°.

The mother oil of XVIIIA amounted to 1.24 g., which (0.10 g.) formed a resinous mixture of 2,4-dinitrophenylhydrazone (0.125 g.). Chromatographic separation on alumina (10 g.) and elution with carbon tetrachloride–chloroform (10:1) afforded the hydrazone of XVIIIB (0.06 g.), m.p. and mixed m.p. 143–145°, after recrystallization from benzene–petroleum ether.

Hydrolysis and decarboxylation of diethyl 9-methyl-Δ^4-3-octalone-6-malonate (XVIII). (*a*) *with the cis-malonate* (XVIIIB). The oily malonate adduct, prepared by the method (*a*) in the preceding paragraph, was hydrolyzed as described for IVA. On standing overnight at room temperature, the alkaline solution of XVIIIB became dirty green. The diacid, 164–165° (dec.), was obtained in 67% yield. Recrystallization from dilute ethanol did not alter the melting point (reported,[6] 165–168°).

The diacid (5.80 g.) was heated at 180–190° (bath temperature) for 10 min. The brown mass so obtained was treated with ethyl acetate–petroleum ether to give a light brown solid (3.96 g.), melting in the range of 54–76°. On fractional recrystallization from benzene, the less soluble fraction furnished 2.33 g. (48%) of the *cis* monoacid (XXB) as colorless needles, m.p. 88–92°. Further recrystallization from the same solvent raised the melting point to 90–94°. Gunstone and Tulloch[6] reported the m.p. 88° for the sample which was said to be not analytically pure.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.53; H, 8.15.

An oil collected from the mother liquors of XXB was seeded and gave 0.92 g. (19%) of the *trans*-isomer (XXA), m.p. 105–111°. Recrystallization from benzene gave white crystalline powder, m.p. 113–115°, undepressed on admixture with a sample described below.

(*b*) *with the trans-malonate* (XVIIIA). The above solid adduct (XVIIIA) was hydrolyzed as described above. The diacid, m.p. 164–165° (dec.), obtained in 81% yield, was recrystallized from dilute methanol to colorless prisms, m.p. 165–166° (dec.).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.23; H, 6.64.

Decarboxylation of the *trans*-diacid by the procedure described above gave in 93% yield the *trans*-monoacid (XXA), melting in the range of 95–114°. Recrystallization from ethyl acetate–petroleum ether furnished white crystalline powder, m.p. 113–115°. Gunstone and Tulloch[6] reported the m.p. 113–115° for the monacid, prepared by the Robinson condensation of VIII and diethylaminobutan-3-one.

XXA was methylated with diazomethane in ether to give almost quantitatively a *methyl ester*, which was distilled to colorless oil, b.p. 156–157° at 3.5 mm.: n_D^{20} 1.5151. It formed a 2,4-dinitrophenylhydrazone, as orange scales, m.p. 160–161°, after recrystallization from benzenemethanol.

Anal. Calcd. for $C_{20}H_{24}N_4O_6$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.73; H, 5.90; N, 13.23.

Methylation of methyl trans-9-methyl-Δ^4-3-octalone-6-acetate (XXA) *with methyl iodide.* To a stirred potassium *tert*-butoxide, prepared from 85 mg. of potassium metal and 3 cc. of *tert*-butyl alcohol, a solution of 0.20 g. of the above methyl ester of the *trans*-monoacid (XXA) in 5 cc. of benzene was added. The solution became brown. Methyl iodide (0.5 g.) was added dropwise, and a white precipitate appeared soon and the color of the solution faded. The mixture was heated to a gentle reflux for 2.5 hr. The solvent was evaporated under reduced pressure, the residue was dissolved in water, and extracted with ether. The ether solution was shaken with sodium bicarbonate solution and then with water. Evaporation of the dried ether solution left a pale yellow oil (0.11 g.), which was chromatographed on alumina (acid-washed, 5 g.) and eluted with benzene and then with benzene-ether (4:1). The first elution with benzene gave the trimethyl ketone (XXIA) (25 mg.), m.p. 39–41°, which was recrystallized from petroleum ether to plates, m.p. 40–40.5°. It had no ultraviolet absorption band corresponding to the α,β-unsaturated ketone.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.28; H, 9.29.

It formed a *2,4-dinitrophenylhydrazone*, yellow fine needles, m.p. 153–154°, after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_{22}H_{28}N_4O_6$: C, 59.44; H, 6.35. Found: C, 59.69; H, 6.72.

The later elution with benzene gave an oil (10 mg.), which was converted to red 2,4-dinitrophenylhydrazone, melting in the range of 158–168°. Chromatography on alumina (1 g.) and elution with benzene furnished red fine needles, m.p. 180–182°, after recrystallization from ethyl acetate–ethanol. It showed no depression of the melting point on admixture with the same derivative of the *trans*-monoacid (IA) methyl ester, described above.

An oil (30 mg.), eluted with benzene-ether contained the starting keto-ester (XXA), characterized as 2,4-dinitrophenylhydrazone, m.p. 160–161° (after chromatography on alumina and recrystallization from ethyl acetate–ethanol).

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[CONTRIBUTION NO. 27 FROM THE OLYMPIC RESEARCH DIVISION, RAYONIER, INC.]

Biogenesis of Heartwood and Bark Constituents. I. A New Taxifolin Glucoside[1]

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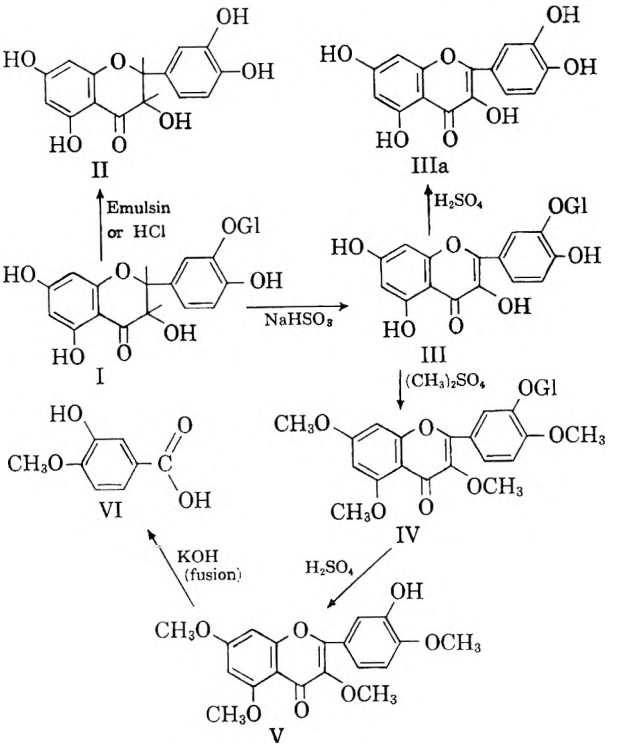
Douglas-fir needles (leaves), cambium, and sapwood have been found to contain two new glucosides, the 3′-β-glucoside of taxifolin (3,3′,4,5,7-pentahydroxyflavanone) and the 3′-β-glucoside of quercetin (3,3′,4′,5,7-pentahydroxyflavone). Taxifolin glucoside has also been found in the wood or bark of true cedar, larch, and spruce. It is suggested that taxifolin is synthesized in the leaves where it is present as the glucoside, and is then transported to the heartwood and outer bark where it is found as the aglycone.

The chemical nature and biosynthesis of heartwood and bark extractives have been the subject of much recent interest. In the case of heartwood flavonoids, Erdtman[2] has suggested that they are formed in the cambium and transported to the heartwood *via* the rays in the sapwood, while the outer bark flavonoids are synthesized in the cork cambium. Hillis[3], on the other hand, has suggested that leucoanthocyanins are synthesized in the leaves or needles and are then transported to the heartwood where they are converted to the corresponding flavones or flavanones. During the course of work on cambial constituents of various conifers, we have found a new flavonoid glucoside. The structure was determined, and from a study of the distribution of this compound in the tree, an alternate hypothesis of flavonoid biogenesis is suggested.

Determination of structure. Column chromatography of a water-soluble extract of Douglas-fir sapwood or cambium gave a white, amorphous fraction (I) which, when hydrolyzed enzymatically or with dilute acid, gave approximately one mole of glucose and one mole of (+)-taxifolin (II), a compound previously found in Douglas-fir heartwood[4,5] and outer bark.[6,7] Paper chromatography of the fraction showed it to be homogeneous, but all efforts to obtain the compound in a crystalline form were unsuccessful. Neutral and alkaline ultraviolet curves[8] were identical with those of taxifolin (II) (Fig. 1). The 7 phenolic hydroxyl group therefore was not substituted, since work on a large series of flavanones demonstrated that



glycosidation of the 7 phenolic hydroxyl in 5,7-dihydroxy flavanones causes a bathochromic shift in alkaline solution to 350 mμ.[9] Since a bathochromic shift to 314 mμ, identical with taxifolin, was observed in aluminum chloride solution, the 5 hydroxyl group was also unsubstituted. The compound gave a rose coloration with aqueous ferric chloride solution. This indicated that either the 3′ or 4′ hydroxyl group was substituted since taxifolin (II), which contains a free catechol grouping, gives a greenish black coloration with ferric chloride reagent.

Treatment with boiling sodium bisulfite[10] converted I to the corresponding quercetin glucoside (III). In contrast to I, III was readily obtainable in crystalline form. Comparison of the infrared spectrum of III (Fig. 2) with that of quercimeritrin

(1) Presented at the 132nd meeting of the American Chemical Society, Division of Cellulose Chemistry, New York, N. Y., September 9, 1957.

(2) H. Erdtman in A. Todd, *Perspectives in Organic Chemistry*, Interscience, New York (1956), pp. 453–494; Erdtman, *Proc. Royal Dublin Soc.*, **27**, 129 (1956).

(3) W. E. Hillis, *Australian J. Biol. Sci.*, **9**, 263 (1956).

(4) J. Pew, *J. Am. Chem. Soc.*, **70**, 3031 (1948).

(5) H. M. Graham and E. F. Kurth, *Ind. Eng. Chem.*, **41**, 409 (1949).

(6) J. K. Hubbard and E. F. Kurth, *J. Am. Leather Chem. Assoc.*, **44**, 604 (1949).

(7) H. L. Hergert and E. F. Kurth, *Tappi*, **35**, 59 (1952).

(8) L. F. Maranville and O. Goldschmid, *Anal. Chem.*, **26**, 1423 (1954).

(9) O. Goldschmid, H. L. Hergert, and L. F. Maranville, unpublished work.

(10) E. F. Kurth, *Ind. Eng. Chem.*, **45**, 2096 (1953).

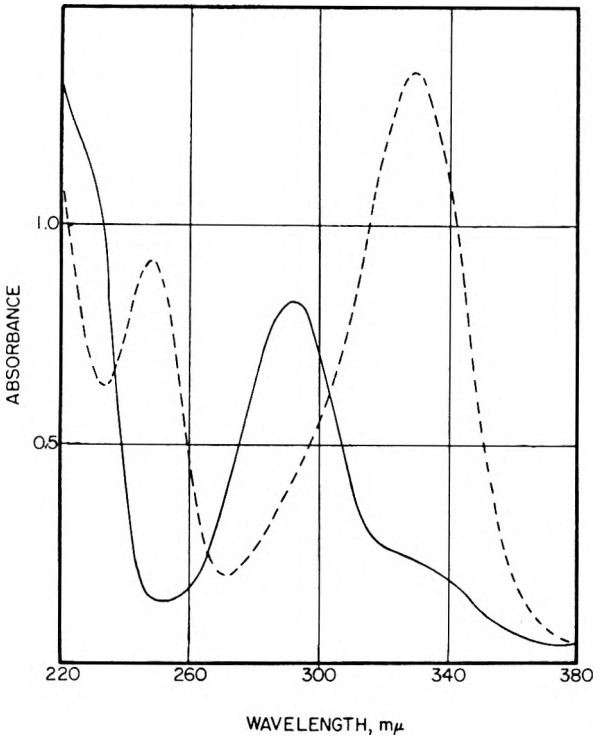


Fig. 1. Ultraviolet spectra of taxifolin-3′-glucoside, 5.68 × 10^{-5} M, in ethanol (——), in 0.006N KOH in ethanol (– – –)

(quercetin-7-glucoside) and isoquercitrin (quercetin-3-glucoside) showed non-identity. Comparison of the properties of III with those reported for spiraeoside[11] demonstrated that III was not quercetin-4′-glucoside. Comparison of the neutral, alkaline, alkaline-borate[12] and aluminum chloride[13] ultraviolet curves of III (Fig. 3) showed slight deviations from those of quercetin (IIIa) but were nearly identical with those of kaempferol (3,4′,5,7-tetrahydroxyflavone). This indicated that III does not have a free phenolic hydroxyl group in the 3′ position, and III was therefore indicated to be quercetin-3′-glucoside.

Methylation of III and subsequent hydrolysis gave a crystalline quercetin tetramethyl ether (V), the properties of which corresponded to those reported for synthetic quercetin-3,4′,5,7-tetramethyl ether[14,15]. Comparison of the neutral and alkaline

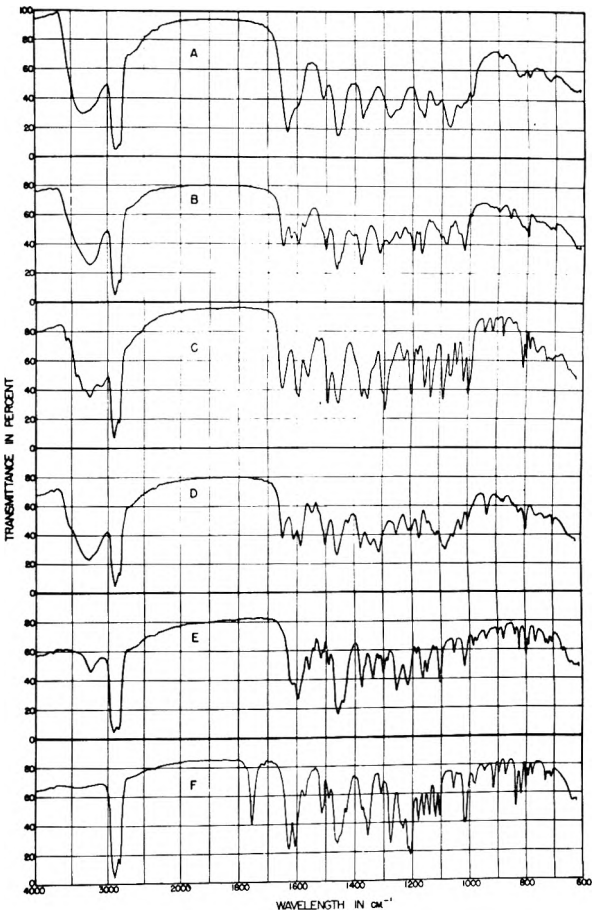


Fig. 2. Infrared spectra (paraffin mulls) of A. Taxifolin-3′-glucoside, B. quercetin-3′-glucoside, C. quercetin-3-glucoside, D. quercetin-7-glucoside, E. 3,4′,5,7-tetra-*O*-methyl quercetin, and F. 3,4′,5,7-tetra-*O*-methyl quercetin acetate

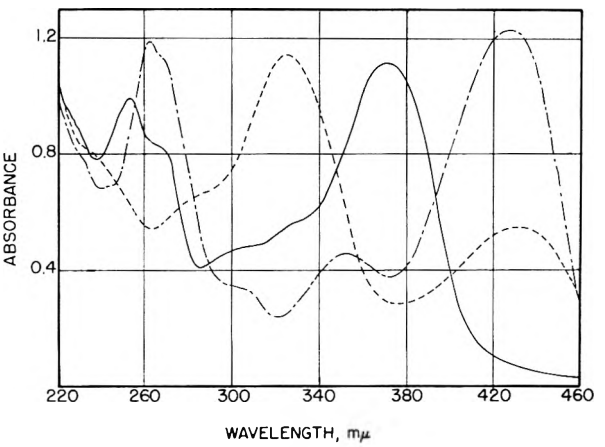


Fig. 3. Ultraviolet spectra of quercetin-3′-glucoside, 5.12 × 10^{-5} M, in ethanol (———), in 0.002M sodium ethoxide (– – – –), in 0.04M aluminum chloride in ethanol (— – —)

ultraviolet spectra of V with those of a series of partially methylated flavones[16] indicated that the free phenolic hydroxyl group was in the 3′ position. In order to confirm further the structure of V, the

(11) E. Steinegger and P. Casparis, *Pharm. Acta Helv.*, **20**, 154, 174 (1945). P. Casparis (*Pharm. Acta Helv.*, **21**, 341 (1946)) subsequently indicated that spiraeoside was either the 3′- or 4′-glucoside of quercetin. Comparison of the properties of their hydrolyzed quercetin tetramethyl ether with those reported for 4′-hydroxy-3′,3,5,7-tetramethoxyflavone [L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 864 (1950)] indicates that spiraeoside must be quercetin-4′-glucoside.

(12) T. Swain, *Chem. & Ind. (London)*, 1480 (1954).

(13) J. B. Harborne, *Chem. & Ind. (London)*, 1142 (1954).

(14) F. E. King, T. J. King, and K. Sellars, *J. Chem. Soc.*, 92 (1952).

(15) N. Narasimhachari, S. Narayanaswami, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **37A**, 104 (1953).

(16) C. G. Nordström and T. Swain, *J. Chem. Soc.*, 2764 (1953).

acetate derivative of V was submitted to an alkaline hydrolysis and isovanillic acid was identified as a degradation product. These experiments showed that III was quercetin-3′-glucoside and that I was taxifolin-3′,β,D-glucoside.

Two-dimensional paper chromatography of the sapwood and cambial extracts of Douglas-fir showed that in addition to I, a flavone glucoside was present. Comparison of R_f values indicated it to be identical with synthetic quercetin-3′-glucoside (III). As far as may be ascertained, neither flavanone or flavone glucosides have been previously reported as conifer wood constituents. Flavonoid glucosides have been reported from conifer leaves, however. Quercitrin (quercetin-3-rhamnoside) has been obtained from sawara cypress,[17] and quercimeritrin was found in cryptomeria.[18] A taxifolin glucoside of undetermined composition has been reported to be present in hinoki cypress leaves[19] and the wood[20] of a Japanese plum.

Distribution of taxifolin-3′-glucoside. Two-dimensional chromatograms were made of extracts from various parts of a Douglas-fir tree. Results are shown in Table I. The presence of taxifolin-3′-glucoside and quercetin-3′-glucoside and the absence of flavanone or flavone aglycones in the needles, inner bark, cambium, and sapwood suggest that quercetin and taxifolin are synthesized and glycosylated in the needles (leaves) and are then transported down the inner bark. They are then transported transversely *via* the rays to the heartwood and outer bark, the sugar being removed at or near the sapwood-heartwood and inner-outer bark boundaries to form the aglucone.

In order to test the applicability of this hypothesis to other coniferous genera, extracts were made of sapwood, heartwood, and/or bark of various representative species. Chromatographic results are shown in Table II.

TABLE I

DISTRIBUTION OF FLAVONOIDS IN DOUGLAS-FIR

Source	Compound			
	Taxifolin-3′-glucoside	Taxifolin	Quercetin-3′-glucoside	Quercetin
Needles[a]	+	−	Tr	−
Branches[a]	+	−	Tr	−
Inner bark	Tr	−	Tr	−
Cambium	+	−	Tr	−
Sapwood[b]	+	−	Tr	−
Sapwood[c]	+	Tr	Tr	−
Heartwood	−	+	−	Tr
Outer bark	Tr	+	−	Tr
R_f in 2% acetic acid	.47	.29	.01	.00
R_f in BuOH-HAc-H_2O (4:1:5)	.54	.81	.38	.71

[a] Additional flavonol glycosides also present. [b] Adjacent to cambium. [c] Adjacent to heartwood. + = compound present, Tr = trace, − = absent.

TABLE II

DISTRIBUTION OF TAXIFOLIN AND TAXIFOLIN-3′-GLUCOSIDE AMONG CONIFERS

Species	Part of Tree	Compound	
		Taxifolin-3′-glucoside	Taxifolin
Atlas cedar	Sapwood	+	−
	Heartwood	−	+
	Bark	Tr	+
Western larch	Needles[a]	+	−
	Bark	Tr	+
	Sapwood[b]	+	−
	Heartwood[b]	−	+
Sitka spruce	Needles[a]	+	−
	Inner bark	+	−
	Outer bark	Tr	+
	Sapwood	+	−
	Heartwood	−	+
Western red cedar	Outer bark	Tr	+
Bald cypress	Outer bark	−	−
Western hemlock	Needles[a]	Tr	−
	Bark	−	−
	Cambium	−	−
	Sapwood	−	−
	Heartwood	−	−
Pacific silver fir	Needles[a]	Tr	−
	Bark	−	−
	Sapwood	−	−
	Heartwood	−	−

[a] Additional flavonol glycosides also present. [b] Aromadendrin present.

All coniferous species thus far examined, when found to contain taxifolin in the heartwood or outer bark, have also been found to contain taxifolin glucoside. Hemlock and true fir, which do not appear to contain taxifolin in the wood or bark, have only trace amounts of taxifolin glucoside in the needles. It is recognized that in order to establish definitely the biogenetic origin of the heartwood flavonoids, the radioactive tracer technique will have to be used, but determination of the nature of the flavonoid constituents in different species appears to be a necessary preliminary to such work.

The present paper is concerned only with those species which have relatively simple flavonoid systems. Taxifolin glucoside has also been found in the pine genus, which contains a considerably more complex system. This will be discussed in a subsequent paper.[21] Preliminary work on the needle extracts of Douglas-fir and western hemlock in-

(17) M. Hasegawa, H. Nakamura, and S. Tsurumo, *J. Jap. Forestry Soc.*, **37**, 488 (1955).

(18) T. Kondo and H. Ito, *J. Agr. Chem. Soc., Japan*, **28**, 290 (1954); T. Kondo and H. Furuzawa, *J. Jap. Forestry Soc.*, **36**, 190 (1954).

(19) T. Kariyone and Y. Fukui, *J. Pharm. Soc., Japan*, **76**, 343 (1956).

(20) M. Hasegawa, *J. Jap. Forestry Soc.*, **38**, 107 (1956).

(21) H. L. Hergert, Paper II of this series.

dicates the presence of other flavonol glycosides which, on the basis of chromatography and hydrolysis products, have not been previously described in the literature.

EXPERIMENTAL[22]

Preparation of extractives. Cambial material was carefully scraped in September, 1955, and June, 1956, from approximately 40-year old Douglas-fir [*Pseudotsuga menziesii* (Mirb.) Franco] trees, growing in the vicinity of Shelton, Wash. The cambial material was immediately placed in methanol and the methanol extract worked up within a day of collection. An individual 60-year old Douglas-fir tree was felled and samples of the heartwood, sapwood adjacent to the heartwood and to the cambium, inner bark, outer bark, one-year old branches, and needles were procured. A large sample of sapwood was prepared by peeling six- to ten-year old branches of several trees. Needles were collected from trees of varying age at monthly intervals during late spring and summer. As soon as each wood or bark sample was procured, it was ground in a Wiley mill to pass a 20-mesh sieve. It was then exhaustively extracted with methanol at 25°. The methanol extracts were concentrated to 10–20% solids content and retained for chromatography or further separation.

Wood, bark, and/or needle samples were procured and extracted from the following coniferous species: Sitka spruce [*Picea sitchensis* (Bong.) Corr], 8, 150, and 450 years, Mason County, Wash.; western hemlock [*Tsuga heterophylla* (Raf.) Sarg.], 75 to 150 years, Mason County, Wash.; western red cedar (*Thuja plicata* Donn), 125 years, near Hoquiam, Wash.; western larch (*Larix occidentalis* Nutt.), branch 12 years of age, Seattle, Wash.; Pacific silver fir [*Abies amabilis* (Dougl.) Forbes], 50 to 75 years, north Vancouver Island, B. C.; grand fir [*Abies grandis* (Dougl.) Lindl.], 125 years, Mason County, Wash.; Atlas cedar (*Cedrus atlantica*, probably var. *glauca* Carriere), 40 years, Shelton, Wash.; and bald cypress (*Taxodium distichum*), 75 to 200 years, southeastern Ga.

Chromatography. The total methanol extract (or in the case of samples which contained tannin, the methyl ethyl ketone-soluble fraction obtained by liquid-liquid extraction of the water-soluble portion of the original methanol extract) was chromatographed two-dimensionally[23] on prewashed Whatman No. 1 paper with the organic phase of butanol–acetic acid–water (4:1:5) and 2% acetic acid by the descending method. Chromatograms were dried, examined under ultraviolet light before and after fuming with ammonia, and then sprayed with 1% ferric chloride–potassium ferricyanide,[24] diazotized sulfanilic acid,[25] bis-diazotized dianisidine,[26] and cinnamaldehyde-HCl.[21]

Taxifolin-3′-glucoside (I). Douglas-fir sapwood (1.0 kg., o.d. basis) was suspended in 20 l. of acetone-methanol (1:5) for 24 hr. at 25° in a covered stainless steel can. The extract was drained, filtered, and evaporated to 100 cc. at 20° in a natural circulation, borosilicate glass evaporator. The recovered solvent was used to make two additional extractions of the wood. The combined extracts were evaporated to a small volume, the methanol replaced with water, and the aqueous extract thoroughly liquid-liquid extracted with ether. The ether extract, consisting of waxes, fats, etc., was discarded. The aqueous extract was treated with one gram of decolorizing carbon, filtered, evaporated *in vacuo* to 25 cc., and applied to a Gryksbo (rolled filter paper) chromatographic column[27] which had been prewashed with distilled water. The column was then eluted with distilled water and 20-cc. fractions were collected. After 2875 cc. of eluent had been collected, 630 cc. of taxifolin-3′-glucoside solution, readily detected by a rose coloration with 1% ferric chloride reagent, was obtained. This fraction was evaporated *in vacuo* and then freeze-dried to yield a white powder, m.p. 203–205°, $[\alpha]_D^{25}$ −23° (water, c. 0.3). Yield, 375 mg., 0.04% based on the oven-dry weight of sapwood. The product was very soluble in water, soluble in methanol and ethanol, insoluble in dry acetone, ethyl acetate, and ether. Attempts to crystallize taxifolin-3′-glucoside from a variety of solvents were unsuccessful.

Anal. Calcd. for $C_{21}H_{22}O_{12}\cdot 2H_2O$: C, 50.20; H, 5.22. Found: C, 49.53; H, 5.57.

The ethanolic solution of the product gave a cerise coloration upon treatment with powdered zinc and hydrochloric acid.[4] The neutral and alkaline ultraviolet spectra are presented in Fig. 1 and the infrared spectrum in Fig. 2A.

Taxifolin-3′-glucoside (75 mg.) in 20 cc. water was mixed with 5 cc. of 5% emulsin (β-glucosidase) solution and allowed to stand 48 hr. at 25°. The aqueous solution was then thoroughly extracted with ether. The ether extract was evaporated to dryness, taken up in 5 cc. hot water, filtered, and allowed to crystallize. White crystals, m.p. 240–241°, undepressed mixed melting point with *d*-taxifolin from Douglas-fir heartwood, 240–242°, were obtained. The infrared spectrum was identical with authentic *d*-taxifolin.[28]

Taxifolin-3′-glucoside [0.0283 mmole (13.7 mg.)], was dissolved in 10 ml. of 1*N* sulfuric acid and refluxed for 4 hr. The cooled solution was exhaustively extracted with ether to give 0.024 mmole (7.36 mg.) taxifolin. The ether-extracted aqueous fraction was neutralized with barium carbonate, filtered, and shaken with IR 120 (Rohm & Haas Co.) resin to remove barium ions. The solution was concentrated and the sugar content determined by a paper chromatographic method similar to that of McCready and McComb.[29] The yield was 0.024 mmole (4.36 mg.) glucose.

Quercetin-3′-glucoside (III). Taxifolin-3′-glucoside (0.4 g.) was dissolved in 100 cc. of aqueous 15% sodium bisulfite solution. The mixture was refluxed for 3 hr., allowed to stand 1 hr., and filtered. The yellow precipitate was recrystallized once from hot water and twice from acetone-water (1:3) to give 0.3 g. of yellow needles, m.p. 216° (softens 196°).

Anal. Calcd. for $C_{21}H_{21}O_{12}\cdot 1.5H_2O$: C, 50.71; H, 4.66. Found: C, 51.03; H, 4.34.

Two-dimensional chromatography gave a single spot, yellow under ultraviolet light, purple-brown with bis-diazotized dianisidine. A spot of identical R_f and color reaction was observed on chromatograms of Douglas-fir cambial and sapwood extracts. Quercetin-3′-glucoside (0.1 g.) was hydrolyzed in 20 cc. of 5% sulfuric acid for 6 hr. Ether extraction of the aqueous hydrolysate and subsequent recrystallization from 30% ethanol gave 40 mg. of yellow crystals, m.p. 308–310°, mixed melting point with authentic quercetin undepressed.

Quercetin-3′-glucoside (250 mg.) and anhydrous potassium carbonate (4 g.) were suspended in 25 cc. dry acetone. The mixture was refluxed for 2.5 hr. during which time 2.5 cc.

(22) All melting points are corrected; microanalyses by Weiler and Strauss, Oxford, England; infrared spectra were obtained as Nujol mulls on a Perkin-Elmer Model 21 double-beam spectrophotometer; ultraviolet spectra were determined on a Cary Model 11 recording spectrophotometer.

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(24) G. M. Barton, R. S. Evans, and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

(25) M. T. Hanke and K. K. Koessler, *J. Biol. Chem.*, **50**, 235 (1922).

(26) R. Neu, *Z. Anal. Chem.*, **151**, 321 (1956).

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(28) H. L. Hergert and E. F. Kurth, *J. Org. Chem.*, **18**, 521 (1953).

(29) R. M. McCready and E. A. McComb, *Anal. Chem.*, **26**, 1645 (1954).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

Compound	λ_{max}, mμ, and (Log ε) 95% Ethanol			Alkaline[a]-EtOH			$AlCl_3$[b]-EtOH			NaOEt-H_3BO_3-EtOH[12]		
Taxifolin-3′-glucoside	227̄ (4.35)	292 (4.19)	329̄ (3.65)	249 (4.24)	329 (4.42)		224 (4.19)	314 (3.96)	377 (3.17)			
Taxifolin	229̄ (4.39)	291 (4.27)	326̄ (3.35)	246 (4.04)	329 (4.38)		224 (4.43)	314 (4.31)	380 (3.52)			
Isosakuranin	227 (4.40)	284 (4.20)	332 (3.46)	242 (4.16)	336 (3.96)	350 (4.13)	224 (4.50)	307 (4.26)	380 (3.52)			
Verecundin	224̄ (4.28)	286 (4.17)		254 (3.88)	331 (4.41)		No shift					
Quercetin-3′-glucoside	253 (4.29)	325 (4.03)	370 (4.34)	240̄ (4.19)	325 (4.35)	432 (4.03)	262 (4.36)	352 (3.95)	428 (4.38)	280 (4.12)	325 (4.26)	423 (4.25)
Kaempferol	268 (4.19)	324 (3.99)	368 (4.26)	246̄ (4.11)	325 (4.27)	430 (3.93)	270 (4.26)	350 (3.92)	428 (4.32)	280 (4.05)	325 (4.19)	419 (4.27)
Quercetin	256 (4.32)	301 (3.89)	373 (4.32)	247 (4.08)	334 (4.27)	420 (3.86)	268 (4.33)	360 (3.88)	431 (4.37)	276 (4.18)	330 (4.05)	410 (4.23)
3,4′,5,7-tetra-*O*-methyl quercetin	251 (4.32)	264̄	341 (4.28)	260 (4.36)	333 (4.10)	380 (3.98)						
4′,5,7-tri-*O*-methyl luteolin[16]	245	—	334	259	—	380						

[a] 0.006*N* KOH for flavanones, 0.002*N* NaOEt for flavones. [b] 0.04*M*. ~ Shoulder or inflection.

of dimethyl sulfate was added in 0.5 cc. portions. The acetone was evaporated at room temperature and the mixture dissolved in 50 cc. water. After standing 24 hr., a white precipitate was filtered off and recrystallized twice from 50% ethanol to yield, 150 mg. of methylated quercetin-3′-glucoside, m.p. 219–220° (sinters 145–150°). The white crystals gave no coloration with ferric chloride reagent and they were insoluble in 5% aqueous sodium hydroxide. This indicated that all phenolic groups had been methylated.

3,4′,5,7-tetra-O-methyl quercetin (V). Methylated quercetin-3′-glucoside (100 mg.) was dissolved in a mixture of 50 cc. 50% ethanol and 1 cc. concentrated sulfuric acid. After refluxing for 2 hr., the ethanol was removed by evaporation and the mixture set aside to crystallize. After two recrystallizations from 80% ethanol, cream colored needles of V, m.p. 224–225°, were obtained (lit., for V, 223–224°,[15] 220–222°,[14] while 3,3′,5,7-tetra-*O*-methyl quercetin has m.p., 200–201°,[30] 202–203°[11]). A yellow coloration was imparted to alkaline solution by the crystalline V.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.66; H, 5.07. Found: C, 64.17; H, 4.94.

The acetate derivative of V was prepared by dissolving V (20 mg.) in 2 cc. acetic anhydride and 0.3 cc. pyridine. After standing 24 hr., the mixture was poured into water and the insoluble precipitate recrystallized twice from methanol to yield 16 mg. of small white needles, m.p. 215–216°. The infrared spectrum (Fig. 2F) showed an acetoxy carbonyl absorption at 1760 cm.$^{-1}$ and a conjugated carbonyl band at 1625 cm.$^{-1}$, which is consistent with the structure, 3′-acetoxy-3,4′,5,7-tetramethoxyflavone.[31]

Degradation of acetate of V. The acetate of V (10 mg.) was dissolved in a mixture of 4.5 cc. ethanol, 1.5 cc. water, and 20 mg. sodium hydroxide. This was heated with shaking for 2 hr. at 175° in a semimicro stainless steel bomb fitted with a Teflon gasket. The degradation mixture was acidified, the ethanol removed by evaporation and the resultant aqueous mixture extracted with ether. Chromatography of the ether extract with butanol saturated with 2% ammonium hydroxide[32] by the descending method gave two spots: R_f 0.06, isovanillic acid, red when sprayed with bis-diazotized benzidine (vanillic acid has R_f 0.09, gives brown color with this spray); R_f 0.90, α,2,4-trimethoxy, 6-hydroxy acetophenone, light brown when sprayed with 2,4-dinitrophenylhydrazine, and yellow with diazotized sulfanilic acid (identical with the same product derived through a similar degradation of penta-*O*-methylquercetin). Repetition of the degradation with less alkali and for only 30 min. gave an additional chromatographic spot, R_f 0.81, isovanillin, tan with bis-diazotized benzidine, and orange-brown with 2,4-dinitrophenylhydrazine spray (vanillin has R_f 0.46 and slightly different colors with the same spray).

The ether extract from the degradation was evaporated to dryness and taken up in 5 cc. of warm water. The acetophenone derivative was relatively insoluble in water and could be filtered out. Upon cooling the filtrate, 1.5 mg. of white crystals were obtained, m.p. 248° (after recrystallization), mixed melting point with authentic isovanillic acid, 248–249°.

Chromatography of needle extract. Two-dimensional chromatograms of the methyl ethyl ketone–water soluble fraction from Douglas-fir needles showed a spot corresponding to (+)-catechin (R_f in butanol–acetic acid and 2% acetic acid, respectively) at 0.56–0.44, orange-brown with cinnamaldehyde–hydrochloric acid spray; flavonol glucoside spots (yellow when fumed with ammonia under ultraviolet light) at 0.31–0.10, 0.44–0.16, 0.58–0.20, 0.24–0.25, 0.30–0.39, 0.41–0.39, and 0.68–0.12; and the taxifolin-3′ glucoside spot at 0.54–0.47. The first three of the flavonol glucoside spots, spots for additional different flavonol glycosides, and spots of catechin, gallocatechin, and taxifolin-3′-glucoside have also been identified on chromatograms of western hemlock and larch needle extracts.

Absorption spectra. The absorption spectra of compounds prepared during the course of this study are recorded in Table III. We wish to thank Dr. Simon Wender for a gift of isoquercitrin, Dr. T. Kondo for quercimeritrin, and Dr. M. Hasegawa for verecundin and isosakuranin.

SHELTON, WASH.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Studies on the Chemistry of Aspenwood. II.[1] Lignans from Aspen Spent Sulfite Liquor.[2,3]

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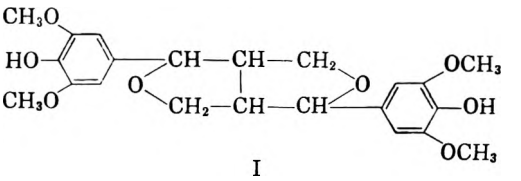
Three isomeric lignans having the structure, tetrahydro-1,4-bis(4-hydroxy-3,5-dimethoxyphenyl)furo[3,4-c]furan have been isolated from the spent sulfite liquor of aspenwood by means of chromatography and countercurrent distribution. Infrared absorption spectra indicate that two of these stereoisomers are forms of syringaresinol and lirioresinol, respectively.

In a recent paper[1] the ether extraction of a commercial spent sulfite liquor from the pulping of mixed aspens (*Populus tremuloides*, *P. grandidentata*, and *P. tacamahaca*) was described. This earlier paper included the fractionation of the ether extractives into bisulfite-, bicarbonate-, and alkali-soluble fractions and the isolation of *p*-hydroxybenzoic acid from the bicarbonate-soluble fraction. The present paper reports the fractionation of the alkali-soluble fraction and the isolation of several related crystalline lignans.

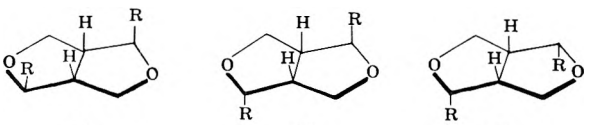
Paper chromatography of the alkali-soluble fraction[1] indicated *p*-hydroxybenzoic acid and materials with R_f values of 0.69 and 0.82 in butanol saturated with 2% aqueous ammonia. A 50:1 benzene-ethanol solution of this fraction was chromatographed on a column of acid-washed Magnesol[4] and developed with the same solvent as a flowing chromatogram. Fractions in the effluent were monitored by paper chromatography, and the fraction containing the largest amount of material was evaporated to dryness. The residue, now free of *p*-hydroxybenzoic acid, was submitted to countercurrent distribution in the Craig machine between both phases of a mixture of butanol and 2% aqueous ammonia at 20°. The tubes containing only the compound with R_f 0.69 were combined to yield a crystalline product (A) melting at 180–181° whose analysis and that of its acetate and ultraviolet and infrared absorption spectra matched those for lirioresinol (B), a lignan having the structure, 1*H*,3*H*-tetrahydro-1,4-bis(4-hydroxy-3,5-dimethoxyphenyl)furo[3,4-*c*]furan (I) recently isolated from the inner bark of *Liriodendron tulipifera*.[5]



I

In another experiment, the ether extract of the same commercial aspen spent sulfite liquor was fractionated in an acid system to yield chloroform-insoluble crystals (C) melting at 235–236° and chloroform-soluble crystals (D) melting at 169–172°. The analysis, infrared spectrum, and positive Mäule reaction indicated that (C) was probably a lignan with the tetrahydrofurofuran structure I, and that (D) as syringaresinol (E) a product having the structure I and obtained by an enzymatic synthesis from syringin.[6]

The probability that tetrahydrofurofuran structure I exists only in its *cis*-form has been discussed earlier.[5] Furthermore, it has been shown that three *d*,*l*-pairs of the *cis*-form of I are possible (II, III, and IV). Lirioresinol (B) and syringaresinol (E)



II III IV

Fig. 1. Possible Stereoisomers

must possess two of these stereoisomeric forms, and products A and D must possess the same two stereoisomeric forms respectively. The infrared curves of compounds B and E with identical structures, but different spatial configurations, are similar for the most part, but the specific differences are marked enough for differentiation. The similarity of the infrared curve of compound C with the curves of both B and E together with the analytical data and similarity or chemical reactions indicate that compound C may have the third possible stereoisomeric form of the tetrahydrofurofuran I.

The differences in melting points recorded for compound A and lirioresinol[5] and for compound D and syringaresinol[6] are probably due to differences

(1) For paper I of this series, see I. A. Pearl and D. L. Beyer, *Tappi*, **40**, 45 (1957).

(2) Presented before the Division of Cellulose Chemistry at the 132nd meeting of the American Chemical Society, New York, New York, September 8–13, 1957.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) I. A. Pearl and E. E. Dickey, *J. Am. Chem. Soc.* **73**, 863 (1951).

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in ratios of optical antipodes present in the crystalline products. Larger scale studies on the optical properties of these lignans are in progress. In addition, studies on the extractives of aspen spent sulfite liquor and on the wood and bark extractives of authentic samples of *Populus tremuloides* and *P. grandidentata* are in progress in an attempt to determine the natural occurrence of these lignans in aspen.

EXPERIMENTAL[7]

Isolation of lirioresinol (compound A). An ether solution containing 2.0 g. of the alkali-soluble fraction from the preliminary fractionation of the ether extractives of a commercial aspen spent sulfite liquor[1] was filtered, and evaporated to dryness in a rotating evaporator at 20°. The residue was taken up in 50:1 benzene-ethanol and adsorbed on a column of acid-washed Magnesol[4] 35 mm. in diameter and 4 ft. in length. The column was developed as a flowing chromatogram with 50:1 benzene-ethanol. A total of 78 30-ml. samples were collected in the effluent. These were monitored by means of paper chromatography employing butanol–2% aqueous ammonia as the developer. At this point traces of materials not present in the original fraction[1] were indicated by the chromatograms. The fraction comprising samples 20–41 and containing 1.40 g. of solids was evaporated to dryness and taken up in a little butanol saturated with 2% aqueous ammonia. The sample was distributed between the two phases of a mixture of butanol and 2% aqueous ammonia at 20° in a 10 ml./10 ml. Craig countercurrent distribution machine. After 60 transfers the tubes were monitored by means of paper chromatography and tubes 12–30 contained only the product with butanol–2% aqueous ammonia R_f 0.69. The combined fraction was evaporated to dryness in a rotating evaporator (total yield, 0.51 g.), and the residue was covered with anhydrous ethanol and allowed to stand at 20° for 24 hr. The crystals were filtered and washed with cold ethanol to yield 0.4 g. compound A melting at 180–181°, giving a strong Mäule test, and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 213 mμ, ε 43850; $\lambda_{shoulder}$ 237 mμ, ε 14600; λ_{max} 273 mμ, ε 2870.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.46; H, 6.25.

Lirioresinol obtained from the inner bark of *Liriodendron tulipifera*[5] melted at 210–211°. The R_f values on paper at 20° for lirioresinol[5] and for compound A were identical in the following three solvent systems: butanol saturated with 2% aqueous ammonia, 10:3:3 butanol-pyridine-water, and benzene saturated with formic acid. Spots were located by means of the Mäule spray reagents.

Acetylation of compound A with acetic anhydride and pyridine and recrystallization from ethanol yielded colorless crystals of its diacetate melting at 188° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 210 mμ, ε 47600; λ_{max} 230 mμ, ε 15870; λ_{max} 272 mμ, ε 2310.

Anal. Calcd. for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.00; H, 6.04.

Isolation of compound C. A 30-g. sample of total ether extract of aspen spent sulfite liquor[1] was substantially freed from *p*-hydroxybenzoic acid by distribution between both phases of a 2:2:1 mixture of benzene, acetic acid, and water[8] at 20° in a 40 ml./40 ml. Craig countercurrent distribution machine. After 172 transfers, the contents of tubes 28–40 were combined to yield a crude fraction with the desired components. The operation was repeated four times until 150 g. of ether extractives had been processed to yield a crude fraction containing 15.9 g. of solids. This combined fraction was then distributed between both phases of a 4:1:5 mixture of toluene, acetic acid, and water[9] in the last noted Craig machine containing 100 tubes. The upper phase overflow from transfers 203 through 300 was concentrated as one sample to give 0.83 g. crystalline solids. The solid was suspended in chloroform at 20° and filtered. The chloroform-insoluble crystals melted at 234–237°. They were recrystallized from 1:1 chloroform-ethanol to yield 43.5 mg. small granular, Mäule-positive, colorless crystals melting at 235–236°. The purified product had R_f's of 0.58 and 0.85 at 20° in butanol–2% aqueous ammonia and 10:3:3 butanol-pyridine-water, respectively.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26; Mol. wt., 418. Found: C, 63.14; H, 6.28; Mol. wt., 418 (Rast, in camphor).

Isolation of syringaresinol (compound D). The chloroform filtrate above was evaporated to dryness, and the residue was recrystallized first from chloroform–petroleum ether (b.p. 65–110°) and then twice from 95% ethanol to yield 272 mg. of almost colorless crystals giving a positive Mäule reaction, melting at 168–172°, and having a rotation $[\alpha]_D^{28}$ 3.93° (*c* 3.9 in chloroform). The purified compound had R_f's of 0.60 and 0.85 at 20° in butanol–2% aqueous ammonia and 10:3:3 butanol-pyridine-water, respectively. These were identical with those of authentic syringaresinol.[6]

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26 Mol. wt., 418. Found: C, 63.18; H, 6.23; Mol. wt., 399 (Rast, in camphor).

Synthetic syringaresinol prepared according to Freudenberg and Dietrich[6] melted at 170–173°.

Spectra. Ultraviolet absorption spectra were determined in 95% ethanol with a Beckman model DU spectrophotometer. Concentrations were approximately 0.02 g. per liter. Infrared absorption spectra of Figure 2 were obtained with a Perkin-Elmer model 21 recording spectrophotometer using a sodium chloride prism and potassium bromide pellets prepared by hand grinding with sample before pressing.

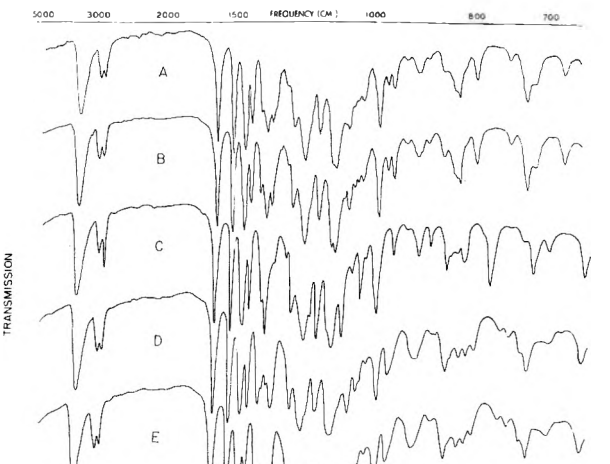

Fig. 2. Infrared absorption curves: A, lirioresinol from aspen spent liquor; B, lirioresinol from *Liriodendron tulipifera;* C, compound C; D, syringaresinol from aspen spent liquor; E, enzymatically synthesized syringaresinol

APPLETON, WIS.

(7) All melting points are uncorrected. Analyses were performed by the Analytical Department of The Institute of Paper Chemistry and by Huffman Microanalytical Laboratories, Wheatridge, Colorado. Infrared spectra were determined by Mr. Lowell Sell.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF MADRAS]

N-Mannich Bases of 3-Substituted Indoles and Alkylations with Some N-Indolylmethyltrimethylammonium Iodides[1,1a]

S. SWAMINATHAN, S. RANGANATHAN, AND S. SULOCHANA

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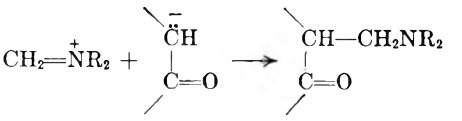
A few selected 3 and 2,3-substituted indoles have been subjected to the Mannich reaction to furnish *N*-Mannich bases. 1-Dimethylaminomethylskatole methiodide has been shown to have alkylating properties comparable with those of 1-methylgramine methiodide. On the other hand, 1-dimethylaminomethylskatole, 1-dimethylaminomethyl-3-cyanoindole, and the methiodide of the latter have been found to be inert as alkylating agents.

The observation that carbazole[2,3] and skatole[4] participate in the Mannich reaction to give *N*-Mannich bases prompted the investigation of the Mannich reaction of other 3 and 2,3-substituted indoles. In fact, though considerable work has been reported on the Mannich reaction of compounds containing acidic hydrogen on carbon, only a few examples of Mannich reaction with compounds containing acidic hydrogen on nitrogen are known. Among these compounds are succinimide and phthalimide,[2,3,5–7] benzimidazole,[8] benztriazole,[8] benzthiazole-2-thione,[9] 4-quinazolone,[10] pyrazole,[11] isatin,[3] 2,4-thiazolidinedione,[12] hydantoins,[12] uracil,[12] alkylnitramines,[12] and pyridazones,[13] all of which give *N*-dialkylaminomethyl bases when subjected to the Mannich reaction.

Indole and indoles substituted in positions other than 3 invariably give 3-dialkylaminomethylindoles. According to Lieberman and Wagner,[14] the Mannich reaction is the result of the addition of a methylene ammonium cation or a protonated dialkyaminomethanol to a carbanion:



The formation of 3-dialkylaminomethylindoles must therefore be due to the attack by one or other of the above cationic intermediates at the 3 carbon which, of course, has a negative charge in one of the resonance forms of indole. It seemed possible that with a substituent present at the 3 carbon the intermediate cation might attack the nitrogen atom itself which has a lone pair of electrons to give rise to an *N*-Mannich base and a few 3 and 2,3-substituted indoles were therefore subjected to the Mannich reaction.

Skatole which was recently reported[4] to give an excellent yield of *N*-dimethylaminomethylskatole (I) also furnished the piperidino and the morpholino bases, although in lower yields. With formaldehyde and dimethylamine under more drastic conditions than those employed for the preparation of *N*-Mannich bases of skatole, 3-ethylindole, 3-cyanoindole, 2,3-dimethylindole, and 2-methyl-3-ethylindole gave the corresponding *N*-dimethylaminomethyl bases in yields varying from 12 to 49%. With the same reactants 3-benzylindole, 2-methyl-3-benzylindole, and tetrahydrocarbazole did not furnish basic products; however neutral products were isolated which on the basis of their analytical values and infrared spectra are considered to be substituted bis-*N*-indolylmethanes.

In view of the ease of formation of C-Mannich bases from pyrrole[15] it was also of interest to see if 2,5-dimethylpyrrole would undergo the Mannich reaction. Indeed, under relatively mild conditions, it gave a 51% yield of 1-dimethylaminomethyl-2,5-dimethyl pyrrole.

C-Mannich bases of the type of gramine and their quaternary salts have been found[16] to be excellent alkylating agents and it was considered desirable to study alkylations using some of the above *N*-Mannich bases and their methiodides. 1-Di-

(1) From theses presented by S. Ranganathan and S. Sulochana to the University of Madras in partial fulfillment of the requirements for the M.Sc. degree.

(1a) While under publication, a similar study of the *N*-Mannich bases of 3-substituted indoles has been reported by J. Thesing and P. Binger, *Ber.*, 90, 1419 (1957).

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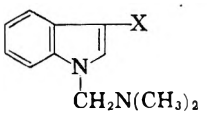
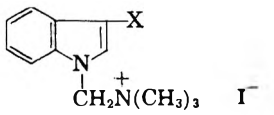
methylaminomethylskatole (I) and 1-dimethylaminomethyl-3-cyanoindole (III) were selected for this purpose so that the effect of such oppositely polar substituents as methyl and cyano on the ease of alkylation may be ascertained.



I, X = CH_3
III, X = CN



II, X = CH_3
IV, X = CN

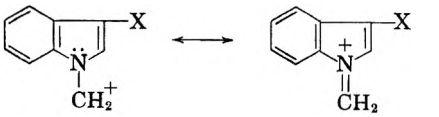
The base I and its methiodide (II) furthermore, as pointed out in an earlier publication,[4] bear a close structural resemblance to 1-methylgramine and its methiodide respectively and it was of interest to compare their reactivities as alkylating agents.

Alkylations of sodium cyanide and ethyl acetamidocyanoacetate with II have been reported.[4] Whereas the reaction of II with sodium cyanide was found to give 1-skatylacetamide and 1-skatylacetic acid in addition to some skatole, the reaction of sodium cyanide with the free base (I) itself gave only skatole and none of the other products. The base (I) was, in fact, found to reverse to skatole by merely heating with water, differing in this respect from gramine and 1-methylgramine. This reversal to skatole was more pronounced in the presence of alkali. With a view to isolating 1-skatylacetonitrile, if formed, the base (I) was treated with a mixture of sodium cyanide and acetic acid, conditions under which 7-azagramine has been converted[17] to the corresponding nitrile. Only skatole was obtained again and no nitrile.

Like 1-methylgraminemethiodide,[18] the methiodide (II) reacted readily with the sodio derivative of diethylmalonate to give the expected alkylated ester which was hydrolyzed to give a 36% yield of β-(1-skatyl)-α-carboxypropionic acid. The latter was decarboxylated in 74% yield to β-(1-skatyl)-propionic acid. The same alkylation when done with the free base (I) did not give the expected product; the product isolated after treatment with alkali was skatole formed by hydrolysis of I. The methiodide (II) resembled[19] 1-methylgramine methiodide also in its reaction with phenylmagnesium bromide whereby 1-benzylskatole was obtained in 63% yield. The same parallelism in alkylating properties between the two sets of compounds was noted with some amine exchange reactions[20] that were run. The methiodide (II) underwent amine exchange readily with piperidine and morpholine to give 1-piperidinomethylskatole and 1-morpholinomethylskatole, respectively. The free base (I) did not undergo any exchange when refluxed with piperidine.

As regards III and its methiodide (IV), both of them proved extremely unreactive as alkylating agents. The base (III) reacted sluggishly toward methyl iodide and IV was obtained only after prolonged treatment. When IV was treated with sodium cyanide either the starting methiodide or 3-cyanoindole was obtained depending upon the conditions of the reaction but no alkylation product. The inertness of IV was further emphasized by failure to effect any reaction between it and the sodio derivative of ethyl acetamidocyanoacetate, both in refluxing ethanol and in refluxing *n*-butyl ether. As in the case of I, III was found to reverse to the parent 3-cyanoindole when refluxed with alkali. Similar treatment of IV furnished after acidification 3-carboxy-1-dimethylaminomethylindole methiodide. In connection with the attempted alkylation of ethyl acetamidocyanoacetate with IV it was also of interest to condense a Mannich base of ethyl acetamidomalonate with 3-cyanoindole under conditions worked out by Butenandt *et al.*[21] for a similar condensation with indole. When ethyl α-piperidinomethyl-α-acetamidomalonate was allowed to react with 3-cyanoindole, only unreacted 3-cyanoindole and 1-piperidinomethyl-3-cyanoindole were obtained and no condensation product.

Structurally, II and IV belong to the class of quaternary ammonium salts which cannot alkylate by a mechanism of elimination and addition;[16] if they alkylate at all, they must do so by a direct substitution mechanism as is the case with 1-methylgramine methiodide. The intermediate in such a mechanism is a carbonium ion of the type V which may be stabilized by resonance with the form VI.



Va, X = CH_3
b, X = CN

VIa, X = CH_3
b, X = CN

Its formation depends on the ease of scission of the bond linking the quaternary nitrogen to the adjacent methylene carbon in the parent quaternary salt. The difference in alkylating properties of II and IV may then be attributed to this scission which, as may be expected, will be favored when X is electron-releasing methyl group and retarded when X is the electron-withdrawing cyano group.

EXPERIMENTAL

1-Piperidinomethylskatole. Acetic acid (4.5 ml.), piperidine (2.6 ml., 0.026 mole), formalin (36%; 3 ml., 0.036 mole), and skatole (4 g., 0.030 mole) reacted together as described[4] in

(17) M. Robison and B. Robison, *J. Am. Chem. Soc.*, **78**, 1247 (1956).

(18) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 663 (1949).

(19) H. R. Snyder, E. L. Eliel, and R. E. Carnahan, *J. Am. Chem. Soc.*, **73**, 970 (1951).

(20) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 4233 (1948).

(21) A. Butenandt, H. Hellmann, and E. Renz, *Z. Physiol. Chem.*, **284**, 175 (1949).

the preparation of 1-dimethylaminomethylskatole. The reaction mixture was then made alkaline and extracted with ether. The base was then extracted from the ether solution with *N* hydrochloric acid and regenerated with alkali. Ether extraction furnished the crude base which was distilled *in vacuo;* b.p. 162°/2 mm.; yield 3.6 g. (51%). The picrate was crystallized from methanol; m.p. 162–165°.

Anal. Calcd. for $C_{21}H_{23}O_7N_5$: C, 55.1; H, 5.1. Found: C, 55.4; H, 5.3.

The base also furnished a methiodide which in spite of several crystallizations had m.p. 160–180° but which analyzed correctly.

Anal. Calcd. for $C_{16}H_{23}N_2I$: C, 51.8; H, 6.2. Found: C, 51.5; H, 6.3.

1-Morpholinomethylskatole obtained similarly was a viscous liquid; b.p. 160°/1 mm.; yield, 31%. It gave a picrate, m.p. 192–193°, after crystallization from methanol.

Anal. Calcd. for $C_{20}H_{21}O_8N_5$: C, 52.3; H, 4.6. Found: C, 52.7; H, 4.7.

1-Dimethylaminomethyl-3-ethylindole. To an ice cold aqueous solution of dimethylamine (17 ml., 16%, 0.060 mole) was added successively glacial acetic acid (11.5 ml.) and formalin (5.5 ml., 36%, 0.066 mole) at such a rate that the temperature did not rise above 0°. The solution was then mixed with 3-ethylindole[19,22,23] (8.4 g., 0.058 mole) and stirred for 4 hr. at room temperature when an additional amount of acetic acid (10 ml.) was added. The mixture was then heated for 4 hr. on a water bath, cooled, made alkaline, and extracted with ether. The ether solution was extracted with an excess of *N* hydrochloric acid, the acid extract made alkaline with 20% sodium hydroxide solution and extracted with ether. The ether extract was dried, the ether was removed and the residual liquid was distilled *in vacuo;* b.p. 132–136°/1.5 mm., yield 2 g. (18%). The base furnished a yellow picrate which was crystallized from methanol; m.p. 204–205°.

Anal. Calcd. for $C_{19}H_{21}O_7N_5$: C, 52.9; H, 4.9. Found: C, 52.8; H, 5.0.

3-Cyanoindole. The following method of preparation proved superior to those previously reported.[24,25] A solution of indole-3-aldoxime (18 g.) in 98% formic acid (100 ml.) was heated on a water bath for 1.5 hr., poured into iced water (600 ml.) and the product filtered and dried; m.p. 170–172°; yield, 10.3 g. (64%).

1-Dimethylaminomethyl-3-cyanoindole (III). To an ice cold aqueous solution of dimethylamine (20 ml., 27%, 0.12 mole) was added successively acetic acid (17 ml.) and formalin (10 ml., 36%, 0.12 mole) maintaining the temperature below 5°. 3-Cyanoindole (10.7 g., 0.075 mole) was then added and the mixture heated on a water bath with stirring in an atmosphere of nitrogen for 8 hr. The mixture was made alkaline with 20% sodium hydroxide solution, cooled, and filtered. The solid thus obtained was dissolved in ether and the solution filtered from some undissolved matter and extracted twice with excess *N* hydrochloric acid. The combined acid extracts when made alkaline furnished the base; m.p. 85–87°; yield, 7.2 g. (49%). After a crystallization from petroleum ether (60–80°) the product had m.p. 88–90°.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.4; H, 6.6. Found: C, 72.8; H, 6.6.

The infrared spectrum of the base in chloroform showed strong absorption at 4.5μ (CN) but no absorption around 3μ (NH).

1-Dimethylaminomethyl-3-cyanoindole methiodide (IV). A solution of methyl iodide (13.6 g., 0.096 mole) in dry ether (50 ml.) was added in one portion to a solution of III (5.6 g., 0.028 mole) in dry ether (100 ml.) cooled in ice. The methiodide crystallized out slowly on leaving aside for a few days at room temperature; m.p. 190–192°, yield 5.6 g. (59%). In some runs the product that separated was found to be a mixture of the free base and the methiodide requiring further treatment with methyl iodide. Also addition of some ethanol appeared to hasten the formation of the methiodide. The analytical sample obtained by recrystallization from hot water had m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{16}N_3I$: C, 45.8; H, 4.7. Found: C, 45.7; H, 4.9.

1-Dimethylaminomethyl-2,3-dimethylindole. To an ice cold solution of dimethylamine hydrochloride (2.5 g., 0.03 mole) in sodium hydroxide solution (12 ml., 10%, 0.03 mole) was added glacial acetic acid (4.5 ml.) and formalin (3 ml., 36%, 0.036 mole) as usual and the solution was then mixed with 2,3-dimethylindole[26] (4.35 g., 0.03 mole). The mixture was stirred for 4 hr. at room temperature and then on a water bath for 4 hr. On working up the reaction mixture as described for the preparation of 1-dimethylaminomethyl-3-ethylindole, crude base (*ca.* 2 g.) was obtained which was distilled *in vacuo;* b.p. 154–156°/4 mm. The distillate solidified when cooled and was crystallized from petroleum ether (60–80°); m.p. 82°; yield 0.7 g. (12%).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0. Found: C, 76.7; H, 8.7.

1-Dimethylaminomethyl-2-methyl-3-ethylindole. Employing a solution of dimethylamine hydrochloride (1.7 g., 0.02 mole) in 10% sodium hydroxide solution (8 ml., 0.02 mole), glacial acetic acid (4 ml.), 36% formalin (2 ml., 0.024 mole), and 2-methyl-3-ethylindole[26] (3.2 g., 0.02 mole) and carrying out the reaction as described above, the base (1.2 g., 28%) was obtained; b.p. 154–158°/2 mm. The picrate was crystallized from ethanol; m.p. 186–187°.

Anal. Calcd. for $C_{20}H_{23}O_7N_5$: C, 53.9; H, 5.2; Found: C, 53.8, H, 5.5.

1-Dimethylaminomethyl-2,5-dimethylpyrrole. To dimethylamine hydrochloride (4.3 g., 0.053 mole) dissolved in water (3 ml.) was added successively 36% formalin (5 ml., 0.06 mole) and 2,5-dimethylpyrrole[27] (5 g., 0.053 mole). The mixture warmed up and was allowed to stand overnight. The homogeneous solution was poured into ice cold 20% sodium hydroxide solution (15 ml.) and extracted with ether. The ether extract after removal of solvent furnished a syrupy liquid which, when distilled *in vacuo* at 100°/2 mm., gave colorless crystalline product (4 g., 51%). A portion was crystallized from petroleum ether (60–80°); m.p. 93–96°.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.0; H, 10.6. Found: C, 70.7; H, 10.3.

3-Benzylindole. The preparation of this indole by the Fischer method is mentioned in a patent,[28] but details are not given. The following procedure proved satisfactory:

The crude phenylhydrazone obtained from phenylhydrazine (10.5 g., 0.097 mole) and hydrocinnamaldehyde (13 g., 0.097 mole) was mixed with anhydrous zinc chloride (1.5 g.) in a flask provided with a condenser and the mixture heated to and maintained at 240° for 0.5 hr. The mixture was cooled and extracted with petroleum ether (60–80°) repeatedly. The extracts when cooled furnished crude product which was recrystallized from the same solvent to give material (2.7 g.) m.p. 98–103°. This was mixed with the petroleum ether insoluble residue and the combined material crystallized from a mixture of benzene and petroleum ether (60–80°) to give product m.p. 107–109°; yield 7 g.

Reaction of 3-benzylindole with dimethylamine and formalin. The reaction was carried out as usual with a solution of dimethylamine hydrochloride (1.8 g., 0.022 mole), in 10% sodium hydroxide (10 ml., 0.025 mole), glacial acetic acid (15 ml.), 36% formalin (1.6 ml., 0.019 mole), and 3-benzylindole (4.15 g., 0.02 mole). On working up the reaction mixture as

(22) G. R. Clemo, *J. Chem. Soc.*, 1695 (1936).

(23) H. Schmid, A. Ebnother, and P. Karrer, *Helv. Chim. Acta*, **33**, 1486 (1950).

(24) R. Pschorr and G. Hoppe, *Ber.*, **43**, 2543 (1910).

(25) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1950).

(26) E. Fischer, *Ann.*, **236**, 126 (186).

(27) D. M. Young and C. F. H. Allen, *Org. Syntheses*, **Coll. Vol. II**, 219 (1943).

(28) German patent, **38,784**.

in previous experiments, the acid extract furnished little basic material. However the ether solution remaining after acid extraction furnished neutral material which was crystallized from a mixture of benzene and petroleum ether; m.p. 173–175°; yield 1.3 g. After two recrystallizations from benzene, the product had m.p. 174–175°.

Anal. Calcd. for $C_{31}H_{26}N_2$: C, 87.3; H, 6.1. Found: C, 87.2; H, 6.0.

The infrared spectrum of this product in chloroform did not show any absorption near 3μ, suggesting the absence of —NH-group. The product is considered to be bis(3-benzyl-1-indolyl)methane.

Reaction of 2-methyl-3-benzylindole with dimethylamine and formalin. Under the same conditions as in the previous experiment, 2-methyl-3-benzylindole[29] (5.5 g.) furnished neutral material (1.16 g., m.p. 162–166°) but no base. The analytical sample was prepared by crystallization from a mixture of benzene and alcohol; m.p. 167–168°.

Anal. Calcd. for $C_{33}H_{30}N_2$: C, 87.2; H, 6.7. Found: C, 86.7; H, 6.5.

The infrared spectrum ($CHCl_3$) showed no absorption near 3μ, suggesting the absence of —NH-group. The product is considered to be bis(3-benzyl-2-methyl-1-indolyl)methane.

Reaction of tetrahydrocarbazole with dimethylamine and formalin. Tetrahydrocarbazole[30] (6.9 g.), under the same conditions as before, gave neutral product (1.4 g.) m.p. 203–204° but no base. After two crystallizations from benzene, the compound had m.p. 205–207°.

Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.7; H, 7.4. Found: C, 84.5; H, 7.3.

The infrared spectrum ($CHCl_3$) indicated the absence of —NH-group. The product is considered to be 9,9′-bis(tetrahydrocarbazolyl)methane.

Reaction of 1-dimethylaminomethylskatole (I) with sodium cyanide. The base I (5 g., 0.027 mole) was refluxed with a solution of sodium cyanide (5 g., 0.102 mole) in water (50 ml.) for 6 hr. and cooled. The solid was collected and crystallized from petroleum ether (60–80°). Skatole (2.1 g.) melting point and mixed melting point with an authentic specimen 91–92.5° was obtained.

Skatole (2 g.) was again obtained when a mixture of I (2.9 g.) sodium cyanide (4.4 g.), acetic acid (6 ml.), and water (45 ml.) was refluxed for 4 hr.

Decomposition of 1-dimethylaminomethylskatole (I) *to skatole.* (*a*) In water: The base (0.5 g.) was refluxed with water (10 ml.) for 24 hr. The mixture was cooled when a semi-solid separated. Crystallization of the semi-solid from petroleum ether (60–80°) furnished skatole (150 mg.) m.p. 89–90° undepressed by authentic skatole.

(*b*) In 10% sodium hydroxide solution: When the base (1 g.) was refluxed with 10% sodium hydroxide solution (10 ml.) for 16 hr. and then cooled, skatole (0.6 g., m.p. 89–91°) was obtained.

β-(1-Skatyl)-α-carboxypropionic acid. To a stirred solution of sodium (0.46 g., 0.02 g. at.) in ethyl malonate (16 g., 0.1 mole) dissolved at 80–90° was added 1-dimethylaminomethylskatole methiodide (6.7 g., 0.02 mole). The temperature was raised to and maintained at 130–140° for 10 hr. with continued stirring. Trimethylamine evolved steadily during this period at the end of which the bath temperature was raised and kept at 140–150° for an additional 2 hr. The mixture was cooled and refluxed with a solution of potassium hydroxide (20 g., 0.36 mole) in 80% ethanol (200 ml.) for 4.5 hr. The mixture was diluted with water (70 ml.) and concentrated to remove excess alcohol. The residue was extracted with two 30-ml. portions of benzene and the aqueous layer acidified. After overnight cooling the crystalline material was collected and redissolved in saturated sodium bicarbonate solution. After treatment with animal charcoal, the bicarbonate solution was acidified and cooled when the product (1.8 g., 36%) crystallized; m.p. 119–120°. After two crystallizations from a mixture of ethyl acetate and petroleum ether (60–80°), the product had m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.2; H, 5.3. Found: C, 63.6; H, 5.5.

β-(1-Skatyl)propionic acid. A solution of the substituted malonic acid (0.9 g.) in pyridine (10 ml.) was refluxed for 20 min. The pyridine was removed *in vacuo*, the residue cooled and acidified with 20% hydrochloric acid (10 ml.). The semi-solid which separated, solidified when cooled and was purified by dissolution and reprecipitation from sodium bicarbonate solution. The crude acid (550 mg., 74%; m.p. 79–80°) was crystallized three times from petroleum ether (60–80°); m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.9; H, 6.5. Found: C, 70.7; H, 7.0.

Attempted alkylation of ethyl malonate with 1-dimethylaminomethylskatole. A mixture of 1-dimethylaminomethylskatole (3.8 g., 0.02 mole) and ethyl malonate (4 g., 0.025 mole) was heated at 150–160° for 3.5 hr. The reaction mixture was worked up as described under the preparation of β-(1-skatyl)-α-carboxy propionic acid. No alkylated product was isolated from the acidified layer; the benzene extract furnished skatole (0.9 g.) m.p. 89–90°.

1-Benzylskatole. A solution of phenylmagnesium bromide (0.1 mole) in dry *n*-butyl ether (80 ml.) was stirred with 1-dimethylaminomethylskatole methiodide (7.2 g., 0.022 mole) for 80 hr. on a steam bath in an atmosphere of nitrogen. The reaction mixture was then cooled and decomposed with 100 ml. of *N* hydrochloric acid. The butyl ether layer was separated and mixed with an additional ether extract of the aqueous solution. The combined ether extracts were washed successively with water, sodium hydroxide solution, sodium thiosulfate solution, and water. After drying over anhydrous magnesium sulfate, the solvent was removed and the residual liquid distilled *in vacuo;* biphenyl distilled at 69–74°/1 mm. (m.p. 67.5–68°) followed by a fraction (3 g., 63%) at 147–152°/1 mm. The latter solidified when chilled and was crystallized from petroleum ether (60–80°); m.p. 70–71.5°. Two further crystallizations yielded material, m.p. 72–73.5° (lit.[31] m.p. 74–75°).

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.9; H, 6.8. Found: C, 87.2; H, 6.8.

Amine exchange reactions of 1-dimethylaminomethylskatole methiodide (II) *with* (*a*) *piperidine,* (*b*) *morpholine.* Piperidine (10 ml.) was refluxed with II (1 g.) for 3 hr. The mixture was cooled and filtered from the precipitated salt. The filtrate was concentrated under reduced pressure, the residue taken up in benzene and repeatedly washed with water. The dry benzene extract after removal of solvent furnished 632 mg. (52%) of liquid which gave a picrate m.p. and mixed m.p. 163–167° with an authentic sample of the picrate of 1-piperidinomethyl skatole.

When morpholine was used instead of piperidine, 315 mg. (26%) of the morpholine base was obtained. The picrate had m.p. and mixed m.p. 192–194° with an authentic sample of the picrate of 1-morpholinomethylskatole.

Attempted alkylation of sodium cyanide with IV. The methiodide IV (1.5 g., 0.0044 mole) was refluxed with a solution of sodium cyanide (1.5 g., 0.031 mole) in water (15 ml.) for 9 hr. The reaction mixture when cooled and filtered furnished the starting methiodide (0.7 g.) having m.p. and mixed m.p. 198–200° with an authentic specimen. Acidification of the filtrate did not furnish any product.

In a modification of the above procedure, an aqueous solution of IV (3.2 g., 0.009 mole) and sodium cyanide (2.5 g., 0.051 mole) was concentrated on a water bath and the dry residue heated to and maintained for 0.5 hr. at 300°. There was a vigorous evolution of gas during this period. The reac-

(29) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 3440 (1953).

(30) C. U. Rojers and B. B. Corson, *Org. Syntheses*, **30**, 90 (1950).

(31) K. H. Bauer and K. Buhler, *Arch. Pharm.*, **262**, 128 (1924); (*Chem. Abstr.* **18**, 3188 (1924)).

tion mixture was then sublimed *in vacuo* and product (200 mg., m.p. 160–172°) collected at 200°/2 mm. After one crystallization from benzene, the material had m.p. and mixed m.p. 174–176° with an authentic specimen of 3-cyanoindole.

Attempted alkylation of ethyl acetamidocyanoacetate with IV. *Procedure A:* To a solution of sodium (0.29 g., 0.013 g. at.) in absolute ethanol (60 ml.) was added successively ethyl acetamidocyanoacetate (2.1 g., 0.012 mole) and IV (4.2 g., 0.012 mole) and the mixture was refluxed for 40 hr. The mixture was freed of solvent *in vacuo* and the residue triturated with water and filtered. The dark residue (2.2 g., m.p. 174–176°) was crystallized from ethanol; yield 1.17 g., m.p. 180–182°. Ether extraction of the aqueous filtrate as such and also after acidification did not furnish any material. The crystalline product was identified as the starting methiodide after a further crystallization from alcohol.

Procedure B: To powdered sodium (120 mg., 0.005 g. at.) in *n*-butylether (9 ml.) was added ethyl acetamidocyanoacetate (1.1 g., 0.006 mole). The mixture was heated with stirring at 130° in an atmosphere of nitrogen for 8 hr. To the resulting semi-solid was added IV (1.5 g.) and the mixture heated for an additional 6 hr. The solution was filtered hot and the filtrate, when cooled, furnished material (1.1 g.) having m.p. and mixed m.p. 198–200° with an authentic sample of IV. No other product could be obtained by concentrating the filtrate.

Treatment of III *with sodium hydroxide.* A mixture of III (0.5 g.) and 10% ethanolic sodium hydroxide solution (3 ml.) was refluxed for 5 hr. and the alcohol was removed. The residue was diluted with water and cooled overnight. The product (m.p. 171–172°, 454 mg.) was collected and recrystallized from benzene; melting point and mixed melting point with authentic 3-cyanoindole 174–176°.

3-Carboxy-1-dimethylaminomethylindole methiodide. The methiodide IV (2.3 g., 0.007 mole) was refluxed for 1 hr. with 10% sodium hydroxide solution (15 ml.). The mixture was cooled, filtered, and made acidic with hydriodic acid. The crude product was collected and crystallized from alcohol; m.p. 185–190°; yield 1 g. Repeated crystallizations from alcohol raised the m.p. to 202–204°.

Anal. Calcd. for $C_{13}H_{17}O_2N_2I$: C, 43.4; H, 4.8. Found: C, 43.6; H, 5.4. Neut. equiv.: Calcd. 360. Found: 353.2.

Ethyl-α-piperidinomethyl-α-acetamido malonate. Piperidine (3.3 g., 0.039 mole) was added to ethyl acetamidomalonate (8.7 g., 0.04 mole). Formalin (4 ml., 36%, 0.048 moles) was then added and the mixture was warmed on a waterbath for 5 min. and refrigerated overnight. The crude base (12 g.) was collected and crystallized from petroleum ether (60–80°); m.p. 67–68°; yield 8 g. (64%).

Anal. Calcd. for $C_{15}H_{26}O_5N_2$: C, 57.3; H, 8.3. Found: C, 57.3; H, 8.5.

Attempted alkylation of 3-cyanoindole with ethyl α-piperidinomethyl-α-acetamidomalonate. Under dry conditions a mixture of ethyl α-piperidinomethyl-α-acetamidomalonate (3.14 g., 0.01 mole), 3-cyanoindole (1.5 g., 0.011 mole), powdered sodium hydroxide (catalytic amount), and xylene (10 ml.) was refluxed with stirring in an atmosphere of nitrogen for 6 hr. The mixture was filtered hot, diluted with benzene, and extracted with dilute hydrochloric acid. The benzene extract furnished unreacted 3-cyanoindole (587 mg.) which after recrystallization from benzene had melting point and mixed melting point with authentic specimen 174–176°. The acid extract was made alkaline and extracted with ether. The ether extract furnished a solid which was crystallized from petroleum ether (60–80°); yield 1.3 g., melting point and mixed melting point with an authentic sample of 1-piperidinomethyl-3-cyanoindole 88–90°.

1-Piperidinomethyl-3-cyanoindole. To piperidine (0.86 g., 0.01 mole) cooled in ice was added successively acetic acid (2 ml.) and 36% formalin (1 ml., 0.012 mole), maintaining the temperature below 5°. 3-Cyanoindole (1.3 g., 0.009 mole) was added and the mixture heated for 8 hr. on a water bath and then poured into sodium hydroxide solution. The liquid which separated solidified when left overnight in the refrigerator and was crystallized from petroleum ether; m.p. 88–90°; yield 1.3 g. (54%).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.3; H, 7.2. Found: C, 75.6; H, 7.1.

Acknowledgment. We are grateful to Mr. Selvavinayakam for the analyses and Dr. Gurbaksh Singh for the infrared data reported herein. Two of the authors (S.R. and S.Su.) are indebted to the government of India and the University of Madras, respectively, for awards of fellowships.

MADRAS 25, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pyrroles. XII. The Reaction of Pyrrolealdehydes with Arylacetonitriles[1,2]

WERNER HERZ AND JAY BRASCH[3]

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Triton B is an excellent catalyst for the preparation of pyrrole-substituted acrylonitriles from 2-pyrrolealdehyde. Secondary cyclic amines like piperidine, morpholine, and pyrrolidine, although capable of functioning as catalysts, enter into reaction with 2-pyrrolealdehyde and form bimolecular pyrrole Mannich bases. The acrylonitriles could not be hydrolyzed satisfactorily. Other attempts to prepare pyrrole analogs of stilbene are described.

In continuation of earlier work on the synthesis of 2-vinylpyrroles,[4] we were interested in preparing pyrrole analogs of stilbene. The decarboxylation of substituted cinnamic acids is a convenient method for the preparation of certain styrenes and stilbenes.[5] However, condensation between 2-pyrrolealdehyde and 2-*N*-methylpyrrolealdehyde, on the one hand, and phenylacetic acid on the other, could not be effected under the usual conditions.[6]

(1) Paper XI, W. Herz, *J. Org. Chem.*, 22, 1260 (1957).

(2) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-436.

(3) Abstracted from the M.S. Thesis of Jay Brasch, August 1957.

(4) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, 76, 576 (1954).

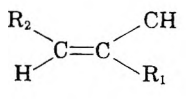
(5) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 44.

(6) See ref. 5, pp. 55–56, for leading references.

We therefore studied the reaction of these aldehydes with arylacetonitriles in the hope that hydrolysis of the condensation products (I) would lead to the desired substituted cinnamic acid analogs.

On condensing 2-pyrrolealdehyde with 2-pyrroleacetonitrile in the presence of piperidine, there was obtained a colorless basic substance of m.p. 160° which did not exhibit the properties expected of 1,2-dipyrroleacrylonitrile (I, R_1,R_2 = 2-pyrrole). When the condensation was carried out between 2-pyrrolealdehyde and phenylacetonitrile, the substance of m.p. 160° was also isolated, but dilution of the mother liquors with water yielded yellow crystals of m.p. 98–99° which proved to be 1-phenyl-2-pyrroleacrylonitrile.

These experiments suggested that there was some reaction between 2-pyrrolealdehyde and piperidine, and indeed, when these reagents were mixed in anhydrous ethanol, the base of m.p. 160° precipitated in 47% yield. Elemental analysis and molecular weight determinations indicated the formula $C_{20}H_{28}N_4$, the infrared spectrum showed the absence of NH and C=O groups, and the ultraviolet spectrum exhibited no absorption bands characteristic of a particular chromophore. Attempts to determine the neutral equivalent of the base failed due to color formation and reactions near the equivalence point. Analogous bases were formed on treatment of 2-pyrrolealdehyde with morpholine and pyrrolidine, but no reaction ensued when the aldehyde was mixed with aliphatic secondary amines or any tertiary amines.[7] Similarly *N*-methyl-2-pyrrolealdehyde proved inert when mixed with alicyclic secondary amines, which suggests that a free NH group on the pyrrole nucleus is necessary for such condensation.



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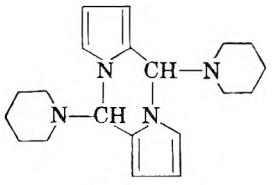
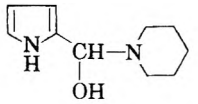
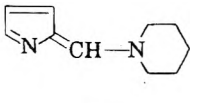


II

All of the above facts can be accommodated by assigning structure II to the base of m.p. 160°, with III or the enamine IV as possible intermediates leading to its formation. A piperidine addition compound whose structure is postulated as corresponding to III is formed when 2, 4, 5-trimethyl-3-pyrrolealdehyde and piperidine are allowed to stand for fifteen days.[8] Structures analogous to II would also represent the adducts resulting from 2-pyrrolealdehyde and morpholine or pyrrolidine.



III



IV

2-Pyrrolealdehyde has been condensed with malonic ester in the presence of piperidine;[9] the expected product was obtained in fair yield and no other products were reported. Certain substituted pyrroles also condense smoothly in a normal way.[10] In these cases the rate of the normal aldol-type condensation is presumably much faster than that of the condensation with the basic catalyst. On the other hand when the aldol condensation is sluggish, the reaction with piperidine takes precedence.[11]

Structure II is supported by the following additional facts. As a pyrrole Mannich base substituted on nitrogen it should be inert toward displacement reactions since it cannot react *via* the elimination-addition mechanism postulated for alkylations of this type.[13] This proved to be the case. On the other hand, quaternary salts derived from such bases may serve as alkylating agents. When attempts were made to prepare the hydrochloride and methiodide of II, however, the salts which were isolated proved to be piperidinium chloride and dimethylpiperidinium iodide, presumably due to spontaneous decomposition of the Mannich base salts.

Since the condensation of 2-pyrrolealdehyde with arylacetonitriles in the presence of piperidine gave low yields and was complicated by side reactions, other catalysts were investigated. Sodium ethoxide improved the yields slightly, but the major product was the sodium salt of the active methylene compound. In the search for a catalyst which would combine high basicity with non-participation in side reactions and minimum salt formation, benzyltrimethylammonium hydroxide finally proved to be the reagent of choice. Thus, in the preparation of 1-phenyl-2-pyrroleacrylonitrile, use of pyridine gave a yield of 16%, use of sodium ethoxide gave 23%, and the quaternary ammonium hydroxide raised the yield to 74%. The compounds prepared in this fashion are listed in Table I. The condensation of 2-pyrrolealdehyde with 2-pyrroleacetonitrile could not be carried out successfully.

Hydrolysis of the compounds of type I did not lead to the desired substituted cinnamic acids.

(7) These amines are probably not strong enough to catalyze the aldol reaction satisfactorily. At the same time the aliphatic secondary amines probably do not have the relatively low steric requirements of piperidine, pyrrolidine, and morpholine, which may result in the formation of compounds of type II.

(8) H. Fischer and C. Nenitzescu, *Ann.*, **439**, 175 (1924).

(9) G. R. Clemo, G. R. Fulton, and R. Raper, *J. Chem. Soc.*, 1140 (1950); W. Kutscher and O. Klamerth, *Z. physiol. Chem.*, **289**, 229 (1952).

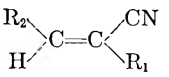
(10) H. Fischer and Z. Ceskas, *Ann.*, **508**, 187 (1934).

(11) Thus the "unidentified product" which is formed when hydantoin and 2-pyrrolealdehyde are boiled in absolute ethanol in the presence of piperidine[12] proved to be identical with the base of m.p. 160°.

(12) W. Herz and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 503 (1948).

(13) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **VII**, 99 (1953); H. Hellmann, *Angew. Chem.*, **65**, 473 (1953).

TABLE I

COMPOUNDS OF TYPE 

	R_1	R_2	Yield, %	M.P., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	Phenyl	2-Pyrrole	74	97–98	$C_{13}H_{10}N_2$	80.38	5.19	14.4	80.80	5.03	14.2
Ib	2-Pyrrole	Phenyl	93	111–112	$C_{13}H_{10}N_2$	80.38	5.19	14.4	80.26	5.33	14.2
Ic	Phenyl	*N*-Methyl-2-pyrrole	72	99	$C_{14}H_{12}N_2$	80.72	5.89	13.4	80.28	5.98	13.2
Id	2-Pyrrole	*N*-Methyl-2-pyrrole	81	161	$C_{12}H_{11}N_3$	73.07	5.62	21.4	72.75	5.27	22.0

Use of mild base resulted in recovery of starting material. Under more drastic conditions the only identifiable products were the arylacetic acids corresponding to the original arylacetonitrile moiety. Undoubtedly a reversal of the condensation reaction takes place, but whether it precedes or follows hydrolysis of the nitrile group was not determined.

Several other attempts to prepare 1,2-dipyrrole ethylene are described briefly in the following. The thermal decomposition of benzaldazine furnishes fair yields of *trans*-stilbene[14] and a recent paper describes the application of this method to the preparation of 1,2-difurylethylene.[15] However, under similar conditions (passage through a hot tube at temperatures up to 450°, unpacked or packed with glass, with or without solvents), 2-pyrrolealdazine exhibited remarkable stability and no substance whose properties corresponded to those of the expected stilbene analog could be isolated. Recovery of 2-pyrrolealdazine was practically quantitative even after exposure to intense gamma-ray flux from a cobalt-60 source. An attempt to prepare the hydrazone of 2-pyrrolealdehyde, which it was hoped to convert to 2-pyrrolediazomethane and then to 1,2-dipyrroleethylene, also failed, the only product being 2-pyrrolealdazine.

EXPERIMENTAL[16]

1-Phenyl-2-(N-methylpyrrole)acrylonitrile (Ic). The following preparation is typical for the compounds described in Table I. A solution of 1.17 g. of phenylacetonitrile and 1.09 g. of *N*-methyl-2-pyrrolealdehyde[17] in 25 ml. of boiling anhydrous ethanol was treated with 2 ml. of 33% aqueous Triton B solution. After boiling for 10 min. and allowing to stand, a yellow precipitate formed; total yield, including material from the mother liquors, 1.5 g. (72%). Several recrystallizations from ethanol furnished yellow crystals of m.p. 99°. The infrared spectrum had characteristic bands at 1610 (phenyl, olefin, or both) and 2232 cm.$^{-1}$ (conjugated nitrile). Compound Ia exhibited a doublet at 1590 and 1600 cm.$^{-1}$, nitrile absorption near 2200 and NH absorption at 3400 cm.$^{-1}$ Substance Ib had these bands at 1590, 2215, and 3430 cm.$^{-1}$; compound Id at 1602, 2212, and 3450 cm.$^{-1}$

Attempted hydrolysis of 1-phenyl-2-pyrroleacrylonitrile. The following is illustrative of many such experiments. Hydrolysis of Ia with 10% sodium hydroxide resulted in recovery of starting material. Hydrolysis of 0.55 g. of Ia with 1 g. of potassium hydroxide in 5 ml. of ethylene glycol at 195° for 2 hr. caused evolution of ammonia. The acid fraction weighed 0.2 g., m.p. 75°, undepressed on admixture of authentic phenylacetic acid.

Attempted condensation of 2-pyrrolealdehyde with phenylacetic acid. A typical reaction is described below. A mixture consisting of 1.74 g. of dry potassium phenylacetate, 0.5 g. of potassium carbonate, 0.5 ml. of dry pyridine, 0.96 g. of 2-pyrrolealdehyde, and 1.53 g. of freshly distilled acetic anhydride was heated at 180–190° in a nitrogen atmosphere for 2 hr., cooled, and decomposed with 35 ml. of water and 4 ml. of 5*N* potassium hydroxide. The mixture was warmed until solution occurred, cooled, extracted with ether, acidified, and again extracted with ether. Distillation of the neutral fraction furnished 0.5 g. of 2-pyrrolealdehyde; evaporation of the acid fraction followed by recrystallization gave 0.86 g. of phenylacetic acid.

Reaction of 2-pyrrolealdehyde with piperidine. A solution of 1.90 g. of 2-pyrrolealdehyde in 50 ml. of boiling anhydrous ethanol was mixed with 2 ml. of piperidine, boiled for an additional 10 min. (cherry red color) and allowed to stand. Filtration yielded 1.52 g. (47%) of dark brown crystals. After several recrystallizations from acetone-water (1:1) they were colorless and melted at 160°. The infrared spectrum showed no significant absorption in the —NH and double bond region.

Anal. Calcd. for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70; N, 17.2; mol. wt. 324. Found: C, 73.90; H, 9.01; N, 16.8; mol. wt. (Rast, in camphene), 354, (ebullioscopic, in methyl ethyl ketone), 275.

The substance gave a negative ferric chloride test. The Ehrlich test was at first negative, but on standing a pink-orange color developed. It was insoluble in water and soluble in dilute sulfuric acid (the solution was initially yellow, but a reddish precipitate formed rapidly). A sealed ampoule containing 0.5 g. of the base and 15 ml. of methyl iodide on standing deposited crystals which after recrystallization from ethanol-water weighed 0.53 g. and were identified as dimethylpiperidinium iodide by analysis and mixed melting point. Dry hydrogen chloride was passed into a solution of 1 g. of the base in 25 ml. of chloroform for 5 min. The reddish brown amorphous material, wt. 1 g., was filtered and recrystallized from ethanol-water. The colorless crystals were identified as piperidine hydrochloride.

Since pyrrole Mannich bases can be hydrogenolyzed

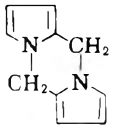
(14) L. B. Howard, G. E. Hilbert, R. Wiebe, and V. L. Gaddy, *J. Am. Chem. Soc.*, **54**, 3628 (1932); G. W. Williams and A. S. C. Lawrence, *Proc. Roy. Soc.*, **156A**, 444 (1936).

(15) N. I. Shuikin, M. V. Yushkevich, and G. S. Belikova, *Sbornik Statei Obshcheĭ Khim.*, **2**, 1112 (1953); *Chem. Abstr.*, **49**, 4616 (1955).

(16) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were determined by Miss M. N. Esquivel on a Perkin-Elmer Model 21 recording spectrometer.

(17) E. F. Ryskiewicz and R. M. Silverstein, *J. Am. Chem. Soc.*, **76**, 5802 (1954).

catalytically,[18] attempts were made to carry out such a conversion. Low pressure hydrogenation resulted in recovery of starting material. High pressure hydrogenation in ethyl acetate (ethanol was not satisfactory) gave an oil of b.p. 60° (1 mm.) which could not be identified satisfactorily but was neither the hoped-for V nor *N*-acetylpiperidine.[19] The relatively large quantity formed (2.52 g. from 2.0 g. of II) indicated that solvent was involved.



V

(18) A. Treibs and A. Zinsmeister, *Ber.*, **90**, 87 (1957).

(19) Piperidine and ethyl acetate at 200° are reported to yield *N*-acetylpiperidine.[20]

(20) F. B. Ahrens, *Ber.*, **27**, 2088 (1894).

Reaction of 2-pyrrolealdehyde with morpholine. Condensation of 2-pyrrolealdehyde with morpholine in the manner described above furnished 3.19 g. (97%) of tan crystals which were decolorized by recrystallization from ethyl acetate and then melted at 197–198°. The product resembled II in chemical behavior and solubility.

Anal. Calcd. for $C_{18}H_{24}N_4O_2$: C, 65.43; H, 7.32; N, 17.0. Found: C, 65.53; H, 7.46; N, 17.1.

Reaction of 2-pyrrolealdehyde with pyrrolidine. A mixture of 9.6 g. of the aldehyde and 14.2 g of pyrrolidine yielded 7.35 g. (50%) of brown product which was purified by recrystallization from ether, m.p. 93–94°. The substance decomposed rapidly on standing, and like its analogs, could not be titrated satisfactorily.

Anal. Calcd. for $C_{18}H_{24}N_4$: C, 18.9. Found: N, 18.8.

Acknowledgment. We are grateful to E. I. du Pont de Nemours and Co., Inc., for the gift of chemicals.

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

Pyridinium Aldoximes[1]

EDWARD J. POZIOMEK, BRENNIE E. HACKLEY, JR., AND GEORGE M. STEINBERG

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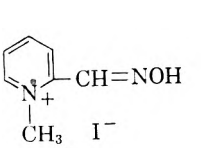
A number of 1,1′-polymethylenebis(4-formylpyridinium bromide) dioximes and *N*-substituted 2- and 4-formylpyridinium halide oximes have been prepared. The bis-quaternary dioximes are active as chemotherapeutic agents in the treatment of nerve gas and other anticholinesterase poisoning in experimental animals, when administered in conjunction with atropine. The most active, 1,1′-trimethylenebis(4-formylpyridinium bromide) dioxime, appears to have advantages over previously reported treatment agents.

The "nerve gases" such as diisopropyl phosphorofluoridate (DFP), isopropyl methylphosphonofluoridate (GB) and *O*-ethyl *N*,*N*-dimethyl phosphoramidocyanidate (GA) as well as many of the organophosphorus insecticides or their metabolites function biologically by inhibition of the enzyme acetylcholinesterase[2]; inhibition being caused by phosphorylation (or phosphonylation) of the active site of the enzyme.

Nerve gas poisoning has been treated symptomatically with drugs which are pharmacologically antagonistic to acetylcholine. Such a compound is atropine and it is presently the recommended remedy.[3] As part of a program aimed at the development of prophylactics and of therapeutics which will act to repair the biological lesion, we have been involved in a search for reagents which (*a*) react rapidly with the nerve gases under physiological conditions of *p*H and temperature and (*b*) reactivate phosphorylated (or phosphonylated) enzymes. Several groups of rapid nerve gas reactants have been reported.[4]



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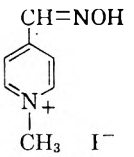


II

Recently, 2-formyl-1-methylpyridinium iodide oxime,[5] Compound I, has been reported to enhance considerably the activity of atropine in the chemotherapeusis of poisoning due to organophosphorus compounds.[6] Compound I shares the

(1) Presented at American Chemical Society, 132nd Meeting, New York, September 1957.

(2) (a) B. J. Jandorf, H. O. Michel, N. K. Schaffer, R. Egan, and W. H. Summerson, *Discussions Faraday Soc.*, **20**, 134 (1955). (b) J. E. Casida, *J. Agr. Food Chem.*, **4**, 772 (1956).

(3) W. H. Summerson, *Armed Forces Chem. J.*, **9**, 24 (1955).

(4) (a) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955). (b) G. M. Steinberg and J. Bolger, *J. Org. Chem.*, **21**, 660 (1956). (c) B. J. Jandorf, T. Wagner-Jauregg, J. O'Neill, and M. Stolberg, *J. Am. Chem. Soc.*, **74**, 1521 (1952). (d) T. Wagner-Jauregg and B. E. Hackley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1952). (e) T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens, and R. Proper, *J. Am. Chem. Soc.*, **77**, 922 (1955). (f) J. Epstein, D. Rosenblatt, and M. Demek, *J. Am. Chem. Soc.*, **78**, 341 (1956).

(5) This compound has been commonly referred to in the pharmacological and biochemical literature as 2-pyridinealdoxime methiodide or 2-PAM.

(6) (a) I. B. Wilson and S. Ginsburg, *Biochim. et Biophys. Acta*, **18**, 168 (1955). (b) D. R. Davies and A. L. Green, *Discussions Faraday Soc.*, **20**, 269 (1955). (c) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **64**, 456 (1956).

property of reacting rapidly with GB *in vitro*, under physiological conditions of *p*H and temperature with many other oximes which are chemotherapeutically ineffective.[7] It does stand out among other oximes, however, in its ability to reactivate inactivated acetylcholinesterase (AChE) *in vitro* with great rapidity.[6] The reactivation process involves removal of the phosphate (or phosphonate) grouping from the enzyme.

Wilson[6a] has offered the hypothesis that the outstanding activity of Compound I results from its ability to strongly associate with the inhibited enzyme at the site of phosphorylation, and that in association complex the reactive oximino group is properly oriented for displacement of the phosphate moiety. By way of comparison, the corresponding 4-formyl-1-methylpyridinium iodide oxime,[8] Compound II, is also comparatively active as a reactivator of phosphate or phosphonate inhibited cholinesterase; however, it is considerably less effective than I. Thus, with isopropyl methylphosphonylated eel acetylcholinesterase the rate constant for reactivation at *p*H 7.4, 25°, in the presence of 7.2×10^{-3} *M* acetylcholine is $2 \times 10^{3} M^{-1}$ for I and $1.4 \times 10^{2} M^{-1}$min.$^{-1}$ for II.

If strong association between oxime and inhibited enzyme were an important factor in reaction, it seemed that one should be able to increase reactivation rate by combining structures which are known to strongly associate with the enzyme, such as the di- and polyquaternary compounds, with the reactive formylpyridinium halide oxime group. To this end a series of 1,1′-polymethylene bis-(4-formylpyridinium) bromide dioximes have been prepared. These compounds, Table I, are even more rapid reactivators of the inhibited eel AChE than I although they are structurally related to the less active II. Under the conditions referred to above, VI, the most active of these compounds reactivates with a rate constant of $10^{4} M^{-1}$min.$^{-1}$ With the exception of VII which is too toxic for chemotherapeutic use, all of the bisquaternary compounds are active, when used together with atropine, as therapeutics and to a lesser but significant extent as prophylactics against GB poisoning. The most effective of the group in the treatment of poisoned animals is compound IV, 1,1′-trimethylenebis(4-formylpyridinium bromide) dioxime,[9] which is not quite as rapid a reactivator as V; its rate constant under the conditions cited is $6 \times 10^{3} M^{-1}$min.$^{-1}$

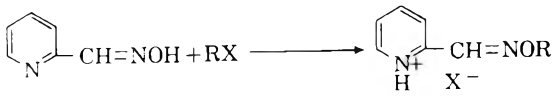
In preliminary studies in animals poisoned with GB, the combination of Compound IV and atropine appears to be more effective in both therapy and prophylaxis than the corresponding combination of I with atropine; although there is a marked species variation in their relative effectiveness. In rats challenged with a $2LD_{50}$ dose (iv) of GB, all of a group of six animals survived if the first combination was administered (iv) immediately after poisoning. The second combination saved only two of the group of six animals. On the other hand, with dogs which were given a $20LD_{50}$ dose of GB (subcutaneous) the survival ratios were the same for the two treatments (4/5) which were given intravenously when symptoms appeared; however, the recovery time was much more rapid for the surviving animals which received the first treatment, *i.e.* 2 hours *vs.* 24 hours.

The *in vitro* reactivation data and the therapy results were kindly provided by Drs. H. O. Michel and E. Bay, respectively. Detailed reports of their studies will be published elsewhere.

This paper also reports the synthesis of several monoquaternary analogs of compounds I and II, Table II. All of the compounds in this group were inferior in chemotherapeutic activity to Compound I.

Two standard procedures were employed for quaternization of the pyridine ring. In procedure A, the pyridine compound and halide were reacted at reflux temperature in absolute ethanol; in procedure B the mixture of amine, halide, and solvent was heated to 60° in a capped bottle of the carbonated beverage variety. The latter procedure was generally found to be more convenient because of its simplicity.

Quaternization of the pyridine oximes was sometimes complicated by a side reaction involving alkylation of the oximino group.[10] This side reaction



became increasingly preponderant with increased steric hindrance at the site of reaction, *i.e.* the pyridine nitrogen atom. With highly hindered oximes such as 2,6-diformylpyridine dioxime, the oxime ether was the sole product of reaction. Similarly, in an attempted preparation of 2-formyl-1-isopropylpyridinium bromide oxime using procedure A, reflux time 60 hours, the only product isolated was the *O*-alkylated derivative in 37% yield. Low yields were general with the 2-formyl derivatives, and attempts to synthesize *N,N′*-bis derivatives of 2-formylpyridinium halide oximes by quaternization of 2-pyridinealdoxime have been unsuccessful to date. The properties, yields, and analyses of the compounds prepared are summarized in Tables I and II.

EXPERIMENTAL

Oximes. 2- and 4-Pyridinecarboxaldehyde oximes were prepared by warming on the steam bath a neutralized

(7) (a) B. E. Hackley, Jr., Ph.D. dissertation, University of Delaware, 1956. (b) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

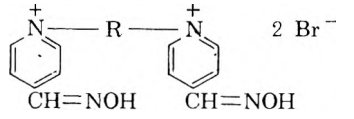
(8) Commonly referred to as 4-PAM.

(9) Commonly referred to as TMB-4.

(10) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, 79, 481 (1957).

TABLE I

1,1′-POLYMETHYLENEBIS(4-FORMYLPYRIDINIUM HALIDE) DIOXIMES

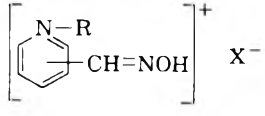


No.	Substituents, R	Conditions	Yield, %	M.P., °C.[a]	Formula	pK_a	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
III	$-(CH_2)_2-$	A, 31 hr. B, 64 hr.	35.0	300	$C_{14}H_{16}Br_2N_4O_2$	8.1	—	—	—	—	12.9	12.7	216	216
IV	$-(CH_2)_3-$	B, 48 hr.	88.2	238–241 (dec.)	$C_{15}H_{18}Br_2N_4O_2$	8.2	40.4	41.2	4.1	4.6	12.6	12.6	223	223
V	$-(CH_2)_4-$	B, 16 hr.	81.0	239–241 (dec.)	$C_{16}H_{20}Br_2N_4O_2$	8.3	41.8	41.2	4.4	4.6	—	—	230	246
VI	$-(CH_2)_5-$	B, 95 hr.	95.0	208–210 (dec.)	$C_{17}H_{22}Br_2N_4O_2$	8.4	42.3	42.3	4.6	4.9	11.6	11.4	237	236
VII	$-(CH_2)_{10}-$	B, 8 hr.	85.0	219–223 (dec.)	$C_{22}H_{32}Br_2N_4O_2$	8.5	48.6	48.3	6.0	6.0	10.3	10.7	272	271

[a] Melting points are uncorrected.

TABLE II

N-SUBSTITUTED 2- AND 4-FORMYLPYRIDINIUM HALIDE OXIMES



Oximino Formyl	R	X	Conditions	Yield, %	M.P., °C.[a]	Formula	pK_a	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
2	Ethyl	I	A, 160 hr.	34.8	176–177 (dec.)	$C_8H_{11}IN_2O$	8.1	34.5	34.3	4.0	3.9	10.1	10.3	278	265
2	Allyl	Br	A, 8 hr.	28.8	300	$C_9H_{11}BrN_2O$	8.0	44.5	44.1	4.5	4.5	11.5	12.9	243	240
4	Allyl	Br	B, 70 hr.	93.0	183–187 (dec.)	$C_9H_{11}BrN_2O$	8.4	44.5	44.3	4.6	4.6	11.5	11.7	243	234
2	2-Hydroxy ethyl	Br	A, 6 hr.	9.9	197–200 (dec.)	$C_8H_{11}BrN_2O_2$	7.8	38.9	39.1	4.5	4.6	11.3	11.4	247	245
4	2-Hydroxy ethyl	Br	B, 54 hr.	44.5	187–190 (dec.)	$C_8H_{11}BrN_2O_2$	8.3	38.9	38.8	4.5	4.5	11.3	11.4	247	241
4	Butyl	Br	A, 24 hr. B, 64 hr.	88.3	138–139 (dec.)	$C_{10}H_{15}BrN_2O$	8.4	46.4	44.9	5.8	5.5	10.8	11.0	259	232

[a] Melting points are uncorrected.

aqueous solution of the corresponding aldehyde (obtained from the Aldrich Chemical Co.) and $NH_2OH \cdot HCl$, m.p. 112.5–113.0° and 130.0–130.5°, respectively.

Quaternizations. In synthesizing the mono 2- and 4-formyl alkyl pyridinium halide oximes a 2:1 molar ratio of halide to tertiary oxime was used. In the "bis" series a 1:3 molar ratio was employed.

Procedure A. A mixture of the pyridine oxime and halide was dissolved in sufficient ethanol and refluxed for the period of time specified in Tables I and II.

Procedure B. A mixture of oxime and halide was dissolved in about 100 ml. of ethanol and heated at 60° in a 200-ml. capped pressure bottle for specified periods of time. The reaction mixtures were cooled to room temperature and the products of reaction removed by filtration. In several cases, it was necessary to add absolute ether to effect complete precipitation. The products were recrystallized from absolute ethanol.

pK_a Values. The pK_a values were determined at room temperature (25–27°), from potentiometric titration data, assuming pK_a to be the pH of half neutralization. In each case approximately 100 mg. of oxime dissolved in 5 ml. of water was titrated with 0.1N sodium hydroxide.

Analysis. Elemental analyses were performed by standard procedures. For determination of nitrogen (Dumas) the weighed samples were layered over with V_2O_5 prior to ignition. Since the oxime ether hydrohalides are isomeric with the desired quaternized oximes it was necessary to establish purity by independent determination. This was achieved readily by potentiometric titration since the oxime ether hydrohalides have pK_a values of less than 5, whereas the pK_a values of the quaternized oximes are 7.8–8.5.

Where mixtures of oxime ether hydrohalide and quaternary oximes were obtained, separation was accomplished by fractional crystallization from ethanol or by separation from neutral aqueous solution. At pH 6–7 the oxime ether (and also any unreacted pyridine aldoxime) could be extracted from aqueous solution with $CHCl_3$ leaving the quaternary compound in the aqueous layer.

Acknowledgment. The authors wish to express their gratitude to the Analytical Research Branch of the Research Directorate, U.S. Army Chemical Warfare Laboratories for the analyses here reported and to Pfc. Gerard Natarelli for many of the potentiometric titrations.

ARMY CHEMICAL CENTER, MD.

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

Polycyclic Compounds Containing Nitrogen. I. The Diels-Alder Reaction of 1-Nitro-1-alkenes

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As a preliminary to investigations involving substituted nitrocyclohexenes and their analogs as intermediates for the preparation of polycyclic compounds containing ring nitrogen, the reaction of various 1-nitro-1-alkenes with 2,3-dimethyl-1,3-butadiene was reexamined. The nitroalkenes studied have the general formula, $RCH{=}CHNO_2$, where R is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl, and 2-ethoxyethyl. The majority of the adducts were characterized by conversion to the corresponding dibromides which were readily purified by crystallization. Two of the dibromides were not crystalline; in these instances the corresponding cyclohexenones were prepared by the Nef reaction. Reduction of the nitrocyclohexenes to the corresponding cyclohexylamines is described.

Investigations concerned with the synthesis of polycyclic compounds containing ring nitrogen by routes involving the Diels-Alder reaction demanded a reinvestigation of the use of 1-nitro-1-alkenes as dienophiles. The present paper records this work.

It has previously been shown that 1-nitro-1-alkenes participate as dienophiles in the Diels-Alder reaction.[3] In general, however, the yield of adduct has been low whenever the preparation has involved an open-chain diene; the number of such cases previously studied is very small.

2,3-Dimethylbutadiene was chosen for our work because of its ready availability and its reactivity. 2-Methoxybutadiene was also employed in a few cases.[4]

Experimental conditions employed for such reactions by previous investigators have varied from heating an ether solution of the reactants under reflux to heating the reactants in a sealed tube at 150°. We have found that no adduct was isolable from 1-nitro-1-pentene and 2,3-dimethyl-1,2-butadiene when a mixture of the two was allowed to

(1) From a thesis submitted by A. B. Ross in partial fulfillment of the requirements for the Ph.D. degree, University of Maryland, June 1957.

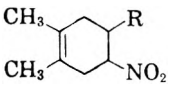
(2) Monsanto Chemical Company Fellow, 1956–57.

(3) H. L. Holmes, *Org. Reactions, IV*, 60 (1948); K. Klager, *J. Org. Chem.*, 20, 650 (1955); W. E. Noland, H. I. Freeman, and M. S. Baker, *J. Am. Chem. Soc.*, 78, 188 (1956); J. D. Roberts, C. C. Lee, and W. H. Saunders, *J. Am. Chem. Soc.*, 76, 4501 (1954); W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, 17, 1641 (1952); W. C. Wildman and D. R. Saunders, *J. Org. Chem.*, 19, 381 (1954); A. Etienne, A. Spire, and E. Toromanoff, *Bull. soc. chim. France*, 750 (1952); E. E. Van Tamalen, and R. J. Thiede, *J. Am. Chem. Soc.*, 74, 2615 (1952); D. V. Nightingale, M. Maienthal, and J. A. Gallagher, *J. Am. Chem. Soc.*, 75, 4852 (1953); W. E. Noland and R. E. Bambury, *J. Am. Chem. Soc.*, 77, 6386 (1955); K. Alder, H. F. Rickert, and E. Windemuth, *Ber.*, 71, 2451 (1938); E. G. Kataev and P. S. Matveeva, *J. Gen. Chem. (U.S.S.R.)*, 23, 405 (1953); *Chem. Abstr.*, 48, 3272 (1954); W. E. Noland, R. E. Counsell, and M. H. Fisher, *J. Org. Chem.*, 21, 911 (1956).

(4) See paper, II, *J. Org. Chem.*, in press.

TABLE I

4-ALKYL-1,2-DIMETHYL-5-NITROCYCLOHEXENES



R	Time of reaction, hrs.	Yield, %	B.P., °C.	Pressure, mm.	n_D^{25}
Methyl[a]	8, 12	68.5[f], 72	71	0.6	1.4796
Ethyl[b]	16	77.5[f]	105	4	—
Propyl[c]	24	69.5	113–114	5	1.4790
Isopropyl[d]	16	31.5, 35[f]	105	3	1.4819
Butyl	33	73	124–126	3	1.4784
Isobutyl	32	65, 68.5[f]	115–116	3	1.4752
Amyl	32	65[f]	129–130	3	1.4756
Hexyl[e]	24	77–78	116	0.3	1.4763
2-Ethoxyethyl	34, 40	69[f], 80.5[f]	112–114	1	1.4785

[a] M.p. 34.5–35.0°; *Anal.* Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.25, 63.22; H, 8.76, 8.84. [b] M.p. 32.5–32.8°; *Anal.* Calcd. for $C_{10}H_{17}NO_2$: C, 65.49; H, 9.35; N, 7.65. Found: C, 65.23, 65.19; H, 9.16, 9.09; N, 7.68, 7.84. [c] Lit.[11] b.p. 146–147° (12 mm.); d_4^{20} 1.0035. M_D^{20} Calcd.: 56.19. Found: 56.32. *Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.53, 67.32; H, 9.41, 9.49. [d] *Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.29, 67.53; H, 9.55, 9.68. [e] *Anal.* Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 69.97, 70.15; H, 10.55, 10.58; N, 6.25, 6.29. [f] Acetonitrile was used as a solvent; in the other reactions no solvent was employed.

stand at room temperature for a week: 79% of the alkene was recovered. Likewise, heating 1-nitro-1-butene or 1-nitro-1-pentene with the same diene under reflux resulted in very low yields of adduct.

Satisfactory yields of adduct were, however, obtained by heating the reactants at 100° in a glass liner contained in a steel vessel of the type used for high pressure hydrogenations. The yield of adduct was little influenced by the presence of a large excess of diene; standard practice was to use a ratio of nitroalkene to diene of 1 : 1.5, but ratios up to 1 : 6.8 were studied. Likewise, use of acetonitrile or nitroethane as solvents gave no improvement of yield; on the other hand, acetic acid, benzene, or benzene containing trichloracetic acid proved unsatisfactory[5] as solvents for the reaction.

The nitroalkenes and diene were stable under the conditions chosen; 1-nitro-1-pentene, 1-nitro-1-octene and 2,3-dimethylbutadiene were heated individually at 100° in the apparatus for 12, 31, and 12 hours respectively. Recoveries of the respective substances were 91, 78, and 92%. Much smaller recoveries of 1-nitro-1-octene were obtained when it was heated under similar conditions in acetonitrile or nitroethane. Apparently the solvent promotes polymerization of the olefin. However, acetonitrile and nitroethane were found to be quite satisfactory solvents for the reaction. It appears, therefore, that the Diels-Alder process can compete favorably with other processes in these solvents. Some of the early reactions were carried out in acetonitrile in the hope that the highly polar solvent might promote an advantageous polarization of the reactants. However, experience proved that the higher yields obtained in these early experiments could also be obtained when excess diene alone was used as solvent. In the later experiments, therefore, no foreign solvent was used.

The times necessary for optimum yields are profoundly influenced by the character of the R-group in the 1-nitro olefin, $RCH{=}CHNO_2$; Table I (see experimental part) shows this influence. Longer reaction times were required as the alkyl group increased in length, and α-substitution appears to have a considerable influence on the yield.[6] These effects are not surprising inasmuch as the yield of adduct is determined by the balance of a number of competing reactions; polymerization of each reactant undoubtedly competes with the normal Diels-Alder addition, and copolymerization is certainly not excluded.

A number of experiments involving 3-methyl-1-nitro-1-butene and 2,3-dimethyl-1,3-butadiene showed that little improvement in yield resulted from increasing reaction time from 16 to 24 hours. On the other hand 1-nitro-1-pentene reacted with the same diene under the same conditions to produce more than twice as much adduct. 4-Methyl-1-nitro-1-pentene behaved similarly. Whether this behavior is a reflection of steric or polar effects, or both, is debatable; we are inclined toward the belief that the low yields of adduct obtainable from 3-methyl-1-nitro-1-butene are attributable to the steric effect of the branch in the chain in a position adjacent to the reaction site.[7]

The nitrocyclohexenes were characterized by conversion to dibromides which were low -melting solids. Two of the dibromides failed to crystallize,

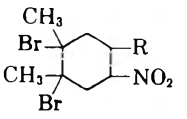
(5) A. Wassermann, *J. Chem. Soc.*, 618, 623 (1942).

(6) W. C. Wildman and W. T. Norton, *J. Am. Chem. Soc.*, 76, 152 (1954).

(7) W. R. Vaughan and K. S. Anderson, *J. Org. Chem.*, 21, 673 (1956).

TABLE II

4-ALKYL-1,2-DIBROMO-1,2-DIMETHYL-5-NITROCYCLOHEXANES



R	M.P., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Bromine Calcd.	% Bromine Found	% Nitrogen Calcd.	% Nitrogen Found
Methyl	52.0–52.3	32.84	33.04	4.59	4.72	48.57	48.59	4.26	4.00
			33.09		4.74		48.70		3.92
Ethyl	53.0	35.01	34.95	4.99	5.08	46.59	46.56	4.08	3.92
			35.12		4.99		46.26		4.15
Propyl	34.5	37.00	36.85	5.36	5.35	44.76	44.72	3.92	4.24
			37.07		5.25		44.48		4.25
Isopropyl	53.7–54.2	37.00	36.89	5.36	5.46	44.76	44.54	3.92	4.80
			36.83		5.42		44.63		4.64
Isobutyl	40.3–41.3	38.83	39.07	5.70	5.69	43.07	42.91	3.78	3.60
			39.12		5.68		42.95		3.75
Amyl	33.0–33.5	40.54	40.44	6.02	5.93	41.50	41.68	3.64	3.48
			40.48		6.04		41.68		3.46
Hexyl	43.6–44.0	42.11	42.16	6.31	6.33	40.03	40.37	3.51	3.51
			42.06		6.11		40.26		3.75

and the parent substances were therefore converted into the corresponding 6-alkyl-3,4-dimethyl-2-cyclohexen-1-ones by the Nef reaction.[8] Evidence for a shift during or subsequent to the Nef reaction in the location of the double bond of the adduct into conjugation with the carbonyl is provided in the ultraviolet spectra of the two ketones. The principal absorption of 3,4-dimethyl-6-*n*-butyl-2-cyclohexene-1-one was found at 226 mμ(ϵ = 11,800); that of 3,4-dimethyl-6-(2-ethoxyethyl)-2-cyclohexen-1-one was found at the same wave-length, (ϵ = 10,800).

The absorption spectra of a series of 3-alkyl-2-cyclohexene-1-ones have been studied.[9] Maxima appear in the range between 223.5 and 226.5 mμ with values of ϵ of 15,000 to 16,600. These absorption maxima are at a longer wave length and have much larger ϵ-values than would substances in which the double bond was not conjugated with the carbonyl.[10]

Hydrogenation of 1,2,4-trimethyl-5-nitrocyclohexene, I, and 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene, II, to the corresponding cyclohexylamines was noteworthy in that the rate of absorption of hydrogen in the presence of an Adams' platinum catalyst was rapid until one molecular equivalent of hydrogen was absorbed and then very slow until four molecular equivalents had been absorbed. When, however, a 10% palladium-carbon catalyst was employed in the reduction of 4-ethyl-1,2-dimethyl-5-nitrocyclohexene, III, and of II, no abrupt change in rate of absorption occurred, and four equivalents of hydrogen were absorbed rather rapidly. When hydrogenation of III was stopped after three molecular equivalents of hydrogen had been absorbed, only the saturated amine could be isolated. This behavior is but another example of the tendency of nitrocyclohexenes, at least those with isolated double linkages, to be converted by hydrogenation over a platinum catalyst to the corresponding cyclohexane prior to reduction of the nitro group.[11]

Dibromides of the nitrocyclohexenes were prepared as reference compounds. The dibromides from the *n*-butyl- and the 2-ethoxyethyl-substituted cyclohexenes melted below room temperature. For further characterization these substances were converted by means of the Nef reaction to the corresponding cyclohexenones which were further characterized by preparation of their 2,4-dinitrophenylhydrazones.

EXPERIMENTAL

Melting points are corrected and were determined in a Hershberg apparatus. Boiling points are uncorrected. We are indebted to Miss Kathryn Gerdeman, Dr. Mary Aldridge, and Miss Jane Swan for the microanalyses. Ultraviolet spectra were determined by use of a Beckman spectrophotometer, Model DU.

Nitroalcohols. The required nitro alcohols were prepared according to the method of Sprang and Degering.[12] Of the alcohols prepared only 4-ethoxy-1-nitro-2-butanol is a new substance. It boils at 107–109° (1 mm.); n_D^{25} 1.4436. Standard procedure was to add 100 ml. of 10*N* sodium hydroxide

(8) K. Klager, *J. Org. Chem.*, **20**, 650 (1955).

(9) G. F. Woods and R. E. Plapinger, University of Maryland; unpublished data.

(10) F. A. Miller, in *Organic Chemistry*, H. Gilman, ed., John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. 3, p. 165.

(11) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954); W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, **17**, 1641 (1952); K. Alder, H. F. Rickert, and E. Windemuth, *Ber.*, **71**, 2451 (1938); E. E. van Tamalen and R. J. Thiede, *J. Am. Chem. Soc.*, **74**, 2615 (1952); J. A. Barltrop and J. S. Nicholson, *J. Chem. Soc.*, 2524 (1951).

(12) C. A. Sprang and E. F. Degering, *J. Am. Chem. Soc.*, **64**, 1063 (1942).

slowly over a period of 40 min. to a cold mixture of 1 mole of freshly distilled aldehyde and 1 mole of nitromethane, well stirred mechanically, in a one-liter, three-necked folded flask. The mixture was held at the same temperature, 5–10°, for an hour after all of the alkali had been added, then neutralized with 500 ml. of cold 2*N* acetic acid, and finally saturated with salt. The product was taken up in ether, and the solution further extracted. Ether, unreacted aldehyde, and nitromethane were removed from the dried ether solution in a nitrogen atmosphere under the pressure of a water pump, and the residue was distilled under reduced pressure in a nitrogen atmosphere through a 10-inch Vigreux column. It was found to be important to avoid heating the alcohol for long periods of time. Concentration of the ether solution under diminished pressure and reasonably rapid distillation of the residual alcohol aid in obtaining satisfactory yields of product.

Nitroalkyl Acetates. Acetates were prepared from the alcohols by treatment at 60° with acetic anhydride in the presence of a bit of concentrated sulfuric acid. About half of the necessary anhydride was added rapidly to the stirred alcohol followed by the balance at such a rate that the temperature remained around 60°. After an additional 2 hr., acetic acid and excess acetic anhydride were removed by distillation in a nitrogen atmosphere under about 25 mm. pressure. The residue was distilled through a 10-in. Vigreux column under a few millimeter's pressure of nitrogen.

Neither boiling point nor refractive index of the following acetates used in this work appear in the literature:-2-methyl-1-(nitromethyl)propyl, b.p. 82–85° (2.5 mm.), n_D^{25} 1.4345; 1-(nitromethyl)amyl, b.p. 105° (3 mm.), n_D^{25} 1.4337; 3-methyl-1-(nitromethyl)butyl, b.p. 86–88° (1 mm.), n_D^{25} 1.4381; 1-(nitromethyl)hexyl, 100–103° (1.5 mm.), n_D^{25} 1.4385; 1-(nitromethyl)heptyl, b.p. 114–116° (1 mm.), n_D^{25} 1.4374; 3-ethoxy-1-(nitromethyl)propyl, b.p. 106–107° (1.5 mm.), n_D^{25} 1.4347.

Nitroalkenes. The nitroalkyl acetates were converted to the corresponding alkenes by heating a vigorously stirred solution of the acetate in benzene in the presence of anhydrous sodium carbonate under reflux in an apparatus provided with a Dean-Stark water trap.[13] The mixture was heated and stirred until no more water was collected. The procedure adopted required 0.5 mole of acetate, 800 ml. of benzene, and 0.5 mole of anhydrous sodium carbonate. After removal of sodium acetate and sodium carbonate by filtration, the benzene solution was concentrated under about 25 mm. pressure in a nitrogen atmosphere, and the residue distilled through a 10-in. Vigreux column under nitrogen (1 to 35 mm.). Either one or both of the following physical constants do not appear in the literature for the following substances:-3-methyl-1-nitro-1-butene, b.p. 67° (14 mm.), n_D^{25} 1.4522; 1-nitro-1-hexene, b.p. 54–55° (1.5 mm.), n_D^{25} 1.4531; 4-methyl-1-nitro-1-pentene, b.p. 50–51° (0.8 mm.), n_D^{25} 1.4500; 4-ethoxy-1-nitro-1-butene, b.p. 75° (2 mm.), n_D^{25} 1.4547.

2,3-Dimethyl-1,3-butadiene. This diene was prepared in the usual way.[14]

4-Alkyl-1,2-dimethyl-5-nitrocyclohexenes. Apparatus for the Diels-Alder additions consisted of a well stirred electrically-heated oil bath which was provided with a thermoregulator and in which was supported at 270-ml. steel bomb of the type used in high-pressure hydrogenations. The bomb was provided with a glass liner, and was approximately two-thirds immersed in the oil.

In the glass liner were mixed 0.05 moles of nitroalkene, 0.25 moles of diene, and sometimes 20 ml. of solvent. A few mg. of hydroquinone was added, and nitrogen was bubbled through the mixture for 5 min. The liner was then stoppered, placed in the bomb, and after closure of the latter, heated in the oil bath at 100° for the desired time. After completion of the reaction, solvent and/or excess diene were removed under reduced pressure; distillation of the residue yielded in succession unreacted nitroalkene and then adduct as an almost colorless oil. Table I summarizes a number of such experiments. The yields reported are for once-distilled products; in some cases the products were redistilled or recrystallized from methanol or ethanol for analysis.

The 3,5-dinitrobenzoyl derivative, m.p. 181–182°, was obtained as a cream colored powder from chloroform-hexane (1:1).

Anal. Calcd. for $C_{17}H_{23}N_3O_8$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.29, 58.18; H, 6.56, 6.28; N, 11.85.

The picrate, yellow needles from 50% ethanol, melted at 222–223°.

2-(2-Ethoxyethyl)-4,5-dimethylcyclohexylamine. A solution of 5.93 g. of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene in 40 ml. of acetic acid and 0.5 g. of Adams' catalyst were shaken with hydrogen at one atmosphere and 23°. One molar equivalent of hydrogen was taken up in 40 min. After 2 more hr. only 4% of the remaining calculated amount of hydrogen had been taken up. The catalyst was removed by filtration and hydrogenation was continued in the presence of 2 g. of 10% palladium on charcoal. The remaining three molar equivalents of hydrogen were taken up in 3560 min. The solution was filtered, evaporated under reduced pressure, and treated with conc. sodium hydroxide The amine was taken up in ether and benzene, and the solvents were evaporated leaving 4.83 g. (93%) of a light yellow oil, n_D^{25} 1.4626.

The picrate formed shiny yellow blades from 50% methanol and melted at 150–151°.

Anal. Calcd. for $C_{18}H_{28}N_4O_8$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.77, 50.83; H, 6.46, 6.28; N, 13.21, 13.25.

The benzoyl derivative separated in clusters of colorless microneedles from 50% ethanol and melted at 132–132.5°.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; —OC_2H_5, 14.85. Found: C, 75.38, 75.08; H, 9.83, 9.80; —OC_2H_5, 15.04.

The α-naphthylurea derivative was prepared and recrystallized from methanol; m.p. 204–205°.

A solution of 6.48 g. of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene in 50 ml. of acetic acid and 3.0 g. of 10% palladium on charcoal were shaken with hydrogen at one atmosphere and 23°. Three molar equivalents of hydrogen were taken up in 45 min., and an additional 240 min. was required for absorption of the fourth molar equivalent of hydrogen. The amine was isolated as described above, to yield 4.49 g. (79.5%) of an almost colorless oil, n_D^{25} 1.4632.

COLLEGE PARK, MD.

(13) H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

(14) L. W. Newton and E. R. Coburn, *Org. Syntheses*, Coll. Vol. **3**, 313 (1955).

[CONTRIBUTION FROM THE CHEMICAL PROCESS IMPROVEMENT DEPARTMENT, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Tetracycline-Urea Compound

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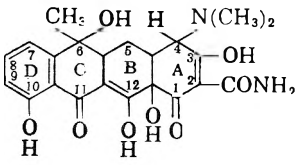
The formation and properties of an equimolecular compound between tetracycline and urea are described. Neither 7-chlorotetracycline nor 5-hydroxytetracycline form insoluble, equimolecular compounds with urea, and tetracycline does not form such compounds with other related amides.

Published methods for isolation and purification of the broad-spectrum antibiotic tetracycline[1] (I) from *Streptomyces aureofaciens* fermentations or from catalytic reduction of 7-chlorotetracycline[1]



I

have generally involved precipitation of the antibiotic as an insoluble form from aqueous or organic solvent solutions. Thus tetracycline has been isolated from concentrated aqueous solutions obtained from fermentation sources or from catalytic reduction of 7-chlorotetracycline by precipitation as the isoelectric form.[2,3] The isoelectric form has also been isolated from organic solvent extracts prepared from fermentation sources.[4] Isolation of tetracycline as the hydrochloride has also been used in situations where concentrated organic solvent solutions of the antibiotic can be caused to crystallize or where the salt can be precipitated by addition of a non-polar solvent.[4] Precipitations of tetracycline as a complex with calcium chloride and other metal salts, with long-chain alkyltrimethylammonium halides, alkyl sulfate esters, and alkyl sulfonic acids, have been variously reported as refining methods for tetracycline.

These techniques can be favorably extended to include precipitation of tetracycline as an insoluble crystalline compound with urea in the molecular proportions of 1:1. The tetracycline-urea compound may be precipitated from aqueous solutions or from organic solvent extracts of the antibiotic. Thus tetracycline-urea may be used in many cases where tetracycline has been precipitated as the isoelectric form.

Tetracycline-urea is most easily prepared from purified tetracycline by slurrying neutral tetracycline in saturated aqueous urea solution or by addition of solid urea to aqueous solutions of tetracycline hydrochloride and appropriate *p*H adjustment. Neutral tetracycline is dissolved by the urea solution and tetracycline-urea is precipitated almost immediately. Under these conditions the tetracycline-urea compound precipitated is a trihydrate with about the same solubility in water as neutral tetracycline prepared at the isoelectric point(*ca.* 300 μg./ml.). When concentrated aqueous (acid) extracts prepared from initial organic solvent extracts of fermentation mashes containing tetracycline are treated with solid urea similarly the tetracycline-urea trihydrate is formed.

Organic solvent extracts of *S. aureofaciens* fermentation mashes prepared as described by Minieri, *et al.*,[2] precipitate tetracycline-urea as a monohydrate when treated with aqueous urea solutions. Thus a methyl isobutyl ketone extract prepared using a quarternary ammonium salt as a "carrier" deposits tetracycline-urea monohydrate when stirred with saturated aqueous urea solution with *p*H adjustment to about *p*H 3.5. Similar treatment of organic solvent solutions of tetracycline pre-

TABLE I

COMPARATIVE SOLUBILITIES OF TETRACYCLINE-UREA MONOHYDRATE AND NEUTRAL TETRACYCLINE

Solvent	Tetracycline-Urea, $1H_2O$, μg./Ml.	Neutral Tetracycline, $3H_2O$, μg./Ml.
Acetone	21,000	45,000
Amyl acetate	545	3,400
Benzene	43	1,400
Butanol	18,200	29,500
Carbon tetrachloride	19	424
Cellosolve	103,000	204,000
Chloroform	520	840
Dimethylformamide	52,000	62,000
Dioxan	24,200	83,000
Ethanol	45,000	43,000
Ethyl acetate	8,300	12,400
Methanol	13,000	26,400
Methyl isobutyl ketone	2,900	57
2-Propanol	11,000	9,200
Tetrahydrofuran	9,300	57,800
Water	325–500	310–1100

(1) The trademarks of the American Cyanamid Co. for tetracycline and 7-chlorotetracycline are Achromycin and Aureomycin, respectively.

(2) P. P. Minieri, H. Sokol, and M. C. Firman, U. S. Patent No. 2,734,018, Feb. 7, 1956.

(3) L. H. Conover, U. S. Patent No. 2,699,054, Jan. 11, 1955.

(4) J. Lein and A. Gourevitch, U. S. Patent No. 2,739,924, Mar. 27, 1956.

pared by catalytic reduction of 7-chlorotetracycline[3,5,6] yields tetracycline-urea.

The tetracycline-urea hydrates have low water solubility and also less solubility in several organic solvents than do neutral tetracycline hydrates. In methanol, butanol, Cellosolve, and acetone, tetracycline-urea hydrate is about half as soluble as neutral tetracycline.

The stability of the tetracycline-urea monohydrate in terms of accelerated stability testing is good. Heating at 60° for eight days does not alter the antibiotic potency or its physical appearance.

TABLE II

ACCELERATED STABILITY TESTS ON TETRACYCLINE-UREA MONOHYDRATE (60° HEATING IN CLOSED CONTAINERS)

Time, Days	Spectrophotometric Assay, μg./Mg.	Microbiological (Turbidimetric) Assay, μg./Mg.	Color Value[a]
0	850	870	0 203
1	850	845	0 257
8	848	843	0 269

[a] An arbitrary value corresponding to $E^{1\%}_{1\,cm.}$ at 450 mμ, measured on a 0.5% solution of 0.1*N* sulfuric acid within 5 minutes after dissolving.

Tetracycline-urea is dissociated into its components by dissolving in any solvent. When dissolved in warm methanol or dilute aqueous acids the solutions have the properties of tetracycline in solution. Ultraviolet spectra in either dilute acid or dilute alkali are identical with tetracycline hydrochloride reference material. Paper chromatographic mobility in the *p*H 3 buffered paper/butanol system[7] or in a 3% aqueous sodium arsenite system[8] is indistinguishable from that of neutral tetracycline or its hydrochloride. Optical rotation of dilute solutions of tetracycline-urea is essentially that of tetracycline neutral. The distribution coefficients of tetracycline and tetracycline-urea between *p*H 2.5 phosphate buffer and 80%–20% (v./v.) chloroform-butanol are the same, 0.13 and 0.14, respectively. The rate of epimerization to 4-*epi*-tetracycline is slightly greater for tetracycline-urea than for neutral tetracycline, the half-epimerization time for tetracycline-urea being 8.4 hr. in 1*M* sodium dihydrogen phosphate–methanol, for neutral tetracycline, 10 hr.

Tetracycline-urea cannot be recrystallized from organic solvents as dissociation to free tetracycline occurs. Recrystallization from saturated aqueous urea solution is possible, the tetracycline-urea dissolving in the saturated urea solution and being precipitated immediately from solution. Neutral tetracycline is precipitated from dilute acid solutions of tetracycline-urea on raising the *p*H, and the neutral material is also recovered from methanol solutions of tetracycline-urea on dilution with water. The facile dissociation of the addition compound in solution is similar to the reported dissociation of the 1:1 urea compounds of the enolic forms of certain β-ketoesters. Ethyl phenylketoparaconate and ethyl oxalacetate both form urea compounds in the molecular ratio of 1:1 and these compounds are easily dissociated on solution.[9] In contrast the 1:1 urea compounds of 2-amino-4,6-dimethylpyrimidine and 2-hydroxy-4,6-dimethylpyrimidine can be recrystallized and require base for their dissociation.[10]

Indeed tetracycline-urea is known as such only in the solid state, as evidenced by the characteristic melting point and by infrared spectrum. In potassium bromide disks tetracycline-urea has an infrared spectrum characteristic of neutral tetracycline but with additional bands at 5.75–5.80 μ and 6.55–6.60 μ.

The specificity of formation of the tetracycline-urea compound is of interest. Whereas tetracycline dissolves in saturated aqueous urea solutions and immediately crystallizes as the urea compound, 7-chlorotetracycline, 5-hydroxytetracycline,[11] 4-*epi*-tetracycline (quatrimycin),[12] 7-chloro-4-*epi*-tetracycline (7-chloroquatrimycin),[12] anhydrotetracy-

TABLE III

SOLUBILITIES OF SEVERAL TETRACYCLINES IN UREA SOLUTIONS AT 25°

Tetracycline	Solubility in Saturated Urea, μg./Ml.	Solubility in Water, μg./Ml.
Tetracycline neutral	1,770	1,000
7-Chlorotetracycline neutral	24,400	500
5-Hydroxytetracycline neutral	9,200	450
4-*epi*-Tetracycline neutral	47,900	18,300
7-Chloro-4-*epi*-tetracycline neutral	41,000	870
Anhydrotetracycline hydrochloride	396,000	52,000
Iso-7-chlorotetracycline neutral	10,300	200

(5) J. H. Boothe, J. Morton, J. P. Petisi, R. G. Wilkinson, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 4621 (1953).

(6) L. H. Conover, W. T. Moreland, A. R. English, C. R. Stephens, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **75**, 4622 (1953).

(7) N. Bohonos, A. C. Dornbush, L. I. Feldman, J. H. Martin, E. Pelcak, and J. H. Williams, *Antibiotics Annual*, **1953/1954**, Medical Encyclopedia Inc., New York, 1953, p. 49.

(8) T. Berti and L. Cima, *Boll. soc. ital. biol. sper.*, **30**, 1123 (1954); *Boll. ist. sieroterap. milan.*, **33**, 643 (1954).

(9) H. Gault and M. Suquet, *Bull. soc. chim. France*, 598 (1950).

(10) S. Birtwell, *J. Chem. Soc.*, 1725 (1953).

(11) The trademark of Chas. Pfizer & Co. for 5-hydroxytetracycline is Terramycin.

(12) J. R. D. McCormick, S. M. Fox, L. L. Smith, B. A. Bitler, J. Reichenthal, V. E. Origoni, W. H. Muller, R. Winterbottom, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **79**, 2849 (1957).

cline, and *iso*-7-chlorotetracycline dissolve but do not precipitate as insoluble compounds. Their solubility in urea solutions is greater than in water. Further, aqueous solutions of thiourea, formamide, acetamide, guanidine, *N*-methylurea, *N,N'*-diethylurea, *N,N*-diethylurea, and *N*-isopropylurea, while generally dissolving tetracycline, do not form insoluble amide compounds.

This high degree of selectivity in combination with the high degree of solubility of 7-chlorotetracycline base in saturated urea solution provides a means of separation of tetracycline from mixtures of tetracycline and 7-chlorotetracycline. 7-Chlorotetracycline is coprecipitated with the tetracycline-urea compound from aqueous solutions; however, the 7-chlorotetracycline is in the isoelectric form, not as a urea compound. The 7-chlorotetracycline content of mixtures is reduced by half on one precipitation of tetracycline as the urea compound.

TABLE IV

FRACTIONATION OF 7-CHLOROTETRACYCLINE (CTC) FROM TETRACYCLINE (TC) BY FORMATION OF TETRACYCLINE–UREA COMPOUND

Composition of Synthetic Mixture		Composition of Insoluble Product		Recovery of Activity	
CTC, μg./mg.	TC, μg./mg.	CTC, μg./mg.	TC, μg./mg.	CTC, %	TC, %
1,000	0	892	—	53.5	—
800	200	650	327	47.5	91.0
600	400	363	576	40.8	92.7
500	500	263	662	39.4	93.5
400	600	215	705	45.3	94.3
200	800	105	794	53.0	95.2
0	1,000	—	905	—	96.2

EXPERIMENTAL

All spectrophotometric assays were performed in 0.1*N* sulfuric acid solutions, compared against a pure standard reference antibiotic (tetracycline hydrochloride = 1000 μg./mg.), and determined on either a Beckman Model DU Quartz spectrophotometer or on a Cary Recording Spectrophotometer, Model 11S. Microbiological assays were turbidimetric assays using *Staphylococcus aureus*. A differential alkaline destruction of 7-chlorotetracycline followed by acid destruction and assay using the long wave length maxima was used for analysis of mixtures of 7-chlorotetracycline and tetracycline.

Tetracycline-urea trihydrate. A. *From tetracycline hydrochloride.* Five grams of pure tetracycline hydrochloride was agitated with 25 ml. of saturated aqueous urea solution until solution was complete. The solution was diluted with 25 ml. of water and filtered immediately. After five hours at room temperature the precipitated crystals were filtered and washed with five 10-ml. portions of water. The crystals were dried *in vacuo* over phosphorus pentoxide, weighing 3.34 g., melting with decomposition at 143–146° (Fisher-Johns block), $[\alpha]_D^{25}$ −222° (0.5%, MeOH), −229° (0.5%, 0.03*N* HCl), assaying 840 μg./mg. (spectrophotometric) and 810 μg./mg. (microbiological). An additional 0.78 g. was recovered from the chilled filtrate.

Anal. Calcd. for $C_{23}H_{34}N_4O_{12}$: C, 49.46; H, 6.14; N, 10.03; potency, 859 μg./mg. Found: C, 49.69; H, 6.42; N, 9.97; potency, 840 μg./mg.

Five grams of tetracycline-urea trihydrate was dissolved with warming in 100 ml. of methanol, and the solution was filtered while warm. Dilution with 100 ml. of water caused a slow precipitation of crystals. A first crop of 1.00 g. was obtained after the mixture had stood at room temperature for three hours. The chilled filtrate (4°) deposited a further 2.88 g. of crystals. Both fractions, assaying 1009 μg./mg. and 870 μg./mg., respectively, represent hydrated tetracycline base.

Conversion of tetracycline-urea hydrates to tetracycline hydrochloride was accomplished by slurrying 9.0 g. of tetracycline-urea in 45 ml. of butanol/Cellosolve (2:1) and adding concentrated hydrochloric acid to reduce the *p*H to 1.7. The mixture was stirred for 60 hr. at room temperature and then filtered. The crystals were washed with 2-propanol and dried in a vacuum oven at 40°, yielding 7.49 g. of tetracycline hydrochloride, assaying 982 μg./mg. (90.2% yield).

B. *From tetracycline neutral.* Five grams of tetracycline neutral assaying 1030 μg./mg. (compared to tetracycline hydrochloride) was slurried in 25 ml. of saturated aqueous urea solution and then shaken on a rotary shaking machine for two hours. The crystals were filtered and washed with water, and dried *in vacuo* over phosphorus pentoxide. A yield of 5.72 g. (95%) of tetracycline-urea trihydrate was obtained, assaying 820 μg./mg.

Ultraviolet spectra of the tetracycline-urea compounds in 0.1*N* sulfuric acid exhibited maxima at 218 mμ, 268 mμ, and 355 mμ, with minima at 233 mμ and 300 mμ. The ratio of the extinctions at 268 mμ and 355 mμ is 1.28; at 255 mμ and 268 mμ, 0.84 (no epimerization[12]). Tetracycline hydrochloride and base have maxima at the same wave lengths with ratios at 268 mμ and 355 mμ of 1.28 and at 255 mμ and 268 mμ of 0.87.[12] In 0.1*N* sodium hydroxide tetracycline-urea compound has the same ultraviolet spectra as tetracycline hydrochloride, with maxima at 248 mμ, 268 mμ, 290 mμ (shoulder), and 380 mμ, and minima at 228 mμ, 255 mμ, and 323 mμ.

Infrared spectra of tetracycline urea trihydrate in potassium bromide disks indicate bands at 2.93 μ, 3.35 μ, 5.77 μ, 6.00 μ, 6.20 μ, 6.55 μ, 6.87 μ, etc.

Moisture determinations on the tetracycline-urea trihydrate preparations cannot be made by hot air drying and loss of weight determination as the tetracycline-urea compounds char easily on heating above 100°. Karl Fischer determinations have generally given higher results than the calculated. Urea determinations by a urease digestion have given slightly higher results than the calculated, mainly due to varying blank determinations.

Isolation of tetracycline as tetracycline-urea monohydrate. Two liters of a *S. aureofaciens* fermentation broth containing tetracycline as the main antibiotic was acidified with 25% sulfuric acid to *p*H 1.8 and filtered with 200 g. of Hyflo filter-aid. The solids were reslurried with 1.5 l. of warm water (45°) at *p*H 1.85, and refiltered. The combined acid filtrates were treated with 88.2 g. of ammonium oxalate, stirred for 30 min. at room temperature, and stored overnight at 4°. The precipitated calcium oxalate was filtered and the cake was washed with 50 ml. of water. To 2.97 l. of aqueous filtrate was added 300 ml. of methyl isobutyl ketone and 15 ml. of 50% cetyltrimethylammonium chloride (Arquad 16)[13] in 2-propanol.

The *p*H was adjusted to *p*H 8.8 with 23 ml. of 18*N* sodium hydroxide solution, and the mixture stirred for 20 min., at which time the phases were separated. The aqueous phase was re-extracted with 100 ml. of methylisobutyl ketone with 5 ml. of Arquad 16 at *p*H 8.8. The combined organic extracts were washed twice with 40 ml. of water.

To 200 ml. of the methyl isobutyl ketone extract containing 40,000 μg./ml. of antibiotic activity was added 32 ml. of a saturated aqueous urea solution and 32 ml. of water.

(13) Arquad 16 is predominantly cetyltrimethylammonium chloride; obtained from Armour Chemical Division, Armour and Co., Chicago, Ill.

Hydrochloric acid was added to bring the *p*H to 5.5. The mixture was shaken on a rotary shaker for 16 hr., at which time the *p*H was adjusted to 3.0 with HCl, and the mixture was agitated for an additional 48 hr. The product accumulated as a precipitate in the aqueous phase, and was filtered without phase separation. The tetracycline-urea compound was dried *in vacuo* at 50°, weight 7.80 g. (90% from organic extract), assay 938 μg./mg. as tetracycline hydrochloride.

Anal. Calcd. for $C_{23}H_{30}N_4O_{10}$: C, 52.80; H, 5.75; N, 10.72. Found: C, 52.85; H, 5.68; N, 10.70.

Determination of solubilities. An unweighed portion of the tetracycline derivative was suspended in the solvent and placed on a rotary shaker for two hours at room temperature, the undissolved material filtered, and the filtrate assayed spectrophotometrically.

Determination of distribution coefficients. Samples were dissolved in *p*H 2.5/0.25*M* sodium dihydrogen phosphate buffer (previously equilibrated against the organic phase) at a final concentration of 50 μg./ml. and equilibrated with a mixture of 80% chloroform-20% butanol (10 ml. of each phase). Each phase was assayed spectrophotometrically after thirty inversions. The distribution coefficient for tetracycline urea compound was 0.14 (organic phase/aqueous phase), for tetracycline base, 0.13.

Fractionation of mixtures of tetracycline and 7-chlorotetracycline. Mixtures containing 7-chlorotetracycline neutral and tetracycline neutral were prepared, and 5.0 g. of the crystal mixture was slurried in 100 ml. of saturated aqueous urea solution. After one hour of shaking the undissolved material was filtered and analyzed.

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PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Preparation of α-Hydroxyguanamines from Cyanohydrins

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Lactonitrile, a typical cyanohydrin, was not stable in an attempted base-catalyzed condensation with dicyandiamide to an α-hydroxyguanamine. The acid-catalyzed condensation of cyanohydrins with vinyl ethers gave α-cyanoacetals, I, which were stable in this condensation. Acid-catalyzed hydrolysis of the resulting diaminotriazines, II, gave the desired α-hydroxyguanamines, III (2,4-diamino-*s*-triazine-6-alkanols). A homologous formal, 2,4-diamino-6-ethoxymethoxymethyl-*s*-triazine, was either recovered quantitatively or converted to resins under comparable conditions.

The base-catalyzed reaction of dicyandiamide with nitriles[1] is usually one of the best methods of synthesizing guanamines (2,4-diamino-6-alkyl-*s*-triazines). However, when a cyanohydrin, such as lactonitrile, was used in the method, no hydroxyguanamine was obtained. It was probable that reversion of the cyanohydrin to the aldehyde and HCN occurred with subsequent base-catalyzed polymerization reactions.

The desired α-hydroxyguanamines[2] (III) were therefore prepared by a sequence of reactions (Fig. 1) involving in the first step the stabilization of the cyanohydrins to basic conditions, in the form of their addition products to various vinyl ethers. The convenience and high yields of this reaction sequence provide a practical and general synthesis for this series of compounds. It is illustrated in the accompanying table and in the experimental section for cyanohydrins from three aldehydes (formaldehyde, acetaldehyde, and benzaldehyde) and two ketones (acetone and cyclohexanone). The only previous synthesis (for lactoguanamine)[3] was from a corresponding α-hydroxy-

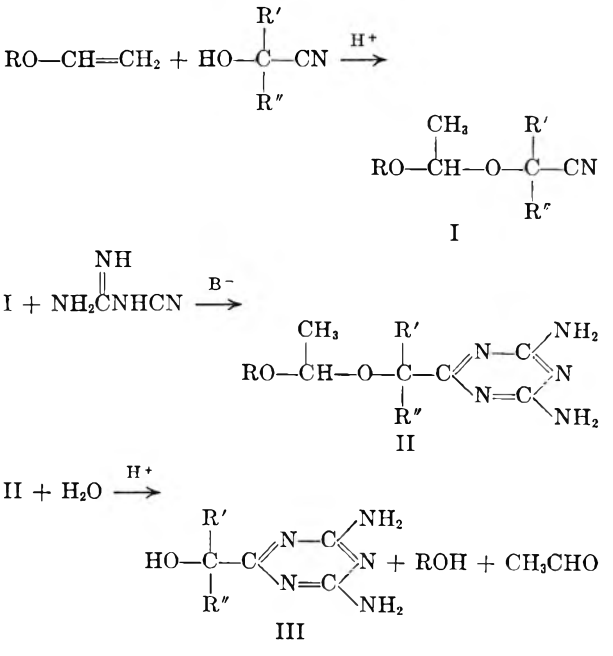


Figure 1

(1) (a) W. Zerweck and W. Brunner, U. S. Patent 2,302,163; *Chem. Abstr.*, 37, 2016 (1943); (b) J. K. Simons, U. S. Patent 2,532,519; *Chem. Abstr.*, 45, 3429 (1951).

(2) The non-systematic term "guanamine" will be used in the discussion section. Compounds III are named after the corresponding hydroxyacids, thus: glycologuanamine (R, = R′ = H), α-hydroxyisobutyroguanamine (R′ = R″ = CH_3), etc.

(3) J. T. Thurston, U. S. Patent 2,394,526 (1946); *Chem. Abstr.*, 40, 5776 (1946).

TABLE I

CYANOACETALS (I)

Compound	R	R′	R″	Yield, %	B.P., °C.	Mm.	n_D^{25}	Empirical Formula	% N Calcd.	% N Found
Ia	*n*-C_4H_9	H	H	91	52–56	1.0	1.4147	$C_8H_{15}NO_2$	8.9	9.1
Ib	C_2H_5	CH_3	H	76	64–70	13	—	$C_7H_{13}NO_2$	9.8	10.1
Ic	*n*-C_4H_9	CH_3	H	74	90–94	17	1.4070	$C_9H_{17}NO_2$	8.2	8.2
Id	C_2H_5	CH_3	CH_3	77	69–71	14	1.4070	$C_8H_{15}NO_2$	8.9	9.2
Ie	*n*-C_4H_9	CH_3	CH_3	76	97–103	18	1.4135	$C_{10}H_{19}NO_2$	7.6	7.6
If	C_2H_5	—$(CH_2)_5$—	[a]	87	70–75	0.9	1.4470	$C_{11}H_{19}NO_2$	7.1	7.3
Ig	C_2H_5	C_6H_5	H	72	Not distilled[b]			$C_{12}H_{15}NO_2$	10.5	9.7[b]

[a] Derived from cyclohexanone. [b] Stripped at 40° at 20 mm. to remove low-boiling components.

TABLE II

α-(ALKOXYETHOXY)GUANAMINES (II)

Compound	R	R′	R″	Yield, %	M.P., °C.	Empirical Formula	% N Calcd.	% N Found
IIa	*n*-C_4H_9	H	H	85	153	$C_{10}H_{19}N_5O_2$	29.0	28.9
IIb	C_2H_5	CH_3	H	66	169–172	$C_9H_{17}N_5O_2$	30.8	30.8
IIc	*n*-C_4H_9	CH_3	H	71	165–169	$C_{11}H_{21}N_5O_2$	27.4	27.4
IId	C_2H_5	CH_3	CH_3	86	170	$C_{10}H_{19}N_5O_2$	29.0	29.0
IIe	*n*-C_4H_9	CH_3	CH_3	78	130–132	$C_{12}H_{23}N_5O_2$	26.0	25.6
IIf	C_2H_5	—$(CH_2)_5$—	[a]	85	220–222	$C_{13}H_{23}N_5O_2$	24.9	24.8
IIg	C_2H_5	C_6H_5	H	74	189–192	$C_{14}H_{19}N_5O_2$	24.2	24.5

[a] Derived from cyclohexanone.

TABLE III

α-HYDROXYGUANAMINES (III)

Compound	R′	R″	Yield, %	M.P., °C.	Empirical Formula	% N Calcd.	% N Found
IIIa	H	H	93	286–288	$C_4H_7N_5O$	49.6	48.9
IIIb	CH_3	H	76	254[a]	$C_4H_9N_5O$	45.2	45.0
IIIc	CH_3	CH_3	97	165–167	$C_6H_{11}N_5O$	41.4	40.8
IIId	—$(CH_2)_5$—	[b]	91	209	$C_9H_{15}N_5O$	33.5	33.3
IIIe	C_6H_5	H	91	182–190	$C_{10}H_{11}N_5O$	31.0	30.7

[a] Yield of crude product, m.p. 226–230°, was 98%. The product was recrystallized from water. Reported m.p.[3] is 254°. [b] Derived from cyclohexanone.

ester and biguanide, two reagents which are usually difficult to obtain.

The preparation of α-cyanoacetals (I) from cyanohydrins and vinyl ethers has been reported.[4] All of them obtained in our work (Table I) were distillable liquids with the exception of Ig prepared from benzaldehyde and ethyl vinyl ether (1-α-cyanobenzyloxy-1-ethoxyethane). When the compounds I were refluxed in alcohol solution with dicyandiamide and potassium hydroxide, and the reaction mixture was cooled, the α-(alkoxyethoxy)-guanamines (II, Table II) precipitated. Undistilled I could be used, although the presence of cyanohydrin in it caused the reaction mixture to become quite dark. This color, probably due to HCN polymer, was easily removed from the solid products by washing them with water.

The hydrolysis of the guanamine acetals (II) to the α-hydroxyguanamines (III, Table III) occurred in very dilute acid solutions. For example, an aqueous suspension of 2,4-diamino-6-(1-*n*-butoxyethoxymethyl)-*s*-triazine (IIa) was hydrolyzed to glycologuanamine in one hour in the presence of 2 mole % of hydrochloric acid. In most experiments, an equivalent of acid was added. This helped to dissolve II, as their hydrochlorides, particularly in the case of the higher members of the series. The α-hydroxyguanamines were easily recovered by adding an equivalent of base.

The successful hydrolysis of II and isolation of III in the presence of the basic diaminotriazine ring apparently depends substantially on the assistance provided by the methyl group on the central acetal carbon atom to the formation of intermediate carbonium ions.[5] The homologous formal, 2,4-diamino-6-ethoxymethoxymethyl-*s*-triazine[6] (IV), was prepared from ethoxymethoxyacetonitrile.

(4) B. Tchoubar, *Compt. rend.*, **237**, 1006 (1953).

(5) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 244.

(6) W. F. Gresham, U. S. Patent 2,491,658; *Chem. Abstr.*, 44, 3538 (1950).

$C_4H_9OCHOCH_2Tr$ (CH$_3$ above) $C_2H_5OCH_2OCH_2Tr$

IIa IV

(Tr = diaminotriazine residue)

Unlike IIa under similar conditions, IV was recovered in quantitative amounts from an attempted hydrolysis in the presence of 2 mole % of hydrochloric acid. In the presence of an equivalent of hydrochloric acid, a gummy solid was obtained in low yield. It had a wide melting range and was resinous in character. It was assumed to be the product of the reaction of glycologuanamine with formaldehyde split out in the hydrolysis, since this reaction is commonly used in the preparation of guanamine aminoplast resins. The choice of the vinyl ether reaction to protect the cyanohydrin was therefore a fortunate one.

The α-hydroxyguanamines display the customary reactions of the diamino-*s*-triazines. In particular, they can be used as the raw materials for a series of resins, based on their reaction with formaldehyde.[3]

EXPERIMENTAL

Acetone cyanohydrin and lactonitrile were commercial products, freshly distilled before use. The commercial 70% aqueous solution of glycolonitrile was stripped using a water aspirator, until removal of water was substantially complete. Mandelonitrile[7] and cyclohexanone cyanohydrin[8] were prepared by the base-catalyzed reaction of HCN with benzaldehyde and cyclohexanone, respectively. The preparative steps were fairly uniform, and will be illustrated below with several examples of each.

Cyanoacetals, I: 1-n-butoxy-1-(cyanomethoxy)ethane (Ia). Commercial (70%) glycolonitrile (81.5 g., 1 mole) was heated on a steam bath at 20 mm. vacuum until the water was substantially removed. To the hot concentrate was added *n*-butyl vinyl ether (100 g., 1 mole) over a period of about 2 hr. at 95°. The acid catalyst present in the commercial glycolonitrile was sufficient to bring about the reaction. The crude product was distilled *in vacuo* through a 4-inch Vigreux column to give 143.5 g. (91%) of colorless liquid, b.p. 52–56°/1 mm.

1-(1'-Cyanocyclohexoxy)-1-ethoxyethane (If). Cyclohexanone cyanohydrin (125 g., 1 mole) was acidified with 3 drops of 5% HCl and heated to 50°. Ethyl vinyl ether was then added over a period of 2 hr. at such a rate as to maintain the temperature between 50 and 75° and to avoid undue refluxing of the low-boiling ether. The reaction mixture was then heated at 90° for 2 hr. and finally distilled through a 6-inch Vigreux column *in vacuo*. to give 172 g. (87%) of colorless liquid, b.p. 70–75°/0.9 mm.

α-Alkoxyethoxyguanamines [2,4-diamino-6-(1-alkoxyethoxyalkyl)-s-triazines], II: 2,4-diamino-6-(1-n-butoxyethoxymethyl)-s-triazine (IIa). A mixture was made of 1-butoxy-1-(cyanomethoxy)ethane, Ia (157 g., 1 mole), dicyandiamide (106 g., 1.25 mole) and isopropyl alcohol (400 ml.). The mixture was brought to reflux and to it was added a solution of potassium hydroxide (16.5 g., 0.25 mole) in isopropyl alcohol (300 ml.) dropwise over a period of 1 hr. The mixture was refluxed for a period of 16 hr., cooled in an ice bath, and filtered. The precipitate was slurried twice with 500-ml. portions of hot water. The product was then dried at 70° to yield 204.5 g. (85%), m.p. 148–150°. Drying at 70° *in vacuo* raised the melting point to 153°. This general procedure was used for all preparations.

α-Hydroxyguanamines (2,4-diamino-s-triazine-6-alkanols), III: glycologuanamine (IIIa). A mixture of 2,4-diamino-6-(1-*n*-butoxyethoxymethyl)-*s*-triazine, IIa (12 g., 0.05 mole), 50 ml. of water and 5 ml. of concentrated hydrochloric acid was heated on the steam bath for 2.5 hr. The mixture became clear. A solution of sodium hydroxide (4 g.) in 30 ml. of water was then added, and the mixture was chilled and filtered. The residue (6.5 g., 93%), m.p. 286–288° was recrystallized from water without change in melting point. *2,4-Diamino-6-(1-hydroxycyclohexyl)-s-triazine* (IIId). A mixture of 2,4-diamino-6-[1-(ethoxyethoxy)cyclohexyl]-*s*-triazine, IIf (28.1 g., 0.1 mole), concentrated hydrochloric acid (10.2 g.) and 150 ml. water was heated for 2 hr. on the steam bath. To the resulting hot solution was added a solution of sodium hydroxide (4 g.) in 25 ml. water. The mixture was cooled in an ice bath and filtered and washed with water. After oven drying at 85°, there was obtained 19 g. (91%), m.p. 209°.

Attempted direct preparation of lactoguanamine. A mixture of lactonitrile (14.2 g., 0.2 m.), dicyandiamide (21 g., 0.25 m.) and isopropyl alcohol (75 ml.) was brought to reflux and to it was added a solution of potassium hydroxide (2.8 g., 0.05 m.) in isopropyl alcohol (50 ml.) over a period of 1.5 hr. The mixture was refluxed with stirring for 20 hr. When the resulting dark-brown mixture was cooled to 0° and filtered, only a small amount of recovered dicyandiamide was obtained. No lactoguanamine could be isolated.

2,4-Diamino-6-ethoxymethoxymethyl-s-triazine[9] (IV). To a mixture of ethoxymethoxyacetonitrile[6] (7 g., 0.06 m.), dicyandiamide (6.1 g., 0.07 m.) and isopropyl alcohol (25 ml.) at reflux was added a solution of 85% potassium hydroxide (0.08 g., 0.012 m.) in isopropyl alcohol (15 ml.), over a period of 20 min. The reaction was refluxed for 16 hr., cooled to 0°, and filtered. The crude product was recrystallized from water, using charcoal, to give 7 g. (58%) of slightly tan crystals, m.p. 179–181°. The reported m.p.[6] is 177.5–178.5°.

Comparative experiments on the hydrolysis of 2,4-diamino-6-(1-n-butoxyethoxymethyl)-s-triazine (IIa) *and 2,4-diamino-6-ethoxymethoxymethyl-s-triazine* (IV). Suspensions of 0.005 mole of each guanamine in 10 ml. of 0.01*N* hydrochloric acid were gently refluxed for 1 hr. They were cooled and to them was added one ml. of 0.1*N* sodium hydroxide. They were heated to boiling and immediately cooled in an ice bath. From the reaction of IIa, there was obtained 0.65 g. (93%) of glycologuanamine, m.p. 283–286°. IV was recovered quantitatively.

When the reaction was repeated with IV (0.005 mole) in 10 ml. of 0.1*N* hydrochloric acid, only a small amount of oil separated after the addition of sodium hydroxide. The oil was not identified.

When the reaction was repeated with IV (0.005 mole) and 10% hydrochloric acid (0.0044 mole), there was recovered 0.39 g. of a yellow, resinous solid which melted with decomposition from 190–285°, and which could not be purified by crystallization from hot water in the manner ordinarily successful for glycologuanamine.

PHILADELPHIA, PA.

(7) A. Albert, *Ber.*, 49, 1383 (1916).

(8) A. J. Ultee, *Rec. trav. chim.*, 28, 1 (1909).

(9) The preparation was originally described using piperidine as a catalyst (ref. 6).

[CONTRIBUTION FROM THE LION OIL CO., A DIVISION OF MONSANTO CHEMICAL CO.]

Formylation of Amines

C. W. HUFFMAN[1]

Received December 11, 1957

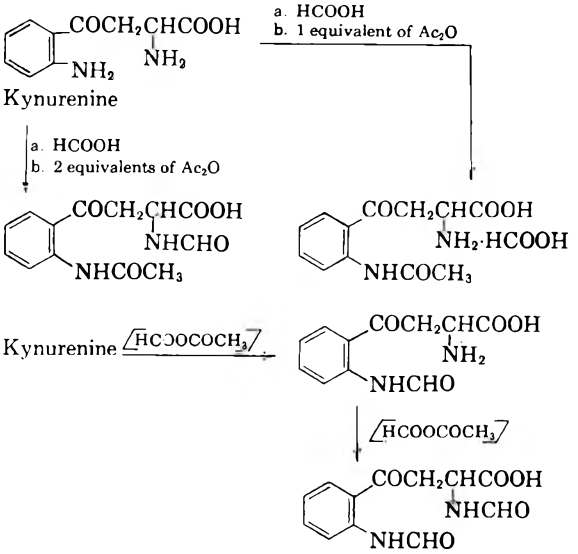
A wide variety of amines were formylated by acetic formic anhydride.

Many procedures have been used to formylate amines, but the range of applicability appears to be limited. Formamido compounds were required for biological testing, so that a general formylation procedure was desired. The results of this research show that acetic formic anhydride is an excellent general reagent for the preparation of formyl derivatives of amines.

A brief summary of the shortcomings of various formylation procedures (particularly as applied to heterocyclic amines in this study) will be of interest. Formamide[2] serves to formylate some aniline derivatives and amines such as benzylamine. It did not give the formyl derivative of 2-amino-5-nitrothiazole. Esters[3] of formic acid gave good results with a number of amines, but sealed tubes or autoclaves are often required. Chloral[4] reacts with many amines to furnish the formamido compound and chloroform. Again, this reagent did not react with 2-amino-5-nitrothiazole. Sometimes chloral gives addition products. For example,[5] 2-aminopyridine and chloral formed the addition compound $C_7H_7Cl_3N_2O$ which sublimed under vacuum (11 mm.) and melted at 106.5°. An odd complex resulted from a reaction between 2-aminoquinoxaline and chloral. This complex decomposed at 176°. It could be crystallized from benzene, but an attempted crystallization from 2-propanol gave the starting 2-aminoquinoxaline (m.p. 154°). Therefore chloral fails to formylate some amines. Formic acid alone formylates varied aniline derivatives such as 3,4-dichloroaniline.[6] Even weakly basic anilines such as 3,5-dinitroaniline[7] gave moderate (50%) yields of the formyl derivative upon reflux with a large excess (8 moles) of formic acid. In some cases, acetic anhydride has been added to a solution of amine in an excess of formic acid. Such a procedure was used to prepare 2-(5-nitrothiazolyl)formamide.[8]

Dalgliesch[9] made a study of the use of mixtures of formic acid and acetic anhydride. Acetylation sometimes occurred rather than formylation. For example, the addition of acetic anhydride to a formic acid solution of anthranilic acid gave the acetyl derivative. Yet these conditions gave the formyl derivative with phenylalanine, phenacylglycine, and tryptophane. His interesting studies with kynurenine are illustrated below.

Formylation and Acetylation of Kynurenine[9]



The simple addition of two equivalents of acetic anhydride to a formic acid solution of kynurenine resulted in the formylation of the aliphatic amino group and the acetylation of the aromatic amino group. Acetic formic anhydride proved to be a better formylation agent. In fact, it was possible to selectively formylate the aromatic amino group by the use of one mole of acetic formic anhydride. A further formylation of aliphatic amino group occurred upon the addition of more acetic formic anhydride. The acetic formic anhydride need not be isolated. Merely allowing a mixture of acetic anhydride and formic acid to warm spontaneously causes the formation of acetic formic anhydride.

(1) Present address: International Minerals and Chemical Corp., Skokie, Ill.

(2) M. Sekiya, *J. Pharm. Soc. Jap.*, **70**, 553 (1950), *Chem. Abstr.*, **45**, 5619h (1951).

(3) J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, **151**, 1457 (1948).

(4) F. F. Blicke and C. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(5) L. Schmid and B. Becker, *Monatsch.* **46**, 675 (1926).

(6) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1241 (1957), do not give the yield or physical constants for 3′,4′-dichloroformanilide.

(7) J. C. Roberts and K. Selby, *J. Chem. Soc.*, **152**, 2788 (1949).

(8) F. C. Copp (to Wellcome Foundation, Ltd.), Brit. Pat. **723,948** (Feb. 16, 1955). *Chem. Abstr.*, **50**, 5036 (1956). This patent was issued after completion of our work and cited a m.p. of 194°.

(9) C. E. Dalgliesch, *J. Chem. Soc.*, **155**, 137 (1952).

TABLE I

FORMAMIDO COMPOUNDS

Compound	Yield, %	M.P., °C.	Crystallized from	Formula	Analysis							
					Calcd.				Found			
					C	H	Cl	N	C	H	Cl	N
2-Quinoxalinoformamide	91	192.5–194 (dec.)	Benzene and ethyl acetate	$C_9H_7N_3O$	62.4	4.07	—	24.3	62.1	3.95	—	24.1
3′,4′-Dichloroformanilide[6]	96	110–112	Benzene and carbon tetrachloride	$C_7H_5Cl_2NO$	44.2	2.65	37.3	7.37	44.4	2.55	37.3	7.17
2-Thiazolylformamide[13]	64	156–161	Benzene	$C_4H_4N_2OS$	37.5	3.14	—	21.9	37.6	3.07	—	20.9
2-(5-Nitrothiazolyl)-formamide[8]	84	192–194	Ethyl acetate	$C_4H_3N_3O_3S$	27.7	1.74	—	—	27.8	1.52	—	—
2-Benzimidazolylformamide	83	260.2–260.8	Dimethylformamide	$C_8H_7N_3O$	59.6	4.38	—	26.0	59.9	4.17	—	25.6
2-Benzothiazolylformamide	94	254.2–256.2 (dec.)	Ethyl acetate	$C_8H_6N_2OS$	53.9	3.39	—	15.7	54.2	3.37	—	15.0

If desired, an excellent[10] preparation of pure acetic formic anhydride can be made from ketene and formic acid. A formylation of 2-amino-3-methylpyridine was accomplished[11] with one mole of acetic formic anhydride in ether. A similar treatment of 2-aminoquinoxaline gave a low yield of crude 2-quinoxalinoformamide which was purified with difficulty. Some of starting 2-aminoquinoxaline was recovered. However, when the quantity of acetic formic anhydride was doubled, an excellent yield (91%) of high purity product was obtained by filtration of the reaction mixture. Evidently, the three basic nitrogen atoms of 2-aminoquinoxaline require that the reaction mixture contain more than a mole of acetic formic anhydride and a mole of acetic acid. It is noteworthy that 2-quinoxalinoformamide and 2-acetamidoquinoxaline[12] have the same melting point (194°). A mixture of the two gave a sharp lowering of the melting point.

The versatility of the acetic formic anhydride formylation procedure is shown by the results given in Table I. All types of amines—especially amines of heterocyclic compounds—gave good yields of the desired formamido derivatives. The experimental section describes the preparation of 2-quinoxalinoformamide as an illustration of the method. In all other cases, an overnight reaction period was satisfactory. Experimental details are given also for 3′,4′-dichloroformanilide because it was the only formyl compound which was soluble in the reaction mixture.

EXPERIMENTAL

Microanalysis by Clark Microanalytical Laboratories, Urbana, Ill. Melting points (uncorrected) were taken with Anschutz thermometers using a Hershberg-type apparatus.

2-Quinoxalinoformamide. The acetic formic anhydride was prepared (but not isolated) by heating acetic anhydride (20.4 ml.) and formic acid (8.6 ml., 98%) for two hours at 50–60° in a flask equipped with a stirrer and drying tube. The solution was cooled to 27°. A gradual addition of 2-aminoquinoxaline (14.6 g., 0.1 mole, Merck) was made over a 15-min. period using a water bath to maintain a temperature below 39°. Some of the 2-aminoquinoxaline dissolved. The reaction mixture was cooled to 30° and ether (50 ml.) was added to the suspension. The mixture was allowed to stir about 60 hr. (no doubt a shorter time would be satisfactory) at room temperature. A filtration removed the product, which was washed with ether (25 ml.). The crude product weighed 15.9 g. (91%). It sintered at 175° and melted at 190–192° (dec.).

A preliminary run with one-half the above quantity of acetic formic anhydride gave a very low yield of 2-quinoxalinoformamide along with recovered 2-aminoquinoxaline.

(10) C. D. Hurd and A. S. Roe, *J. Am. Chem. Soc.*, **61**, 3355 (1939).

(11) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, **148**, 603 (1945).

(12) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, 66, 1958 (1944).

(13) G. Fravagli and O. Barnabei, *Atti. accad. sci. Ferrara*, 29, 133 (1951–52); *Chem. Abstr.*, 48, 807 (1954). No physical constants are given in *Chem. Abstr.*

An analytical sample was obtained by crystallization of the crude material from benzene followed by 3 recrystallizations from ethyl acetate. It softened at 150° and melted at 192.5–194.0°.

A mixed melting point of 2-quinoxalinoformamide and 2-acetamidoquinoxaline (m.p. 192.6–193.8°)[12] showed a sharp depression.

3′,4′-Dichloroformanilide. Acetic formic anhydride was prepared from acetic anhydride (40.8 ml.) and 98% formic acid (17.2 ml.). This mixture was cooled in an ice bath to 12°. A gradual addition of 3,4-dichloroaniline (32.4 g., 0.2 mole) was made so that the temperature did not rise above 40°. The dark red solution was held at room temperature (35°) for five hours after which ether (100 ml.) was added. The following day the dark purple solution was extracted with 2 × 100 ml. of water. The ether layer was evaporated on the steam bath to furnish 36.7 g. (96.5%) of crude material, m.p. 94–103°. A hot benzene (150 ml.) solution of the crude product was treated with Nuchar C. The filtrate was cooled for several hours prior to collecting the product by filtration. A cold benzene wash was applied to the gray solid. The purified 3′,4′-dichloroformanilide weighed 30.4 g. It sintered at 99° and melted at 110–112°. Recrystallization from a large volume of carbon tetrachloride furnished off-white crystals with no change in melting point. The product is soluble in chloroform and cyclohexene but insoluble in petroleum ether or cyclohexane. Possibly a reduction in the quantity of acetic formic anhydride to slightly over one mole would give a satisfactory result for this type of preparation.

SKOKIE, ILL.

[CONTRIBUTION FROM THE RESEARCH CENTER, HERCULES POWDER COMPANY]

Preparation of Ethenesulfonamide[1]

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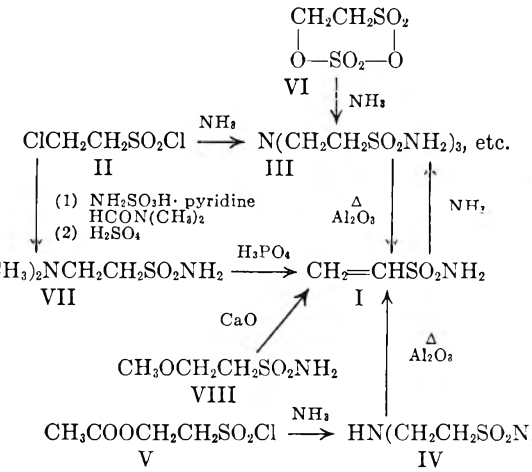
Ethenesulfonamide has been prepared in moderate yields by heating 2-sulfamylethylamines and their salts.

The literature records three different sets of properties for ethenesulfonamide (I).[2–9] None of these are those that would be predicted from the properties of the closely related ethanesulfonamide.[10,11] These discrepancies prompted a reinvestigation of the preparation of I.



Ethenesulfonamide has now been prepared in 53% yield by heating with alumina a mixture obtained by ammonolysis of 2-chloroethanesulfonyl chloride (II). After crystallization from ether it melted at 24° and was soluble in ethanol, water, ethyl acetate, and acetone but insoluble in benzene and hexane. Ammonia added readily to I to form tris(2-sulfamylethyl)amine (III) and thiophenol added to I to form 2-phenylthioethanesulfonamide. No Diels-Alder reaction occurred with anthracene on heating with I at 100° for 72 hr.

The formation of I on heating is believed to occur by elimination of ammonia from the mixture of 2-sulfamylethylamines obtained by ammonolysis of II.[12] The preparation of I (in 35% yield) from bis-(2-sulfamylethyl)amine (IV) under the same conditions lends support to this view. Heating the hydrochloride of IV also gave I in 30% yield. The sample of IV used was prepared by ammonolysis of 2-acetoxyethanesulfonyl chloride (V).

Another source of mixtures containing 2-sulfamylethylamines was the reaction of ammonia

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(1) Presented in part at the Delaware Chemical Symposium, University of Delaware, February 19, 1955.

(2) J. W. James, *J. prakt. Chem.*, **34**, 348 (1886).

(3) E. P. Kohler, *Am. Chem. J.*, **19**, 744 (1897).

(4) P. W. Clutterbuck and J. B. Cohen, *J. Chem. Soc.*, **121**, 120 (1922).

(5) H. F. Park and R. I. Longley, Jr., U.S. Patent **2,710,-882** (1955).

(6) H. F. Park, U.S. Patent **2,700,055** (1955).

(7) H. F. Park, U.S. Patent **2,715,142** (1955).

(8) H. F. Park, U.S. Patent **2,709,707** (1955).

(9) Two patents report the use but not the preparation or properties of I: V. R. Grassie, U.S. Patent **2,580,351** (1951) and J. B. Dickey and H. W. Coover, U.S. Patent **2,533,207** (1950).

(10) I. Kolker and A. Lapworth, *J. Chem. Soc.*, **127**, 314 (1928).

(11) A. P. N. Franchimont, *Koninkl. Akad. Wetenschap. Amsterdam*, **22**, 285 (1913); *Chem. Zentr.*, **84**, *II*, 1960 (1913).

(12) H. W. Coover and N. H. Shearer, Jr. [U.S. Patent **2,719,178** (1955)] report the preparation of *N,N*-dimethylmethacrylamide by passing its dimethylamine adduct over alumina at 550°.

with carbyl sulfate (VI).[13] Pyrolysis of this mixture with alumina gave a 15% yield of I.

Another 2-sulfamylethylamine, 2-dimethylaminoethanesulfonamide (VII), was obtained unexpectedly (in 31% yield) when II was treated with sulfamic acid in pyridine-dimethylformamide. No I was obtained when the reaction was carried out without the dimethylformamide. That the dimethylamino group and not an unsubstituted amino group was present in the 2 position was shown by formation of a methiodide involving the addition of only one methyl group. Heating the phosphate of VII gave I in 36% yield whereas heating the quaternary hydroxide corresponding to the methiodide gave none at all.

Several other approaches to the preparation of I were examined briefly. Heating 2-methoxyethanesulfonamide (VIII) with calcium oxide apparently gave I in 40% yield but mixed with unchanged starting material from which it could not be readily separated. 1-Chloroethanesulfonamide[14] was not dehydrochlorinated on boiling with pyridine for 5 days. Boiling with quinoline for 3 hr. gave only a tar. When II was treated at −60° with pyridine and one mole of ammonia or with two moles of ammonia, the products resembled those made at higher temperatures.[2] Ammonium carbamate with II at −10 to 0° gave no I.

Sodium[15] and α,α'-azodiisobutyronitrile catalyzed polymerization of I to polymers of low molecular weight.

EXPERIMENTAL[16]

All melting points are corrected. A trace (0.5–1.0%) of *N*-phenyl-2-naphthylamine, as a polymerization inhibitor, was included in all distillations of I. The yields given have been determined by quantitative hydrogenation in aqueous solution with palladium-charcoal catalyst and are believed to be accurate to ±3%. In several instances yields of I were also determined by isolation of its thiophenol adduct, a typical procedure being given under the heating of bis(2-sulfamylethyl)amine.

Ethenesulfonamide (I) *from 2-chloroethanesulfonyl chloride* (II). Ammonia was passed into a stirred solution of II (15.5 g.) in dioxane (150 ml.) at 10° until no further solid precipitated. The ice bath was removed and the passage of ammonia continued while the mixture warmed up to room temperature. The solid, after removal by filtration, was extracted with hot dimethylformamide. The combination of filtrate and extract was taken to dryness *in vacuo* leaving a 12.7-g. residue. A 6.7-g. portion was ground in a mortar with alumina (10 g.), then heated in a small distilling flask at 0.1 mm. with a free flame until no more liquid distilled, alumina frequently being carried over with the distillate. The residue from an acetone extract of the material in the condenser and receiver (3.5 g.) absorbed 1.23% of its weight of hydrogen (theory 1.87%). Redistillation gave 2.8 g., b.p. 114° at 0.1 mm., which absorbed 1.51% hydrogen. The samples then were 66% and 81% pure, respectively, the yield of ethenesulfonamide being 53% (based on the unsaturation in the initial product). The product was taken up in a small amount of ether, cooled to −10°, and seeded; seed crystals being obtained by cooling the 81% pure sample in Dry Ice. The crystals were removed by filtration in a cold room at 0–3°. After two more crystallizations large colorless prisms, m.p. 24°, were obtained. A fourth crystallization (giving 1.0 g.) did not raise the melting point.

Anal. Calcd. for $C_2H_5NO_2S$: C, 22.42; H, 4.70; N, 13.08; hydrogen uptake, 1.87. Found: C, 22.52; H, 4.75; N, 13.5; hydrogen uptake, 1.85.

Derivatives of ethenesulfonamide (I). I (1.00 g.) was dissolved in water (2 ml.) containing ammonia (0.053 g.). After standing overnight at room temperature it was taken to dryness. The residue of tris(2-sulfamylethyl)amine (III) was crystallized from aqueous ethanol and then twice from acetone-water-ether to give crystals melting at 182°.

Anal. Calcd. for $C_6H_{18}N_4O_6S_3$: C, 21.29; H, 5.36; N, 16.56. Found: C, 21.38; H, 4.92; N, 16.74.

The addition of two drops of Triton B (25% methanolic solution) to a solution of I (0.50 g.) and thiophenol (0.51 g.) in dioxane (10 ml.) produced a mildly exothermic reaction. After standing 3 days at room temperature the mixture was neutralized with acetic acid and the solvent removed *in vacuo*. After three crystallizations from ethyl acetate the thiophenol adduct (colorless plates) melted at 109–110°.

Anal. Calcd. for $C_8H_{11}NO_2S_2$: C, 44.21; H, 5.10; N, 6.45. Found: C, 44.09; H, 5.01; N, 6.62.

Preparation and heating of bis(2-sulfamylethyl)amine (IV) *and its salts.* 2-Acetoxyethanesulfonylchloride[17] (247 g.) was added dropwise to concentrated aqueous ammonia (1 liter) cooled in an ice bath. After standing at 25° for 3 days it was evaporated to dryness *in vacuo*. The residue was extracted successively with chloroform, absolute ethanol, and dimethylformamide. Removal of solvent from the last extract followed by crystallization from aqueous ethanol gave a material, 27 g. (8%), m.p. 160°, which was apparently a hydrate of bis(2-sulfamylethyl)amine. A second crystallization raised the melting point to 179.0–179.5°. It was analyzed as the hydrochloride, m.p. 177°.

Anal. Calcd. for $C_4H_{14}ClN_3O_4S$: C, 17.94; H, 5.27; N, 15.69. Found: C, 18.23; H, 5.25; N, 15.32.

Heating the hydrate of IV (2.0 g.) with alumina (3.0 g.) (as described in the preparation of I from II) gave a liquid (0.8 g.) which after redistillation (0.7 g.) absorbed 1.69% hydrogen, corresponding to ethenesulfonamide of 90% purity, a yield of 35%. A portion (0.52 g.) was treated with thiophenol to give the adduct (first crop 1.51 g., m.p. 106–108°, after two crystallizations from ethyl acetate, 109–110°; second crop, 0.53 g., m.p. 97–101°). This showed the product to be about 85% ethenesulfonamide.

Heating the hydrochloride (0.76 g., at 0.1 mm.) gave a liquid (0.39 g.) which after redistillation (0.21 g.) absorbed 1.68% hydrogen, corresponding to 90% purity. The isolation of the thiophenol adduct indicated 78% purity. Based on hydrogenation the yield of ethenesulfonamide was 30%.

Ethenesulfonamide (I) *from carbyl sulfate* (VI). VI[18] (23 g.) was added in small portions to liquid ammonia (150 ml.) cooled in Dry Ice. The excess ammonia was removed with a water aspirator before the mixture warmed to room temperature. A sample of the product (2.7 g.) was dissolved in a solution of sodium carbonate (2.0 g.) in water. After standing overnight at room temperature it was taken to dryness *in vacuo* and the residue extracted with acetone in a Soxhlet extractor. The residue left after removing the solvent from the extract (0.61 g.) was crystallized three times from ace-

(13) Although it is not possible to stop the reaction with ammonia at I, reaction with aniline gives good yields of the unsaturated sulfonanilide; F. Ebel, U.S. Patent 2,666,788 (1954).

(14) R. L. Shriner and A. H. Land, *J. Org. Chem.*, 6, 888 (1941).

(15) D. S. Breslow, G. E. Hulse, and A. S. Matlack, *J. Am. Chem. Soc.*, 79, 3760 (1957).

(16) Analyses were carried out by the Analytical Division of the Hercules Research Center.

(17) R. Anschutz, *Ann.*, 415, 97 (1918).

(18) D. S. Breslow and R. R. Hough, *J. Am. Chem. Soc.*, 79, 5000 (1957).

tone-water-ether to give crystals melting at 182–183°. A mixed melting point with authentic tris(2-sulfamylethyl)-amine showed no depression.

A second sample of the carbyl sulfate–ammonia product (5.3 g.) was heated with alumina (6 g.) (as described under the preparation of I from II) to give 0.67 g. liquid which on redistillation gave 0.53 g. that was 71% ethenesulfonamide as indicated by isolation of the thiophenol adduct, corresponding to a 15% yield of I.

2-Dimethylaminoethanesulfonamide (VII). A solution of II[19] (60 g.) in dimethylformamide (200 ml.) was added dropwise at 25° to a stirred suspension prepared by adding pyridine (100 ml.) to sulfamic acid (35.7 g.) in dimethylformamide (750 ml.). After standing overnight the solvent was removed *in vacuo*. The residue was treated with aqueous sodium carbonate and again evaporated to dryness. Evaporation of a methanol extract of this residue left a viscous liquid (85 g.). Sulfuric acid (19 g.) in water (500 ml.) was allowed to stand with 57 g. of it for 4 hr. at 25°, then the solution was neutralized with sodium carbonate and evaporated to dryness. This residue was extracted repeatedly with acetone. The hydrolysis procedure was now repeated on the residue with sulfuric acid (10 g.). The combined acetone extracts were evaporated to dryness and the residue crystallized from benzene to give 2-dimethylaminoethanesulfonamide (11.6 g., m.p. 94.5–96.5°, 31%). Colorless plates, m.p. 95.5–97.0°, were obtained by recrystallization from benzene.

Anal. Calcd. for $C_4H_{12}N_2O_2S$: C, 31.56; H, 7.94; N, 18.41. Found: C, 31.51; H, 7.78; N, 18.31.

The hydrochloride was prepared by dissolving the compound in a slight excess of 1*N* hydrochloric acid followed by evaporation to dryness under reduced pressure. Two recrystallizations from 95% ethanol gave a colorless solid melting at 177.5–178.5°.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2S$: C, 25.46; H, 6.94; N, 14.85. Found: C, 25.68; H, 6.95; N, 14.68.

VII was converted to its methiodide by heating under reflux overnight with excess iodomethane. The product (m.p. 190.0–193.0°, 100% yield) was removed by filtration. After two recrystallizations from aqueous ethanol it melted at 196.5–197.0°.

Anal. Calcd. for $C_6H_{15}IN_2O_2S$: C, 20.41; H, 5.14. Found: C, 20.47; H, 5.36.

VII (1.03 g.) was treated with phosphoric acid (0.27 g. in 3 ml. of water). The residue from evaporation gave on heating at 0.1 mm. a liquid (0.63 g.) which contained 41% ethenesulfonamide, determined by isolation of the thiophenol adduct, a 36% yield.

2-Methoxyethanesulfonamide (IX). Sodium isethionate (1000 g.) was converted to sodium 2-bromoethanesulfonate by the method of Rumpf.[20] The product (1134 g.) was heated for 18 hr. with a boiling solution of sodium (80 g.) in methanol, then the sodium bromide removed by hot filtration. The solvent was removed and the residue taken up in phosphorus oxychloride. Phosphorus pentachloride (1450 g.) was added in portions with cooling. After completion of the addition, the mixture was heated for 2 hr. at 100°. The cooled mixture was extracted with dry ether and the extract distilled to give 354 g. (42%) of the sulfonyl chloride, b.p. 100–105° at 18 mm. Ammonia was passed into a chloroform solution of the product at 5–10° until no further formation of precipitate occurred. After removal of the chloroform by distillation, the product was separated from most of the ammonium chloride by extraction with dimethylformamide. Two distillations gave the sulfonamide (169 g.), b.p. 135° at 0.3 mm., 55% yield, based on the sulfonyl chloride.

Anal. Calcd. for $C_3H_9NO_3S$: S, 23.0. Found: S, 23.2.

This sulfonamide (10.4 g.) was dropped through 15 cm. of 6-mesh calcium oxide (topped with 0.5 cm. of glass beads) at 270° (0.3 mm.) over a period of 65 min. The acetone-soluble portion of the product (5.0 g.) was distilled to give a light yellow oil (4.0 g.), b.p. 118° at 0.06 mm. It contained 11.8% nitrogen (theory for ethenesulfonamide 13.1%, for 2-methoxyethanesulfonamide 10.1%) and took up 0.89% hydrogen (theory for ethenesulfonamide 1.87%). It gave solid adducts with both ammonia and 2,2′-thiodiethanethiol[21] (with Triton B). These facts suggest the production of ethenesulfonamide in 40% yield (based on material actually consumed in the reaction). At lower temperatures no demethanolation occurred; at higher temperatures tar formation predominated. Increased contact time gave a greater degree of unsaturation (up to 78%) at the expense of yield of pyrolyzate. The substitution of alumina for calcium oxide gave similar results.

Polymerization of ethenesulfonamide (I). A solution of α,α'-azodiisobutyronitrile (0.01 g.) in I (1.00 g.) was covered with nitrogen and heated overnight at 60°. The product was soluble in hot water (but insoluble in cold) and insoluble in acetone and ethyl acetate. It was triturated with acetone, taken up in dimethylformamide, and precipitated by pouring into acetone. The brittle solid (0.3 g., after drying) did not melt on ignition. A 1% solution in dimethylformamide had a specific viscosity of 0.172.

Acknowledgment. The author is indebted to Dr. G. E. Hulse for many helpful suggestions during the course of this work.

WILMINGTON, DEL.

(19) A. A. Goldberg, *J. Chem. Soc.*, 464 (1945).

(20) P. Rumpf, *Bull. soc. chim.*, [5], 5, 879 (1938).

(21) J. Harley-Mason, *J. Chem. Soc.*, 146 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE AND THE BIOMEDICAL RESEARCH GROUP, LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

1,3,5-Triaryl-2-pyrazolines for Use as Scintillation Solutes

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A series of new 1,3,5-triaryl-2-pyrazolines has been synthesized for evaluation as solutes in liquid scintillation counting systems. These compounds were formed in good yields by reaction between the appropriate chalcone and arylhydrazine in glacial acetic acid at water bath temperatures. The ultraviolet and infrared spectra of these 2-pyrazolines have been analyzed. The chalcones necessary for the formation of the 1,3,5-triaryl-2-pyrazolines were formed by condensing aryl methyl ketones and aromatic aldehydes in alcohol at room temperature using alkoxide catalysis. In some cases the product isolated from such reaction mixtures was a 1,3,5-triaryl-1,5-pentanedione resulting from a Michael addition of the methyl ketone to the expected chalcone. The ultraviolet and infrared spectra of the chalcones are shown to be consistent with the *trans* configuration. The new 2-pyrazolines and some which were previously known were evaluated as solutes in liquid scintillation counting systems. The ability of this type of molecule to function as an efficient scintillator is related to aryl substitution at sites one and three and bears no resemblance to molecular types now in use.

Previous endeavors in the synthesis and evaluation of organic solutes for liquid scintillation counters have been concerned with ring systems such as terphenyl and diphenyloxazole which possess continuous conjugation.[4-13] At this time we wish to report upon the synthesis and characterization of a variety of new 1,3,5-triaryl-2-pyrazolines and the evaluation of these compounds and some previously known pyrazolines as solutes in conventional liquid scintillation counting systems.[14,15] These compounds are extremely interesting because they show considerable relative pulse height as indicated by the scintillation data in Table VI; are sufficiently soluble for practical use; and they are not appreciably self-quenching. These pyrazolines are of considerable theoretical importance because they represent the first significant departure from the usual planar, linearly conjugated systems encountered in organic scintillation solutes.

Pyrazolines are available by many synthetic approaches; however, 1,3,5-triaryl-2-pyrazolines are most conveniently available by condensation of the appropriate arylhydrazine with an α,β-unsaturated ketone homologous with chalcone (II) under acidic conditions. The generally accepted interpretation of this reaction involves the initial formation of an arylhydrazone (III) with subsequent attack of nitrogen upon the carbon-carbon double bond. Condensations involving similar systems have been run in alcoholic hydrochloric acid;[16] however, we have found that the operation is best carried out by heating equimolar quantities of the two reactants in an excess of glacial acetic acid for several hours on a steam bath. At the end of this time the product has usually begun to precipitate. The yields obtained using this procedure vary from 59% to 99% as shown in Table I.

In addition to forming pyrazolines by the method outlined above we have also observed their formation in the reaction of several 1,3,5-triaryl-1,5-pentanediones with phenylhydrazine. This preparation of triarylpyrazolines by elimination is similar to the formation of this ring system from Mannich bases[17] and β-aroyl ethanols.[18] In view of the known reversibility of Michael addition reactions it is quite probable that the formation of pyrazolines from these ketones involves a regression. In this reaction sequence the equilibrium between the triarylpentanedione and the chalcone is displaced by the formation of pyrazoline from the chalcone.

Previous studies on the ultraviolet spectra of pyrazolines have shown that when there is no substituent at position one the spectrum consists of

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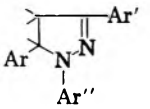
TABLE I

NEW PYRAZOLINES



Ar''	Ar'	Ar	M.P., °C.	Yield,[a] %	Analysis Nitrogen Calcd.	Found
p-Biphenyl	Phenyl	*p*-Biphenyl	181–183	70, B/E	6.22	6.19
p-Biphenyl	Phenyl	Phenyl	178–178.5	73, B/E	7.48	7.45
p-Biphenyl	Phenyl	*p*-Methoxyphenyl	150–151	65, E	6.93	7.14
Phenyl	Phenyl	9-Anthryl	231–233	75, B	7.03	7.25
Phenyl	Phenyl	*p*-Biphenyl	168–169	59, T	7.48	7.70
Phenyl	2-Naphthyl	*p*-Biphenyl	231–233	61, T	6.60	6.66
Phenyl	*p*-Biphenyl	*p*-Methoxyphenyl	185	68, A	—	—[b]
Phenyl	*p*-Biphenyl	3,4-Diethoxyphenyl	165–167	76, E	6.06	5.96
Phenyl	*p*-Biphenyl	*p*-Isopropylphenyl	165.5–167	55, E	6.73	6.58
Phenyl	*p*-Biphenyl	1-Naphthyl	210	65, T/G	6.60	6.48
Phenyl	*p*-Biphenyl	*p*-Diethylaminophenyl	178–179	64, T	9.52	9.53
Phenyl	Phenyl	1-Naphthyl	173–174	[c], E	8.04	7.86
p-Carboxyphenyl	Phenyl	*p*-Methoxyphenyl	213–215	[c], E	7.52	7.25
Phenyl	*p*-Biphenyl	Phenyl	204–206	[c], E	7.48	7.75
Phenyl	*p*-Methoxyphenyl	*p*-Methoxyphenyl	147–148	[c], E	7.82	7.53
Phenyl	Phenyl	*p*-Dimethylaminophenyl	142–143	[c], E	12.31	12.51
Phenyl	*p*-Hydroxyphenyl	Phenyl	129–134	[c], E	8.91	8.60
Phenyl	Phenyl	*p*-Hydroxyphenyl	148.5–149.5	[c], E	8.91	8.95

[a] Recrystallized from A, acetone; B, benzene; E, ethanol; G, glacial acetic acid; T, toluene. [b] *Anal.* Calcd. for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98. Found: C, 83.25; H, 6.08. [c] These compounds were supplied through the generosity of the Tennessee Eastman Co., Kingsport, Tenn.

one maximum at about 240 mμ.[19] When the one position is substituted by a benzene ring a second maximum appears at about 280 mμ. This long wave length band is relatively stable except when a second benzene ring is introduced at position three, in which case the band is shifted to 354 mμ.[20] Our data, as indicated in Table II, show that the introduction of a third phenyl group at position five on the pyrazoline ring causes no alteration in this established spectral pattern. The information in this table indicates that the band at 354 mμ is relatively free of substitution effects, the greatest shifts being due to large extentions of conjugation. In contrast to the relative stability of this band the maxima at 240 mμ is extremely sensitive to substitution on any of the benzene rings. The effects produced by such alteration as noted in Table II do not appear to be predictable.

In addition to the two maxima basic to 1,3,5-triarylpyrazolines certain of these compounds show an additional band at an intermediate or longer wavelength which can be attributed to specific portions of the molecule. Thus, those materials containing *p*-methoxyphenyl substitution show a band in the 285–290 mμ region which is related to the 278-mμ band in anisole.[21] The compounds possessing *p*-dimethylaminophenyl groups show a third maxima in the 310-mμ range that is comparable to the 305-mμ band of *p*-methyl-*N*,*N*-dimethylaniline.[21] A third band also shows up in the spectrum of those compounds having either 1-naphthyl or 2-naphthyl groups on the pyrazoline ring. This band is in the 268–282 mμ region and represents the variable 270 mμ-band of the methylnaphthylenes. Similarly the 365-mμ frequency of 9-methylanthracene is found at 368 mμ in 1,3-diphenyl-5-(9-anthryl)-2-pyrazoline.

The infrared spectra of the pyrazolines were examined in the region from 6 to 16 μ; the results are recorded in Table II. Possibly the most interesting portion of the spectrum is that range around 6 μ where one would anticipate a band due to the conjugated —C=N— as well as the usual —C=C— aromatic stretching vibration. In this region, however, there is only one strong band, and this is at 6.25 to 6.3 μ. The lack of information regarding the effect of salt formation on this band makes it impossible to assign accurately its source; however, due to its strength, its origin is probably in the —C=N— bond and the associated benzene ring. If this explanation is correct the effect of conjugation on the —C=N— band is greater in pyrazolines than in those instances previously studied.[22]

The chalcones from which the 1,3,5-triarylpyrazolines were prepared were synthesized by

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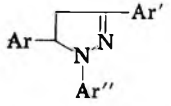
TABLE II

SPECTRAL CHARACTERISTICS OF 1,3,5-TRIARYLPYRAZOLINES



Ar″	Ar′	Ar	Ultraviolet				Infrared				
			λ_{max}[a]	log ε	λ_{max}	log ε	C=N	CH_2	Ar—N	—CH—N	C—H
Phenyl	Phenyl	Phenyl	242	2.24	354	4.28	6.3(vs)	7.2(s)	7.5(m)	9.0(s)	14.4(vs)
Phenyl	Phenyl	*p*-Hydroxyphenyl	229	4.41	358	4.37	6.3(vs)	7.2(s)	7.55(s)	8.9(s)	14.6(vs)
Phenyl	Phenyl	*p*-Methoxyphenyl	229	4.37	357	4.29	6.3(vs)	7.2(s)	7.55(m)	8.9(s)	14.6(vs)
Phenyl	Phenyl	*p*-Dimethylaminophenyl	254	4.42	356	4.27[b]	6.3(s)	7.2(s)	7.5(s)	8.9(s)	14.5(vs)
Phenyl	Phenyl	1-Naphthyl	224	4.92	354	4.27[c]	6.3(vs)	7.3(s)	7.6(s)	9.0(s)	14.5(vs)
Phenyl	Phenyl	*p*-Acetamidophenyl	247	4.49	355	4.27	6.3(vs)	7.2(s)	7.6(s)	8.9(s)	14.6(vs)
Phenyl	Phenyl	*p*-Biphenyl	261	4.00	373	4.46	6.3(vs)	7.2(s)	7.5(m)	8.9(s)	14.6(s)
Phenyl	Phenyl	9-Anthryl	255	5.13	353	4.40[d]	6.3(s)	7.2(s)	7.5(s)	8.9(s)	14.5(s)
Phenyl	*p*-Methoxyphenyl	Phenyl	248	4.23	352	4.33	6.3(vs)	7.2(s)	7.55(s)	9.0(s)	14.5(s)
Phenyl	2-Naphthyl	Phenyl	236	4.58	369	4.36	6.3(vs)	7.1(m)	7.6(m)	8.9(s)	14.3(s)
Phenyl	*p*-Hydroxyphenyl	Phenyl	229	4.41	358	4.37	6.3(vs)	7.2(s)	7.5(m)	9.0(s)	14.4(vs)
Phenyl	*p*-Methoxyphenyl	*p*-Methoxyphenyl	248	4.27	349	4.33	6.3(vs)	7.2(s)	7.6(m)	8.9(m)	14.5(m)
Phenyl	*p*-Biphenyl	Phenyl	262	4.37	372	4.73	—	—	—	—	—
Phenyl	*p*-Biphenyl	*p*-Methoxyphenyl	262	4.43	373	4.49	6.3(vs)	7.2(s)	7.55(m)	9.0(s)	14.6(vs)
Phenyl	*p*-Biphenyl	*p*-Isopropylphenyl	262	4.34	372	4.40	6.3(vs)	7.2(s)	7.5(m)	8.9(s)	14.55(s)
Phenyl	*p*-Biphenyl	*p*-Dimethylaminophenyl	264	4.56	377	4.42	6.3(vs)	7.2(m)	7.5(m)	9.0(s)	14.5(s)
Phenyl	*p*-Biphenyl	1-Naphthyl	225	4.83	374	4.38[e]	6.3(vs)	7.1(s)	7.55(m)	8.9(s)	14.5(vs)
Phenyl	*p*-Biphenyl	*p*-Diethylaminophenyl	264	4.46	345	4.24	6.25(vs)	7.1(m)	7.5(m)	8.8(vs)	14.5(vs)
Phenyl	*p*-Biphenyl	3,4-Diethoxyphenyl	262	4.44	373	4.50	6.3(s)	7.2(s)	7.7(m)	8.9(vs)	14.6(s)
Phenyl	2-Naphthyl	*p*-Biphenyl	241	4.25	367	4.00	6.3(vs)	7.1(s)	7.55(m)	8.9(s)	14.5(vs)
p-Biphenyl	Phenyl	Phenyl	296	4.27	367	4.55	6.3(s)	7.3(m)	7.4(w)	8.9(m)	14.5(vs)
p-Biphenyl	Phenyl	*p*-Methoxyphenyl	228	4.56	369	4.54[f]	6.25(s)	7.2(s)	7.5(m)	9.1(s)	14.5(vs)
p-Biphenyl	Phenyl	*p*-Biphenyl	252	4.45	369	4.43	6.3(vs)	7.1(s)	7.6(w)	8.8(m)	14.6(m)
p-Carboxyphenyl	Phenyl	*p*-Methoxyphenyl	229	4.39	364	4.58[g]	6.3(vs)	7.1(s)	7.6(w)	8.8(m)	14.6(m)
p-Carboxyphenyl	*p*-Methoxyphenyl	*p*-Methoxyphenyl	—	—	361	4.55	6.25(vs)	7.15(s)	7.7(vs)	9.17(m)	14.5(w)

[a] Values are expressed in mμ. [b] λ_{max}, 313 mμ; log ε, 4.00. [c] λ_{max}, 282 mμ; log ε, 4.09. [d] λ_{max}, 368 mμ; log ε, 4.41. [e] λ_{max}, 268 mμ; log ε, 4.34. [f] λ_{max}, 291 mμ; log ε, 4.32. [g] λ_{max}, 285 mμ; log ε, 4.15.

TABLE III

NEW CHALCONES

$$ArCH{=}CH{-}\overset{\overset{O}{\|}}{C}Ar'$$

Ar	Ar'	M.P., °C.	Yield,[a] %	Analysis			
				Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
p-Phenylene	3-bis-1(3′-pyridyl)-acrylyl[c]	233–234	85, E	—	—	—	—[b]
1-Naphthyl	2-Naphthyl	158–160	79, B	89.58	89.40	5.23	5.45
p-Diethylaminophenyl	*p*-Biphenyl	164–165	82, C	84.47	84.41	7.09	6.87
Phenyl	2-Naphthyl	106	98, E	88.34	88.05	5.46	5.52
3,4-Diethoxyphenyl	*p*-Biphenyl	147.5–149	98, E	80.62	80.54	6.50	6.52
1-Naphthyl	*p*-Biphenyl	149	67, A	89.79	89.98	5.43	5.62
p-Dimethylaminophenyl	*p*-Biphenyl	160–163	60, G/W	84.37	83.93	6.47	6.45
9-Anthryl	Phenyl	124–125	76, B	89.58	89.43	5.23	5.20
p-Biphenyl	Phenyl	111.5–112.5	72, E	88.70	88.86	5.67	5.68
p-Biphenyl	2-Naphthyl	141–142	81, B	89.79	89.81	5.43	5.62
p-Biphenyl	*p*-Biphenyl	195–197	80, B	89.97	89.73	5.59	5.67

[a] Recrystallized from A, acetone; B, benzene; C, cellosolve; E, 95% ethanol; G, glacial acetic acid; W, water. [b] *Anal.* Calcd. for $C_{22}H_{16}N_2O_2$: N, 8.23. Found: N, 8.05. [c] The chalcone from terephthalaldehyde and 3-acetopyridine.

TABLE IV

MICHAEL ADDITION PRODUCTS

$$Ar'\overset{\overset{O}{\|}}{C}{-}CH_2{-}\overset{\overset{Ar}{|}}{C}H{-}CH_2{-}\overset{\overset{O}{\|}}{C}Ar'$$

Compound	M.P., °C.	Yield,[a] %	Analysis			
			Carbon		Hydrogen	
			Calcd.	Found	Calcd.	Found
1,5-Di-(*p*-biphenyl)-3-phenyl-1,5-pentanedione	185.5–186.5	93, C	87.47	87.92	5.87	6.36
1,5-Di-(*p*-biphenyl)-3-(*p*-isopropylphenyl)-1,5-pentanedione	210	92.5, C	87.32	86.91	6.56	6.56
1,3,5-Tri-(3-pyridyl)-1,5-pentanedione	145–146	80, E/W	—	—	—	—[b]

[a] Recrystallized from C, cellosolve; E, ethanol; W, water. [b] *Anal.* Calcd. for $C_{20}H_{17}N_3O_2$: N, 12.68. Found: N, 12.56.

condensing the appropriate aromatic aldehyde and methyl ketone in alcohol at room temperature using sodium methoxide catalyst. This type of reaction is generally known to proceed through the sequence outlined in formulas I and II.[23] In those cases outlined in Table III this procedure gave high yields of the desired α,β-unsaturated ketone with no undesirable side reactions. The products precipitated from the reaction mixture in a relatively pure state and were easily recrystallized. In addition to obtaining chalcones from these aldol-type condensations it is likewise possible as shown in formulas II and IV to obtain 1,3,5-triaryl derivatives of 1,5-pentanedione resulting from Michael addition of the methyl ketone across the double bond formed in the initial condensation of aldehyde and ketone. Contrary to a previous report[24] we have observed this to occur in the condensation of benzaldehyde with *p*-phenylacetophenone as well as the other cases presented in Table IV.

The relationship between the ultraviolet spectrum and the possible structures of chalcone has been thoroughly discussed[25,26] as have the ultraviolet spectra of many simple derivatives of chalcone.[27,28] This prior work has shown that the *trans* chalcone structure has two maxima (230 mμ, log ϵ = 3.77; 312 mμ, log ϵ = 4.38) in the ultraviolet that are due to the planar, cross conjugated system as a whole and which generally undergo a bathochromic shift due to electron-donating substituents on either Ar or Ar′. The data in Table V show that for the more complicated structures presented here the two maxima characteristic of *trans* chalcones are usually observed and that electron donor substitution results in bathochromic shifts. The most outstanding example in this series is *p*-dimethylaminophenyl-*p*-phenylacrylophenone which has its long wave length maximum at 425 mμ (log ϵ = 4.53).

(23) E. R. Alexander, *Ionic Organic Reactions*, J. Wiley and Sons, New York, N. Y., 1950, p. 175.

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(27) H. H. Szmant and H. J. Planinsek, *J. Am. Chem. Soc.*, **76**, 1193 (1954).

(28) H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, **74**, 4397 (1952).

TABLE V

SPECTRAL CHARACTERISTICS OF CHALCONES

O
||
ArCH=CH—C—Ar′

Ar	Ar′	Ultraviolet				Infrared				
							Conj.	*Aormatic*		*Trans*
		λ_{max}[a]	log ε	λ_{max}	log ε	C=O	C=C	C=C	C=C	RHC=CHR
3,4-Diethoxyphenyl	Phenyl	259	4.24	357	4.35	6.2(vs)	—	6.3(s)	6.6(m)	10.2(m)
9-Anthryl	Phenyl	252	5.11	369	3.79	6.1(m)	6.18(w)	6.3(vs)	6.6(m-sh)	10.05(s)
p-Phenylene	bis-1-Phenylacrylyl	276	4.15	352	4.71[b]	6.1(s)	—	6.3(vs)	6.6(m-sh)	10.2(vs)
Phenyl	2-Naphthyl	260	4.25	312	4.44[c]	6.1(s)	6.15(w)	6.3(vs)	6.7(m)	10.2(s)
1-Naphthyl	2-Naphthyl	253	4.39	345	3.92[d]	6.1(m)	6.17(w)	6.3(vs)	6.6(m-sh)	10.2(s)
p-Biphenyl	2-Naphthyl	253	4.50	336	4.43	6.1(m)	—	6.3(vs)	6.9(m)	10.3(s)
p-Methoxyphenyl	*p*-Biphenyl	293	4.30	346	4.19[e]	6.1(s)	6.10(w)	6.3(vs)	6.7(m)	10.3(m)
p-Dimethylaminophenyl	*p*-Biphenyl	299	4.30	425	4.53[f]	6.1(m)	—	6.3(vs)	6.6(m)	10.2(m)
1-Naphthyl	*p*-Biphenyl	222	4.76	301	4.36	6.1(s)	—	6.3(vs)	6.7(m)	10.2(m)
p-Diethylaminophenyl	*p*-Biphenyl	283	4.60	390	2.90	6.03(vs)	—	6.3(s)	6.7(m)	10.45(s)
p-Biphenyl	*p*-Biphenyl	305	4.38	328	4.38	6.1(m)	6.15(w)	6.25(s)	6.7(m)	10.2(m)
3,4-Diethoxyphenyl	*p*-Biphenyl	311	4.31	361	4.38	6.1(m)	—	6.3(vs)	6.7(m)	10.3(m)

[a] Values are expressed in mμ. [b] λ_{max}, 229 mμ; log ε, 4.16. [c] λ_{max}, 220 mμ, log ε, 4.71. [d] λ_{max}, 222 mμ; log ε, 4.82; λ_{max}, 288 mμ; log ε, 4.12. [e] λ_{max}, 220 mμ; log ε, 4.19. [f] λ_{max}, 247 mμ; log ε, 4.12.

The infrared spectra of these chalcones show that the carbonyl frequencies at 6.03 μ to 6.2 μ (Table V) are displaced to a significant degree from the values reported for chalcone itself.[29,30] The band due to the conjugated —C=C— bond can be resolved in relatively few cases and then only as a weak shoulder at 6.10 μ to 6.18 μ on either the carbonyl band or the 6.3 μ band associated with the aromatic C=C bond. The two major aromatic C=C frequencies in the 6μ to 7 μ region are among the strongest observed and occur from 6.3 μ to 6.4 μ and 6.7 μ to 6.9 μ. For purposes of structure assignment the most useful portions of these infrared spectra are the 7.6 μ to 7.8 μ and 10.2 μ to 10.4 μ regions where the CH deformation frequencies characteristic of *trans* ethylenes are found. In these compounds the usefulness of the 7 μ region is diminished because the normally weak *trans* ethylenic C—H in-plane deformation frequencies are obscured by the many strong maxima from the aromatic portions of the molecules. The 10-μ region, however, is relatively free of maxima and the *trans* ethylenic C—H out-of-plane deformation frequencies are easily seen. These bands occur as medium to strong maxima from 10.0 μ to 10.45 μ and serve to identify the compounds as *trans* chalcones.

Toluene solutions of the 2-pyrazolines were subjected to conventional scintillation[9] and spectral[31] tests. The results are presented in Table I. The parameters, I_{max} and c_{max}, are the maximum relative light output and the concentration at which this occurred. The spectral quantities, λ_{max} and $\bar{\lambda}$, obtained from corrected fluorescence spectra, are the most probable wave length and the mean wave length.

The 2-pyrazoline ring will function as an inner ring in a scintillation solute molecule when aryl groups are substituted in positions 1 and 3. This bears little similarity to the usual situation in which the central ring is aromatic and substituted in a manner for simultaneous resonance interaction with the substituent groups.

1,3-Diphenyl-2-pyrazoline substituted with a variety of groups in the 5-position yields compounds whose light-producing ability is only slightly inferior to that of 2,5-diphenyloxazole. The pulse height improvement found in polyaryl scintillation solutes by lengthening the chain is not found here. A phenyl substituent is fully as good as a 4-biphenylyl substituent. A small degree of self-quenching is exhibited in this series.

Aryl groups on position 5 have little effect on I_{max} or the spectral parameters. An increase in the complexity of the aromatic systems attached to po-

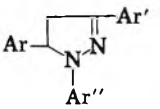
(29) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, New York, N. Y., 1954, p. 119.

(30) H. Hergert and F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

(31) D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Am. Chem. Soc.*, **77**, 5448 (1957).

TABLE VI

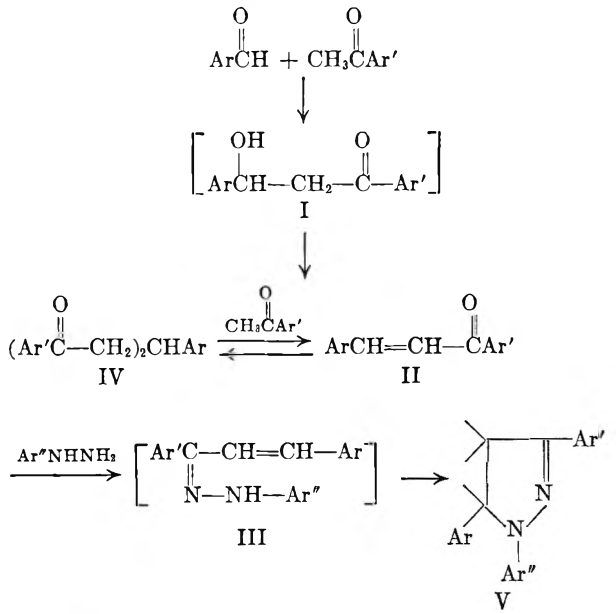
SCINTILLATION AND FLUORESCENCE DATA ON PYRAZOLINES



Solute			Scintillation Data		Fluorescence Spectral Data[a]	
Ar″	Ar′	Ar	I_{max}[b]	c_{max}', g./l.	λ_{max}, mμ	$\bar{\lambda}$, mμ
Phenyl	H	Phenyl	[c]	—	[c]	[c]
Phenyl	Methyl	Phenyl	[c]	—	[c]	[c]
Phenyl	Phenyl	Phenyl	0.88	6.5	440	460
Phenyl	Phenyl	*p*-Hydroxyphenyl	0.74	2.8	440	464
Phenyl	Phenyl	*p*-Methoxyphenyl	0.88	5.5	437	472
Phenyl	Phenyl	*p*-Dimethylaminophenyl	0.83	3.8	448	464
Phenyl	Phenyl	*p*-Acetamidophenyl	0.79	3.1[d]	442	464
Phenyl	Phenyl	1-Naphthyl	0.30	5.8	437	468
Phenyl	Phenyl	*p*-Biphenyl	0.77	4.6	444	464
Phenyl	Phenyl	9-Anthryl	[c]	—	[c]	[c]
Phenyl	*p*-Hydroxyphenyl	Phenyl	0.63	2.3	432	472
Phenyl	*p*-Methoxyphenyl	Phenyl	0.90	5.8	436	440
Phenyl	*p*-Methoxyphenyl	*p*-Methoxyphenyl	0.85	4.9	436	456
Phenyl	2-Naphthyl	Phenyl	0.58	2.0	458	480
Phenyl	2-Naphthyl	*p*-Biphenyl	0.62	1.4[d]	456	476
Phenyl	*p*-Biphenyl	Phenyl	0.86	5.2	458	480
Phenyl	*p*-Biphenyl	*p*-Isopropylphenyl	0.79	6.0	462	482
Phenyl	*p*-Biphenyl	*p*-Methoxyphenyl	0.81	5.3	462	482
Phenyl	*p*-Biphenyl	3,4-Diethoxyphenyl	0.82	5.5	461	484
Phenyl	*p*-Biphenyl	*p*-Dimethylaminophenyl	0.78	5.4	466	484
Phenyl	*p*-Biphenyl	1-Naphthyl	0.78	5.2	460	480
p-Carboxyphenyl	Phenyl	*p*-Methoxyphenyl	0.78	3.0[d]	432	448
p-Carboxyphenyl	*p*-Methoxyphenyl	*p*-Methoxyphenyl	[c]	—	432	452
p-Biphenyl	Phenyl	Phenyl	0.76	5.6	459	476
p-Biphenyl	Phenyl	*p*-Methoxyphenyl	0.64	3.1	458	476
p-Biphenyl	Phenyl	*p*-Biphenyl	0.74	5.4	458	484
5,5′-*p*-Phenylenebis(1,3-diphenyl-2-pyrazoline)			0.09	1.3[d]	446	464

[a] 314 mμ Hg-arc line excitation. [b] Measured relative to 3 g./l. 2,5-diphenyloxazole, as pulse heights[9] with a Ba^{137} electron source, an evaporated aluminum reflector and a photomultiplier having average S-11 spectral characteristics. [c] Response too weak for measurement. [d] Concentration of saturated solution.

sitions 1 and 3 gives larger values of λ_{max} and $\bar{\lambda}$, but does not increase I_{max}.



EXPERIMENTAL[32]

The *p*-phenylacetophenone, substituted benzaldehydes, acetonaphthones, and 9-anthraldehyde were obtained from commercial sources. The 4-biphenylcarboxaldehyde[33] and 4-biphenylhydrazine[34] were prepared by previously described procedures. Typical procedures for the preparation of the various products obtained are given in the following paragraphs. Details of the other preparations are given in Tables I, III, and IV.

4,4′-Diphenylchalcone. A solution of 3.64 g. of 4-biphenylcarboxaldehyde and 3.92 g. of *p*-phenylacetophenone in 130 ml. of 95% ethanol was mixed with 4 ml. of 20% sodium methylate in methanol and allowed to stand for 20 hr. at room temperature. The crystalline precipitate was filtered, washed with 95% ethanol, and recrystallized twice from benzene to give 5.74 g. (80%) of pale yellow crystals, m.p. 195–197°.

Anal. Calcd. for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.81; H, 5.62.

1,5-Di(p-biphenyl)-3-phenyl-2-pyrazoline. A solution of 0.71 g. of 4-phenylchalcone and 0.46 g. of 4-biphenylhydrazine in 15 ml. glacial acetic acid was heated on a water bath at 100° for 2 hr. After 0.5 hr. crystallization commenced and was complete upon standing at room tempera-

(32) Analyses by Micro Tech Laboratories, Skokie, Ill.
(33) D. H. Hey, *J. Chem. Soc.*, 2476 (1931).
(34) H. Müller, *Ber.*, 27, 3105 (1894).

ture for 14 hr. The product was filtered, washed with 95% ethanol, and recrystallized from a mixture of benzene and 95% ethanol to give 0.79 g. (70%) of yellow crystals, m.p. 180–183°.

Anal. Calcd. for $C_{33}H_{26}N_2$: N, 6.22. Found: N, 6.19.

1,5-Di(p-biphenyl)-3-(p-isopropylphenyl)-1,5-pentanedione. A 75% solution of sodium ethoxide in 95% ethanol was added to a mixture of 3.0 g. of *p*-isopropylbenzaldehyde and 4.0 g. of *p*-phenylacetophenone in 75 ml. of 95% ethanol. After standing for 24 hr. the crude product was filtered, washed with water, and recrystallized from Cellosolve to give 4.2 g. (80.6%) of white needles, m.p. 210°.

Anal. Calcd. for $C_{38}H_{34}O_2$: C, 87.32; H, 6.56. Found: C, 86.91; H, 6.56.

1-Phenyl-3-(p-biphenyl)-5-(p-isopropylphenyl)-2-pyrazoline. A solution of 5.0 g. of 1,5-di(*p*-biphenyl)-3-(*p*-isopropylphenyl)-1,5-pentanedione and 1.1 g. of phenylhydrazine in 25 ml. of glacial acetic acid was heated at 80° for 2 hr. After cooling to room temperature the product was filtered, washed with water, and recrystallized once from benzene and twice from 95% ethanol to give 1.2 g. (55%) of yellow plates, m.p. 167°.

Anal. Calcd. for $C_{30}H_{28}N_2$: N, 6.73. Found: N, 6.58.

Ultraviolet and infrared absorption data. The ultraviolet absorption measurements were made with Beckman DU and DK-2 spectrophotometers using 1.00-cm. silica cells and hydrogen discharge light sources. Absolute methanol solutions were used. The infrared spectral measurements were made with a Baird double beam recording spectrometer using potassium bromide pellets.

Acknowledgment. This research was supported in part by the Atomic Energy Commission under Contract No. AT-(40-1)-2162 between the University of Louisville and the Atomic Energy Commission. The authors acknowledge this support and also express their appreciation to the National Science Foundation for Grant NSF-G4074 which provided a recording ultraviolet spectrophotometer.

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

1,1-Diethoxy-3-(triphenylstannyl)-2-propyne

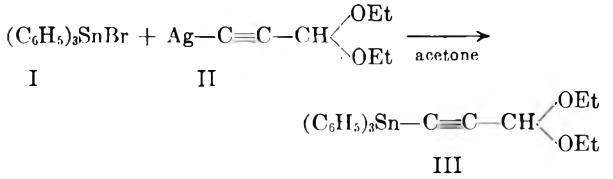
O. H. JOHNSON[1] AND J. R. HOLUM[2]

Received November 7, 1957

The synthesis and properties of an acetylenic tin compound containing a potential aldehyde group are presented.

The only organotin derivatives of acetylene, bis(triphenyltin)acetylene and bis(triethyltin)acetylene, found in the literature were reported by Beermann and Hartmann.[3] These two acetylenic tin compounds were found to have weak tin-carbon bonds. The ethyl derivative slowly hydrolyzed to triethyltin hydroxide and acetylene. Both reacted readily with base forming triorganotin hydroxides and acetylene. Acids also split the tin-carbon bond. In the presence of silver ion or ammoniacal copper(I) ion, silver or copper(I) acetylide formed. Iodine also broke the tin-carbon bond. Ethylmagnesium bromide reacted with bis(triphenyltin)acetylene to form ethyltriphenyltin and acetylenedimagnesium bromide. The stability of both the trialkyl or triaryltin cation and the acetylenic anion contributed greatly to the ease of cleavage of the tin-carbon bonds in these cases.

We have prepared an acetylenic organotin compound containing a potential aldehyde group and have found that the tin-carbon bond wherein the carbon atom is part of an acetylenic linkage is indeed very readily broken. 1,1-Diethoxy-3-(triphenylstannyl)-2-propyne, III, was prepared by the action of the silver salt of propiolaldehyde diethylacetal, II, on triphenyltin bromide, I,



I II III

The structure of 1,1-diethoxy-3-(triphenylstannyl)-2-propyne was assigned primarily on the basis of origin and analytical data. Its infrared spectrum in chloroform did not show absorption in the region 2000-2400 cm^{-1} but this does not rule out the possible existence of a disubstituted acetylene.[4] The chemical behavior indicated a very weak tin-carbon bond. Action of dilute hydrochloric acid (1%) gave triphenyltin chloride. Dilute alkali reacted with 1,1-diethoxy-3-(triphenylstannyl)-2-propyne to give triphenyltin hydroxide. The search for other products was not fruitful. Attempts to prepare a 2,4-dinitrophenylhydrazone of 1,1-diethoxy-3-(triphenylstannyl)-2 propyne by *in situ* hydrolysis of the acetal linkage was unsuccessful and a control experiment with

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF 18(600)-984.

(2) Supported by a Grant-in-Aid of Research from the Graduate School of the University of Minnesota. Present address: Department of Chemistry, Augsburg College, Minneapolis 6, Minnesota.

(3) C. Beermann and H. Hartmann, *Z. anorg. Chem.*, **276**, 20 (1954).

(4) L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1954, pp. 48–53.

propiolaldehyde diethyl acetal also did not respond under those conditions.

In the presence of palladium on carbon, 1,1-diethoxy-3-(triphenylstannyl)-2-propyne absorbed three moles of hydrogen per mole at room temperature and a pressure of slightly above atmospheric pressure. These results are consistent with the structure assigned if one mole of hydrogen cleaved the tin-carbon bond.

Attempts to prepare 1,1-diethoxy-3-(triphenylstannyl)-2-propyne by the action of the Grignard derivative of propiolaldehyde diethylacetal on either triphenyltin chloride or triphenyltin bromide were not successful. When the bromomagnesium derivative of the acetylenic acetal was used with triphenyltin chloride, the principal product was triphenyltin bromide which formed in a yield of 59%. When tri-*n*-butyltin chloride was used instead of triphenyltin chloride, a similar reaction occurred and tri-*n*-butyltin bromide was isolated in 46% yield. Use of triphenyltin bromide and a catalytic amount of copper(I) bromide with the bromomagnesium Grignard reagent gave no isolable product

During the course of these studies, it was found that the infrared spectra of chloroform solutions of triphenyltin chloride and triphenyltin bromide were identical within the range 650 cm^{-1} to 3500 cm^{-1}.

EXPERIMENTAL

Propiolaldehyde diethylacetal. This compound was prepared from acrolein by a modification of the method of Grard.[5] The method involved bromination of acrolein, conversion of the resulting α,β-dibromopropionaldehyde to its diethylacetal by action of ethyl orthoformate and dehydrobromination of the product in concentrated alcoholic potassium hydroxide.

Acrolein (112 g., 2 moles, Tech.) was stirred and cooled (ice bath) while bromine (320 g., 2 moles) was added dropwise over a period of 5.5 hr. Ethyl orthoformate (328 g., 2.2 moles, C & B reagent) and absolute ethanol (276 g., 6 moles), both chilled to ice bath temperature, were added. The solution was stirred and cooled for 1 hr. and then placed in the refrigerator for 4 days. The volume was reduced *in vacuo* until the temperature of the distillate reached 98° at 7 mm. to insure removal of unreacted ethyl orthoformate. The residue, crude α,β-dibromopropionaldehyde diethyl acetal (max. of 2 moles) was cooled and added in a thin stream to a chilled, stirred solution of potassium hydroxide (280 g. of 85% min. KOH, minimum of 238 g. KOH, 4.25 moles) in absolute ethanol (1900 ml.). The mixture was stirred as it warmed to room temperature. After 1 hr., it was filtered. The solid was collected and washed with ethanol (100 ml.). The ethanol was added to the filtrate and the solution was allowed to remain at room temperature overnight. It was then stirred and refluxed 6 hr. During the last 1.5 hr. of this period, ethanol (1 l.) was collected by distillation. To facilitate isolation of the product, the mixture was divided into two equal aliquots and each was processed as follows: The aliquot was poured into cold water (3 l.) and extracted with chloroform (four 300-ml. portions). The chloroform extracts from both aliquots were combined, washed with water (two 200-ml. portions), and dried ($CaCl_2$). The chloroform was removed at atmospheric pressure and the residue fractionated through a 20 cm. spiral glass column. The product (116.5 g., 0.91 mole, 45% from acrolein) was collected as a colorless liquid at 70–72°/70 mm. A portion was redistilled, b.p. 82°/109 mm., $n_D^{22.6}$ 1.4106.

Silver salt of propiolaldehyde diethylacetal. Grard's procedure[5] was used with slight modification. A solution of ammoniacal silver nitrate (from 13.6 g., 0.08 mole, $AgNO_3$, together with just enough dilute ammonium hydroxide to effect solution) in water (approx. 100 ml. total volume) was stirred while a solution of freshly distilled propiolaldehyde diethyl acetal (9.6 g., 0.075 mole) in an equal volume of acetone was added dropwise over a period of 45 min. (When acetone was omitted, the precipitate became gummy.) The white solid which separated was collected on a filter, washed twice with water, and recrystallized from abs. ethanol. When dry, it weighed 13.4 g. (76%) and had a grayish cast.

Action of the silver salt of propiolaldehyde diethylacetal on triphenyltin bromide. 1,1-Diethoxy-3-(triphenylstannyl)-2-propyne. A solution of the silver salt of propiolaldehyde diethylacetal (10 g., 0.43 mole) in warm acetone (75 ml.) was stirred while a solution of triphenyltin bromide (18 g., 0.43 mole) in acetone (75 ml.) was added dropwise. The mixture was stirred 90 min. and then allowed to stand overnight at room temperature. The clear supernatant liquid was decanted from the grayish precipitate and the acetone was removed under reduced pressure. A clear, almost colorless oil remained which gradually solidified. After drying *in vacuo*, the solid weighed 16.3 g. and after two crystallizations from petroleum ether-B (b.p. 60–68°) melted at 58–60° (uncorr.).

Anal. Calcd. for $C_{25}H_{26}O_2Sn$: C, 62.9; H, 5.49; Sn, 24.9; —OEt, 18.9; mol. wt. 477. Found: C, 62.8, 62.3; H, 4.91, 5.50; Sn, 25.4, 25.4; —OEt, 16.3; mol. wt., 458, 454.[6]

The product gave a negative Beilstein test, rapidly absorbed bromine in carbon tetrachloride and reduced potassium permanganate. It gave a positive Zeisel test.[7] The standard procedure for the preparation of a 2,4-dinitrophenylhydrazone of an aldehyde involving in this case *in situ* hydrolysis of the acetal linkage gave no precipitate.[8] Propiolaldehyde diethylacetal under the same conditions also gave no precipitate.

In absolute ethanol (15 ml.) containing 10% palladium on charcoal (approx. 100 mg.), 1,1-diethoxy-3-(triphenylstannyl)-2-propyne (500 mg., 1.05×10^{-3} moles) absorbed 3.18×10^{-3} moles of hydrogen at a temperature of 26–29° and a pressure of 734 mm. This represents an uptake of 3.03 moles hydrogen per mole if the molecular weight is taken as 477.

Action of dilute hydrochloric acid on 1,1-diethoxy-3-(triphenylstannyl)-2-propyne. Water (5 ml.) was added to a solution of 1,1-diethoxy-3-(triphenylstannyl)-2-propyne (4.4 g., 9.2×10^{-3} mole) in acetone (20 ml.). To this solution 10% aqueous hydrochloric acid (3 ml.) was added. The mixture was cloudy but became clear when warmed. It was boiled for 5 min. and poured into ice water (700 ml.). Collection of the solid on a filter and drying *in vacuo* over phosphorous pentoxide resulted in 3.6 grams of a solid melting at 85–95° (uncorr.). Two recrystallizations from petroleum ether-B (b.p. 60–68°) raised the melting point to 105.5–107.5° (uncorr.). A mixed melting point with

(5) J. Grard, *Ann. chim.*, **13**, 337 (1930); see also J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **71**, 1436 (1949).

(6) Microanalytical results for C, H and —OEt are from two different laboratories. One laboratory reported that the compound exploded during the analysis.

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, New York, 1956, p. 116.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, New York, 1956, p. 219.

authentic triphenyltin chloride, m.p. 106–107° (uncorr.), was not depressed.

Action of potassium permanganate on 1,1-diethoxy-3-(triphenylstannyl)-2-propyne. A solution of 1,1-diethoxy-3-(triphenylstannyl)-2-propyne (2.4 g.) in acetone (25 ml.) was stirred while 10% aqueous potassium permanganate (10 ml.) was added portionwise. The color was discharged and manganese dioxide formed. More potassium permanganate was added in the form of a saturated solution in acetone until the color persisted two minutes at room temperature. The solids were separated and the filtrate evaporated. Glistening white crystals of triphenyltin hydroxide, identified by m.p. and origin, remained and were washed and dried at 80°; weight, 1.4 g. (77%), m.p. 115–121° (uncorr.). After one crystallization from ethanol, the solid was snow white and melted at 120–120.5° (uncorr.). Triphenyltin hydroxide melts at 119–120° (uncorr.).[9]

Action of the bromomagnesium derivative of propiolaldehyde diethylacetal on triphenyltin chloride. Grard's procedure for the preparation of the Grignard reagent was used.[6] A solution of ethylmagnesium bromide (from 8.4 g. magnesium, 0.34 g.-atom) in ether (100 ml.) was added dropwise to a stirred, cooled (ice bath) solution of propiolaldehyde diethylacetal (44 g., 0.34 mole) in ether (950 ml.). Evolution of ethane occurred smoothly. When the addition of ethylmagnesium bromide was completed, the ice bath was removed and the mixture was refluxed 1 hr. A grayish viscous mass separated early in this operation. To the stirred, refluxing mixture triphenyltin chloride (115 g., 0.34 mole) was added as follows: Approximately one third was added in the form of a saturated solution in ether (total vol., 1 liter). A reaction occurred with the addition of each drop of triphenyltin chloride solution, as evidenced by the appearance of cloudiness. The remainder of the triphenyltin chloride was added as the solid in one portion. The mixture was stirred and refluxed 1.5 hr. and then it remained at room temperature overnight, after which it was stirred and refluxed during the next day and set aside at room temperature overnight.

The mixture was filtered and the filtrate concentrated to 500 ml. and filtered. The filtrate was cooled and a tan solid separated weighing 47 g. and melting at 118–122° (uncorr.) when dry. After one recrystallization from carbon tetrachloride, it melted at 121–122° (uncorr.). Evaporation of the filtrate gave 39 g. more of the solid melting at 118–121° (uncorr.); total yield, 86 g. (59%). It gave a positive sodium fusion test for bromine. A mixed melting point of this compound with an authentic sample of triphenyltin bromide was not depressed.

Anal. Calcd. for $C_{18}H_{15}SnBr$: C, 50.3; H, 3.5; Sn, 27.6; Br, 18.6; mol. wt., 430. Found: C, 50.6; H, 3.60; Sn, 28.1, 28.3, 27.8, 27.8; Br, 18.0, 18.2, 18.4, 18.6; mol. wt., 410, 409.

The infrared spectrum of this product in chloroform was indistinguishable from the spectra of either authentic triphenyltin bromide *or triphenyltin chloride* in chloroform.

In another experiment in which benzene replaced the ether as the "solvent" for the Grignard derivative of propiolaldehyde diethylacetal, the same product, triphenyltin bromide, formed in a yield of 52%.

Action of the bromomagnesium derivative of propioaldehyde diethylacetal on tri-n-butyltin chloride. Ethylmagnesium bromide (from 2.7 g., 0.11 g. atom magnesium) in ether (approx. 50 ml.) was added dropwise over a period of 25 min. to a cooled, stirred solution of freshly distilled propiolaldehyde diethylacetal (12.8 g., 0.10 mole) in thiophene-free benzene (150 ml.). The mixture was allowed to warm to room temperature and was stirred 1 hr. until the evolution of ethane ceased. The mixture of the viscous, gummy Grignard derivative and benzene was stirred while a solution of freshly distilled tri-*n*-butyltin chloride (32.4 g., 0.10 mole, b.p. 138–9°/4.5 mm., $n_D^{28.2}$ 1.4883) in thiophene-free benzene (100 ml.) was added dropwise. The gummy Grignard reagent was slowly consumed, the mixture became opaque, and a brownish solid separated. The mixture was filtered and the filtrate was fractionated *in vacuo* using a 10-cm. Vigreux column. At 105–110°/0.55 mm. a colorless oil was collected which weighed 17 g., n_D^{25} 1.4984. This oil gave a positive Beilstein test and an instantaneous precipitate with sodium iodide in acetone. A sodium fusion test for bromine was positive. Authentic tri-*n*-butyltin bromide has a refractive index of n_D^{20} 1.5000.[10] For tri-*n*-butyltin chloride, n_D^{23} 1.4908 has been reported.[11] On the basis of these data, it was concluded that the oil was tri-*n*-butyltin bromide. Accordingly, the yield was 46% of the theoretical. The residue was very viscous and brownish-black. Further distillation was accompanied by considerable decomposition, but at 133–316°/4 mm., an unidentified yellow oil weighing 3.5 g., $n_D^{25.5}$ 1.4799 was obtained.

Acknowledgment. The authors wish to thank Mr. Thomas Severeid for performing the tin analyses, determining the molecular weights and preparing tri-*n*-butyltin chloride and tri-*n*-butyltin bromide.

MINNEAPOLIS 14, MINN.

(9) E. Krause and A. V. Grosse, *Die Chemie der Metall-Organischen Verbindungen*, Gebrüder Borntraeger, Berlin, 1937, p. 343.

(10) W. J. Jones, D. P. Evans, T. Gulwell, and D. C. Griffiths, *J. Chem. Soc.*, 1935, 45.

(11) Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), 18, 299 (1948); *Chem. Abstr.*, 42, 6742 (1948).

Notes

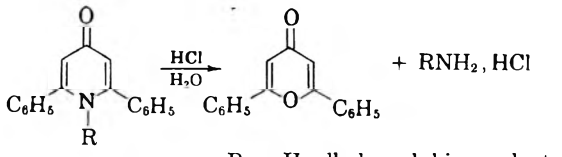
A department for short papers of immediate interest.

Hydrolysis of 4-Pyridones

L. Neelakantan

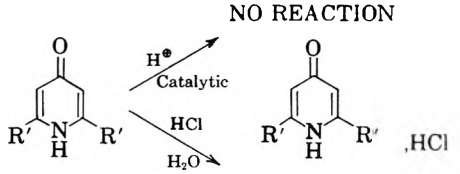
Received March 25, 1957

During the course of studies on 2,6-diphenyl-4-pyridones as potential antimalarials[1] attempts were made to prepare the hydrochlorides of these compounds. It was found that these pyridones do not yield the desired hydrochlorides in aqueous medium but are converted back to 2,6-diphenyl-4-pyrone and the amine hydrochlorides. It was subsequently observed that this hydrolysis could be achieved by traces of mineral acid. It was also found that 2,6-diphenyl-4-pyridone hydrochloride is hydrolyzed to the pyrone in presence of water.



R = H, alkyl, aryl, biguanyl, etc.

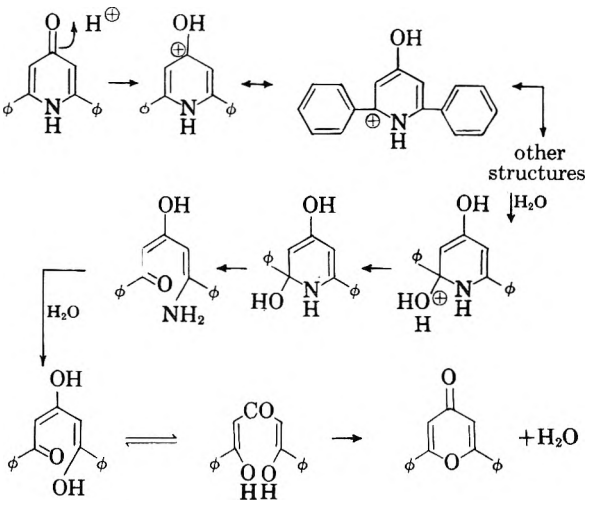
To find if this unusual hydrolysis was due to the presence of the phenyl substituents at the alpha positions a study using pyridones with the substituents H, CH_3, COOH, and COOEt was made. It was noticed that only 2,6-diphenyl-4-pyridones give the corresponding pyrone in the presence of catalytic amounts of acid. The other pyridones are unaffected by the presence of small amounts of mineral acid.



R′ = H, CH_3, COOH, COOEt

Examination of the Fischer-Hershfelder molecular models of these compounds indicated no particular strain induced by the two phenyl groups. The acid catalyzed hydrolysis probably proceeds by the following mechanism.

If the pyridone is considered as a vinylog of an acid amide the addition of a proton to the acyl oxygen results in the formation of a carbonium ion. Addition of a molecule of water follows and subsequent rearrangement results in the formation of the pyrone. The phenyl groups stabilize the carbonium ion due to resonance and indirectly even might facilitate the formation of the carbonium ion. This effect is absent in the case of pyridones where the alpha substituents are not phenyl groups.



EXPERIMENTAL

2,6-diphenyl-4-pyridone. To 5 g. of 2,6-diphenyl-4-pyrone was added 50 ml. of alcoholic ammonia. The whole was evaporated to dryness and the process repeated. The residue was crystallized from benzene to give the product; m.p., 178°; yield, 4.8 g. (m.p. reported,[2] 178°). The hydrochloride was prepared by passing dry HCl gas through a solution of the pyridone in benzene; m.p., 248–249° (m.p. reported,[2] 249°).

Hydrolysis of 2,6-diphenyl-4-pyridone. Two grams of the pure pyridone was dissolved in 20 ml. of water; to the aqueous solution was added two drops of concentrated hydrochloric acid. The white crystalline precipitate thrown out was collected, washed with water, and dried as product A. Yield, 1.9 g; m.p. 137°; recrystallized from water gives m.p. 138° (m.p., reported,[3] for 2,6-diphenyl-4-pyrone, is 138°). A small quantity of the product A on evaporation to dryness with alcoholic ammonia leaves a residue, m.p. 178°, which gives with HCl gas in benzene a hydrochloride, m.p. 248–249°.

Hence product A was identified as 2,6-diphenyl-4-pyrone. Mixed melting point with an authentic sample showed no depression.

N-(p-chlorophenylbiguanyl)-2,6-diphenyl-4-pyridone. Five grams of 2,6-diphenyl-4-pyrone and 4.2 g. of *p*-chlorophenylbiguanide were refluxed in 30 ml. of alcohol for 8 hr. The product which separated on cooling was collected and crystallized from alcohol, m.p. 154°; yield, 6 g.

Anal. Calcd. for $C_{25}H_{20}N_5ClO$: N, 15.84. Found: N, 16.02.

Hydrolysis. Three grams of this pyridone was treated with 15 ml. of dilute hydrochloric acid (1:1). After standing for 15 min. the solid was collected, washed with water, and recrystallized from hot water, m.p. 137–138°. (This product was identified as 2,6-diphenyl-4-pyrone.)

The aqueous solution on basifying with sodium hydroxide gave a solid which after crystallization from alcohol gave

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m.p. 139° (reported[4] m.p. for *p*-chlorophenyl biguanide 139–140°, mixed melting point showed no depression).

Action of dilute HCl on diethyl chelidamate. Four-grams of the pyridone was suspended in 20 ml. of water and treated with 0.5 ml. of concentrated HCl; after standing for an hour the solid was collected and washed with water; m.p., 80–81°; yield, 3.8 g. (Reported[5] m.p. for diethyl chelidamate, 81°.) The product shows no depression in melting point when mixed with an authentic sample. Hence the pyridone was not hydrolyzed to the corresponding pyrone.

Action of dilute HCl on chelidamic acid. The chelidamic acid was treated with HCl using the same conditions as in the previous experiment. The product was identified as unchanged chelidamic acid.

Action of dilute HCl on 2,6-dimethyl-4-pyridone. Five grams of the pyridone was dissolved in 30 ml. of water and treated with three drops of concentrated HCl. On evaporation of the water a residue was obtained which was crystallized from water with m.p., 224–225°. This substance also gave a hydrochloride salt, m.p. 246–247°. (Reported[6] m.p. for the pyridone is 225° and for the HCl salt 247°.) It may be concluded that no hydrolysis took place.

Action of dilute HCl on 4-pyridone. Using the same procedure as the previous one, 4-pyridone and HCl gave only unchanged pyridone as the product. The product gave a hydrochloride, m.p. 138–139°. (Reported[7] m.p. 139°.)

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Synthesis and Rate of Acetolysis of 1-Bicyclo-[2.2.1]heptylmethyl Tosylate

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The mechanism and driving force of the Wagner-Meerwein rearrangement has been investigated by Winstein *et al.*[1] and it has been concluded that the acetolysis of neopentyl type halides proceeds with minimal solvent participation and neighboring group effects. Furthermore, the relief of steric strain *via* formation of an intermediate carbonium ion appears to have no accelerating effect on the reaction.

Acetolysis of 1-bicycloheptylmethyl[2] tosylate also may involve a minimum amount of solvent participation, and formation of an intermediate carbonium ion should not have any different steric effect on the rate than in the case of neopentyl tosylate. Should the migrating group not participate in the rate determining step of the rearrangement, it would be expected that the rates of acetolysis of neopentyl tosylate and bicycloheptylmethyl tosylate would be nearly the same. However, should the migrating group participate in the rate controlling step, essentially through a nucleophilic displacement, it might be predicted that the acetolysis of bicycloheptylmethyl tosylate would be faster than that of neopentyl tosylate, for participation by the former would involve rearrangement to a bicyclo [2.2.2]octyl radical, with relief of some steric strain, and concomitant increase in driving force.

The preparation of 1-bicycloheptylmethyl derivatives has not been reported. However, methods have been described which lead to their synthesis, *via* bridgehead substituted bicycloheptanes. Many attempts to prepare bridgehead substituted bicycloheptanes have failed. Thus, *trans*-halogenation of bicycloheptane with *t*-butyl chloride and aluminum chloride gave only *exo*-2-chloro-bicycloheptane,[3] and the peroxide-directed chlorination of bicycloheptane gave the same product.[4] On the other hand, vapor phase nitration of bicycloheptane gave 1-nitrobicycloheptane,[5] and 1-chlorobicycloheptane has been reported,[6] although its method of preparation and physical properties were not described.

The Wagner-Meerwein rearrangement of 2-chlorobicycloheptane gives only the mirror image of the starting material, but rearrangement of 2,2-dichlorobicycloheptane should give 1,2-dichlorobicycloheptane. This reaction has been carried out in the camphane series by Houben and Pfankuch.[7] The 2-chloro substituent can be selectively removed either by catalytic hydrogenation in the presence of base,[8] or by means of a trans-halogenation reaction.[9] The dichloride can be obtained from 2-ketobicycloheptane using phosphorus pentachloride.[10] The ketone can be prepared by the method of Alder and Rickert.[11] Thus, 1-chlorobicycloheptane synthesized *via* the ketone, 2,2-dichloride and 1,2-dichloride, was converted to 1-carboxybicycloheptane *via* the lithium salt of bicycloheptane, the acid reduced to 1-hydroxymethylbicycloheptane, and the latter converted to its tosyl derivative.

The rate of acetolysis of the tosylate was determined in anhydrous acetic acid at 99.7°, using the method described by Winstein, Grunwald and

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Ingraham.[12] The first-order rate constant was found to be $11.69 \pm 0.29 \times 10^{-6}$ sec.$^{-1}$, compared with the value of $1.66 \pm 0.09 \times 10^{-6}$ sec.$^{-1}$ observed for neopentyl tosylate at 99.58°.[1] These results suggest that anchimeric assistance may occur in the former solvolysis reaction. If the solvolysis of neopentyl derivatives involves no anchimeric assistance,[1,13] and if the carbonium ions derived from neopentyl tosylate and bicycloheptylmethyl tosylate have the same solvation energy, it would be possible to relate the increase in rate of the bicyclic derivative over the neopentyl derivative to relief of steric strain. However, at the present, there is no definite evidence that this is possible, particularly since the possibility of differing steric effects on the solvation of the ion first produced cannot be excluded.

EXPERIMENTAL[14,15]

endo-2-Hydroxybicycloheptane. A total of 604 g. (9.15 moles) of freshly distilled cyclopentadiene and 906 g. (9.55 moles) of technical vinyl acetate was sealed in 20 Pyrex tubes and heated at 185° for 10–15 hr. The contents of the tubes were aspirated for 20 hr., and the residue distilled *in vacuo* to give 568 g. (40%) of crude endo-2-acetoxybicycloheptane, b.p. 88.5–103°/33 mm., lit.,[13] 82–83°/17 mm. The crude product was hydrogenated in a low-pressure apparatus using Adam's catalyst in methanol solution. The catalyst was removed by filtration, and the filtrate concentrated until the crude *endo*-2-acetoxybicycloheptane was dissolved in *ca.* 1250 ml. of methyl alcohol. To this solution was added 200 g. (3.58 moles) of potassium hydroxide and the mixture held at reflux for 4 hr. The reaction mixture was cooled, diluted with 2200 ml. of water, extracted with 3 1200-ml. portions of 30–60° petroleum ether, the ethereal extracts combined and dried over sodium sulfate. The petroleum ether solution was passed through a column packed with 3000 g. of alumina. Three fractions were collected and the infrared spectra taken of each. Fractions one and two contained essentially no bicyclic alcohol, while fraction three did. The column was eluted with 4 l. of dry ethanol, and the eluate combined with the third fraction above. The solvents were removed *in vacuo* to give an oily residue, which, after recrystallization from hexane, gave 253 g. (25% based on cyclopentadiene) of product, m.p. 151–151.5°, lit.,[13] 152–153°.

2-Ketobicycloheptane. To an ice-cooled 5-l. round-bottomed flask, fitted with a stirrer, were added 1500 ml. of water, 74 ml. (1.39 mole) of 96% sulfuric acid, 99.5 g. (0.338 mole) potassium dichromate, and 600 ml. of glacial acetic acid. To the ice cold solution was added 115 g. (1.025 moles) *endo*-2-hydroxybicycloheptane and the solution stirred for 6 hr. The ice bath was allowed to melt, and the solution to stand overnight. A cold solution of 500 g. of technical sodium hydroxide in 800 ml. of water was then added, keeping the temperature of the reaction mixture between 0–10°. The resulting slurry was steam distilled and 1500 ml. of distillate collected. The distillate was saturated with sodium chloride, extracted with 3 500-ml. portions of ether, the ethereal extracts combined and dried over calcium sulfate. The solution was then filtered and the ether removed by distillation. The residue was distilled *in vacuo* to give 85.4 g. (76%) of 2-ketobicycloheptane, b.p. 89–94°/60 mm.; 2,4-dinitrophenylhydrazone, m.p. 131.5–132.0°, lit.,[16] 131.5–132.5°.

2,2-Dichlorobicycloheptane. To a 500-ml. round-bottomed flask protected by a calcium chloride drying tube and containing 29 ml. of phosphorus trichloride cooled to 0° in an ice-salt bath was added 45.1 g. (0.41 mole) of 2-ketobicycloheptane. After the ketone had dissolved, 96.7 g. (0.463 mole) of phosphorus pentachloride was added portionwise over a period of one hour with vigorous shaking and cooling. The solution was allowed to stand overnight, then poured onto 500 g. of ice and the hydrolysis allowed to proceed, keeping the temperature below 0° at all times. After 30 min. the reaction was allowed to come to room temperature. There were two phases. The mixture was extracted with 4 250-ml. portions of pentane, the pentane extract washed with 2 300-ml. portions of water and then dried over magnesium sulfate. The pentane was removed by distillation and the residue distilled *in vacuo* to give 1 g. of forerun, 47.8 g. (64%) of dichloride, b.p. 65.0–68.1°/12.0–12.4 mm., and *ca.* 5 g. of residue. The product solidified to a low-melting solid.

Anal. Calcd. for $C_7H_{10}Cl_2$: C, 50.9; H, 6.1. Found: C, 51.0; H, 6.3.

1-Chlorobicycloheptane. Aluminum chloride, 16.9 g. (0.127 mole), was added in four portions over a period of five hours to a solution of 43.9 g. (0.266 mole) of the dichloride dissolved in 700 ml. of pentane previously dried over aluminum chloride. Hydrogen chloride was slowly evolved and a red brown sludge formed. After six hours the walls of the flask were covered with sludge. The mixture stood for 43 additional hours before the clear pentane solution was decanted from the oil and the oil washed with 100 ml. of dry hexane. The combined hexane and pentane solution was washed with 4 300-ml. portions of water and then dried over magnesium sulfate. The solvent was removed and residue distilled *in vacuo* to give 1.1 g. of forerun, 14.9 g. (43%) of 1-chlorobicycloheptane, and 5.6 g. of residue. The product b.p. 70–72°/54 mm., $n_D^{25.7}$ 1.4722 solidified at 0° and gave a slight test with an alcoholic silver nitrate solution at room temperature. This positive test may have been due to the presence of small amounts of either *exo*-2-chlorobicycloheptane or 1-chloro-*exo*-2-chlorobicycloheptane, or both. The infrared spectrum showed no absorption of *exo*- or *endo*-2-chlorobicycloheptane[17] and no absorption in the 12.5 μ region characteristic of nortricyclene derivatives.[18] A redistilled sample, b.p. 70–71°/54 mm., $n_D^{25.7}$ 1.4722, gave no halide test.

Anal. Calcd. for $C_7H_{11}Cl$: C, 64.4; H, 8.5; Cl, 27.2. Found: C, 64.1; H, 8.5; Cl, 27.3.

1-Carboxybicycloheptane. Lithium wire, 2.4 g. (0.345 mole), was placed under 20 ml. of mineral oil in a 200-ml. round-bottomed three-necked flask equipped with a stirrer, separatory funnel, condenser with drying tube attached and a Y-inlet for carbon dioxide and nitrogen. The equipment was flamed, then purged with dry nitrogen for 30 min., before the lithium and oil were added. The vigorously stirred oil was heated to boiling with a bare flame and the suspension of lithium so obtained allowed to cool. The mineral oil was removed under nitrogen and the lithium sand washed with 3 20-ml. portions of dry cyclohexane. A glass-sealed magnetic stirring bar was introduced and the flask sealed. One half of a solution of 10.0 g. (0.0767 mole) of 1-chlorobicycloheptane in 40 ml. of dry cyclohexane was added to the lithium sand and the suspension, while being stirred, was heated to 90°. An exothermic reaction soon started, and was main-

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tamed by the addition of the other half of the solution of the halide. The suspension was heated for one hour at reflux under a positive nitrogen pressure, then cooled, and 65 ml. of dry pentane added. Carbon dioxide, dried by passage through concentrated sulfuric acid, was passed over the vigorously stirred suspension for two hours. The excess lithium was removed by the addition of 20 ml. of absolute ethanol, followed by 60 ml. of water. Following the addition of 50 ml. of ether, the aqueous phase was acidified with concd. hydrochloric acid. The phases were separated, and the aqueous phase, after saturation with salt, was extracted with 3 100-ml. portions of ether. The combined ethereal extracts were extracted with 3 100-ml. portions of aqueous sodium carbonate, the sodium carbonate phase acidified with 12*N* hydrochloric acid, saturated with salt, and extracted with 3 100-ml. portions of ether. The ethereal extracts were dried and the solvent removed by distillation through a 12-inch column. The product was sublimed at 10 mm. and 80° to give 5.48 g. (51%) of 1-carboxybicycloheptane, m.p. 113.8–115.5°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.5; H, 8.5.

The reported melting points for *exo*- and *endo*-2-carboxybicycloheptane are 48°[19] and 65°,[20] respectively. The acid has an odor similar to that of butyric acid.

1-Hydroxymethylbicycloheptane. The above acid, 2.19 g. (0.0156 mole), was reduced in 130 ml. of ether with 3.0 g. (0.0790 mole) lithium aluminum hydride. The excess hydride was destroyed by addition of water and the contents of the flask poured into 100 ml. of 10% aqueous sulfuric acid. The phases were separated, and the aqueous phase extracted with 2 25-ml. portions of ether. The combined ethereal extracts were washed with water, saturated aqueous sodium bicarbonate and water and dried over magnesium sulfate. The solvent was removed by distillation through a 12-inch Vigreux column to yield an oily residue. The residue was sublimed at 6 mm. and 65° to give 1.76 g. (91%) of product, m.p. 59.0–60.2°, soft waxy needles.

Anal. Calcd. for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 75.9; H, 11.3.

1-Bicycloheptylmethyl tosylate. To an ice cold solution of 0.70 g. (5.56 mole) of the above alcohol dissolved in 6 ml. of dry pyridine was added 1.06 g. (5.56 mole) of tosyl chloride. The solution was allowed to stand overnight at 4° and then added to 12 ml. of ice cold 6*N* hydrochloric acid. An oil formed and began to crystallize whereupon the mixture was stirred with 25 ml. of carbon tetrachloride until all of the solid had dissolved. The phases were separated and the aqueous phase extracted with 15 ml. of carbon tetrachloride. The organic phases were combined and dried. The solvent removed by evaporation and the residue was recrystallized from 6 ml. of hexane to give 1.33 g. (86%) of tosyl derivative, m.p. 78.9–80.0°.

Anal. Calcd. for $C_{15}H_{20}O_3S$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.2.

Rate of acetolysis of 1-bicycloheptylmethyl tosylate. The acetolysis was conducted in anhydrous acetic acid, according to the method of Winstein, Grunwald, and Ingraham.[12] Anhydrous acetic acid was prepared by adding sufficient acetic anhydride to react with the water present in glacial acetic acid as determined by its freezing point, allowing the mixture to reflux for 3 hr. and then distilling. The distillate was made approximately 0.5% in acetic anhydride, held at reflux for 3 hr., cooled, and then stored in sealed containers.

Approximately 0.05*N* perchloric acid in acetic acid was prepared by dilution of a 9*N* aqueous solution with the anhydrous acid. This solution was standardized against potassium acid phthalate to a brom phenol blue end point.[21] Approximately 0.10*N* sodium acetate in acetic acid was prepared by the addition of anhydrous sodium carbonate to the anhydrous acid and was standardized against the perchloric acid solution. The acetic anhydride in the anhydrous acid was determined to be 0.50% by the method of Kilpi,[22] *i.e.*, the addition of anthranilic acid to the anhydrous acid and titration with perchloric acid. In all titrations, 8 drops of 1% brom phenol blue indicator in the anhydrous acid were used per 5 ml. of solution.

The acetolysis was conducted as follows: 6-ml. aliquots of a 0.03547*M* solution of the tosyl derivative in the anhydrous acid were placed in ampoules, the ampoules sealed, placed in an oil bath at 99.66 ± 0.02°, single ampoules removed at selected time intervals, immediately cooled, opened, 5.00-ml. aliquots removed, and titrated with the sodium acetate solution. The time was computed from the time of opening the ampoules. The aliquots were titrated with the aid of a syringe buret,[23] previously calibrated by titration of the perchloric acid solution with the sodium acetate solution. The first order rate constants were calculated from the expression $kt = \ln(a/a - x)$. The hydrolysis was followed to 64%. The results are summarized in Table I.

TABLE I

RATE OF ACETOLYSIS OF 1-BICYCLOHEPTYLMETHYL TOSYLATE[a]

Time, Sec.	Base,[b] Ml.	$(a - x)$ (M)	$k \times 10^6$ Sec.$^{-1}$
0[c]	0.1933	0.03147	...
9549	0.3529	0.02816	11.63
21860	0.5435	0.02472	11.97
34676	0.7000	0.02098	11.70
44576	0.8213	0.01847	11.95
74040	1.0938	0.01283	12.13
86384	1.1129	0.01243	10.76
95565	1.2147	0.01033	11.66[d]

[a] In an hydrous acetic acid containing 0.50% acetic anhydride at 99.66 ± 0.02°. [b] 0.1035*N* sodium acetate per 5.00-ml. aliquot. [c] $a_0 = 0.03547$ *M*. [d] $k_{mean} = 11.69 \pm 0.29 \times 10^{-6}$ sec.$^{-1}$

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Reaction of Bis(chloromethyl) Ether with Methanol and with Ethanol[1,2]

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Bis(methoxymethyl) ether (I) was first prepared by Descudé[4] in 1904 by reaction of bis(chloro-

(1) Taken in part from the thesis submitted by R. E. Martin to the Graduate School of New Mexico A&M in partial fulfillment of the requirements for the degree Master of Science, August 1956.

methyl) ether (II) with sodium methoxide. Neither conditions nor yield are recorded. The preparation of I by reaction of paraformaldehyde, methanol, and methylal is reported[5] in 26% yield.

Bis(ethoxymethyl) ether (III) was prepared by Descudé[4] in 25% yield from II and sodium ethoxide. Ali-Zabe *et al.*[6] report the preparation of III from ethanol, sodium hydroxide, and bis(bromomethyl) ether. No yield is given. Diethyl formal and paraformaldehyde react catalytically to form III in 43% yield.[5]

Our results indicate that neither I nor III can readily be prepared from II and the corresponding sodium alkoxide in inert solvents. The reaction between II and the alcohols occurs readily, but in the absence of a base the principal products are methylal or diethyl formal and formaldehyde.

The reaction between II and methanol in the presence of sodium methoxide at 55–60° produced I in 32% yield. The yield of I was only 15% and isolation was complicated by substituting sodium hydroxide for sodium methoxide.

When II was treated with ethanol at 55–60° in the presence of sodium hydroxide, III was formed in 60% yield. No improvement in yield was obtained by using sodium ethoxide in place of sodium hydroxide. The yield of III was 41% when II was treated with ethanol in the presence of sodium methoxide. No I could be isolated from the reaction mixture.

EXPERIMENTAL

Bis(methoxymethyl) ether (I). A one-liter, three-necked flask, equipped with a thermometer, condenser, dropping funnel, and magnetic stirring bar, was charged with 4 moles sodium methoxide and 500 ml. methanol. A temperature of 55–60° was maintained by cooling while 2 moles of II was added dropwise over a period of 6 hr. The filtrate from the reaction mixture was fractionated in a 12-plate column to remove methanol. The pot residue was filtered to remove salt. When the upper layer from the filtrate was fractionated, 0.63 mole (32% yield) of I was obtained, b.p. 64.5–65°/200 mm., n_D^{25} 1.3769, d_4^{25} 0.945.

Anal. Calcd. for $C_4H_{10}O_3$: mol. wt., 106.1; C, 45.27; H, 9.60. Found: mol. wt., 107; C, 44.83; H, 9.74.

When conditions essentially the same as just described were employed except that carbon tetrachloride or 1,4-dioxane was substituted for methanol, no I was isolated. When II and methanol were reacted in the absence of a base, methylal and formaldehyde were formed, but no I. Small yields (about 15%) of I were obtained when sodium hydroxide or calcium oxide was substituted for sodium methoxide in the reaction between methanol and II.

Bis(ethoxymethyl) ether (III). The equipment described under the preparation of I was charged with 1.25 moles sodium hydroxide and 4.3 moles ethanol. The temperature was maintained at 50–60° while 0.5 mole of II was added over a period of 3 hr. The product was filtered and the filtrate fractionated to yield 0.3 mole of III, b.p. 67–67.5°/60 mm., d_4^{25} 0.903, n_D^{25} 1.3861.

Anal. Calcd. for $C_6H_{14}O_3$: mol. wt., 134.2; C, 53.71; H, 10.52. Found: mol. wt., 132; C, 52.68; H, 11.25.

Under similar conditions ethanol and II react in the absence of a base, but the products are diethyl formal and formaldehyde rather than III.

When a reaction was conducted using 4.3 moles ethanol, 1.25 moles sodium methoxide, and 0.5 mole II, a 41% yield of III was obtained, but no I was isolated.

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(2) A portion of this study was conducted under contract No. AF 33(616)-455 sponsored by the U.S. Air Force and is contained in AF Technical Report No. 43-434.

(3) Present address: El Paso Natural Gas Co., Farmington, N. M.

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Preparation of Certain Polychlorodimethyl Ethers[1]

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The liquid-phase chlorination of chloromethyl methyl ether yields bis(chloromethyl) ether (I) and methyl dichloromethyl ether (II). The ratio of I:II is approximately 7. In the vapor-phase chlorination of dimethyl ether with excess chlorine,[3] the ratio of I:II varies from 1.6 to 3.0 based on contact time, temperature, and ratio of reactants. Salzberg and Werntz[4] prepared I and II by chlorinating dimethyl ether with excess chlorine in an inert solvent, but reported no data on the relative amounts of the two compounds.

When I is further chlorinated, chloromethyl dichloromethyl ether III is formed. The properties of our product are in agreement with those of Sonay who reported the preparation of III by a similar process.[5]

Chlorination of II in a similar manner also yields III but no methyl trichloromethyl ether (IV) was isolated. Compound IV has been prepared by the chlorination of bis(methoxythiocarbonyl) disulfide.[6]

The monochlorination of III also forms only one product although two products are possible. This product was identified as bis(dichloromethyl)

(1) Taken in part from the thesis submitted by R. A. Gray to the Graduate Committee of New Mexico A&M in partial fulfillment of the requirements for the degree of Master of Science, August 1952.

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(3) L. R. Evans, U. S. Patent 2,811,485 (1957). The results of this study by L. R. Evans and R. E. Neligan are to be published soon.

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(6) I. B. Douglass and G. H. Warner, *J. Am. Chem. Soc.*, **78**, 6070 (1956).

ether (V) by both chemical and instrumental analysis.

Attempts to prepare more highly chlorinated dimethyl ethers by the chlorination of V were unsuccessful. The reaction with chlorine was very sluggish and no products boiling higher than V could be isolated.

Both pentachlorodimethyl ether[7] (VI) and hexachlorodimethyl ether[5,8] (VII) have been reported. However, Regnault's and Sonay's values for the boiling point and density of VII are not in agreement with the values to be expected based on the other chlorinated dimethyl ethers.

EXPERIMENTAL

Chlorination of chloromethyl methyl ether. A 2-liter, 3-necked flask which was equipped with a mechanical stirrer, condenser and ice trap, thermometer, and sintered-glass disk inlet tube was charged with 322 g. (4.0 moles) of chloromethyl methyl ether and 1232 g. (8.0 moles) carbon tetrachloride. The flask was illuminated with a 275-watt ultraviolet bulb. Chlorine was admitted through the sintered disk at a rate of 200 ml./min. until 142 g. (2.0 moles) had been introduced. The heat of reaction maintained the system at reflux. Fractionation of the product produced 163 g. (1.4 moles) bis(chloromethyl) ether (I); b.p. 103–105°, n_D^{20} 1.4421 and 24 g. (0.2 mole) dichloromethyl methyl ether (II); b.p. 82–84°, n_D^{20} 1.4353.

Anal. Calcd. for $ClCH_2OCH_2Cl$: Sapon. Equiv., 57.5; Cl, 61.68. Found: Sapon. Equiv., 57.3; Cl, 61.81.

Calcd. for CH_3OCHCl_2: Sapon. Equiv., 38.3; Cl, 61.68. Found: Sapon. Equiv., 38.4; Cl, 61.77.

Chlorination of bis(chloromethyl) ether (I). The equipment described under chlorination of chloromethyl methyl ether was charged with 460 g. (4.0 moles) (I) and 1232 g. (8.0 moles) carbon tetrachloride. After heating to reflux, chlorine was passed in at a rate of 407 ml./min. until 212 g. (2.98 moles) had been introduced. The heat of reaction maintained the system at reflux. Fractionation of the product yielded 190 g. (1.27 moles) (42.6% yield) of (III) with b.p. 129°, n_D^{20} 1.4622 and d_4^{30} 1.464.

Anal. Calcd. for $ClCH_2OCHCl_2$: mol. wt., 149.4; Cl, 71.19. Found: mol. wt., 150; Cl, 70.5.

Chlorination of dichloromethyl methyl ether (II). The equipment described under chlorination of chloromethyl methyl ether was charged with 196 g. (1.7 moles) (II) and 616 g. (4.0 moles) carbon tetrachloride. After heating to reflux, chlorine was admitted at a rate of 275 ml./min. until 64 g. (0.90 mole) had been introduced. Only initial heating was necessary to hold the temperature at reflux. Upon fractionation, 109 g. (0.73 mole) (81.1% yield) of chloromethyl dichloromethyl ether (III) was obtained with b.p. 128–129°, n_D^{20} 1.4630, and d_4^{30} 1.464. No methyl trichloromethyl ether was isolated. The physical constants and analysis of this product agreed well with those obtained by the chlorination of bis(chloromethyl) ether.

Chlorination of dichloromethyl chloromethyl ether (III). The equipment described under chlorination of chloromethyl methyl ether was charged with 284 g. (1.9 moles) (III) and 616 g. (4.0 moles) carbon tetrachloride. The solution was heated to reflux and chlorine was bubbled in at a rate of 114 ml./min. until 81g. (1.15 moles) had been introduced. The heat of reaction maintained the system at reflux. By fractionation at reduced pressures, 63 g. (0.34 mole) (29.6% yield) of bis(dichloromethyl) ether (V) was obtained having b.p. 143°, n_D^{20} 1.4728 and d_4^{30} 1.558.

Anal. Calcd. for $CHCl_2OCHCl_2$: mol. wt., 183.9; Cl, 77.13. Found: mol. wt., 190; Cl, 76.4.

Only one product resulted from this reaction whereas two products are possible. Since neither of the two expected products is reported in the literature, the identity of the product was confirmed by mass spectrometer and infrared patterns.[9] The mass pattern showed relative peak heights at 83, 85, and 87 of 1.00:0.64:0.116 which is in good agreement with the values expected for $CHCl_2$ based on the relative abundance of the chlorine isotopes. The ratios of the heights of the 117, 119, 121, and 123 peaks are 1.00:4.67:4.00:1.17. These values are not in agreement with the heights expected for a CCl_3 group which should be 1.0:1.0:0.3:0.04. The infrared pattern as interpreted by Dr. W. H. Calkins is in agreement with the pattern to be expected for the *sym*-tetrachloro derivative. Furthermore, the relative areas from a gas chromatogram indicated that the sample was about 95% pure.

Chlorination of bis(dichloromethyl) ether (V). The equipment described under chlorination of chloromethyl methyl ether was charged with 616 g. (4.0 moles) carbon tetrachloride and 368 g. (2.0 moles) (V). The solution was heated to reflux and chlorine was introduced at a rate of 142 ml./min. until 43 g. (0.6 mole) had been admitted. It was necessary to apply external heat to maintain reflux. Fractionation of the product at reduced pressures resulted in the recovery of phosgene, unreacted (V) and 709 g. (4.6 moles) carbon tetrachloride. The excess carbon tetrachloride over that charged presumably resulted from the same decomposition which produced phosgene. No chloroform or more highly chlorinated ether was recovered.

This experiment was repeated reducing the temperature to 50° and the chlorine flow to 100 ml./min. Again phosgene, unreacted V, and 115% of the charged carbon tetrachloride were obtained by fractionation at reduced pressures.

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(7) I. Rabcewicz-Zabkowski, and S. Chwalinski, *Roczniki Chem.*, **10**, 686 (1930).

(8) V. Regnault, *Ann.*, **34**, 24 (1840).

(9) The authors wish to thank Dr. W. H. Calkins and E. I. du Pont de Nemours and Co., Inc., for the mass spectrometric and infrared analyses.

Preparation of 1,5-Dibromo-4,8-diiodonaphthalene[1]

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Received September 30, 1957

We have recently prepared 1,5-dibromo-4,8-diiodonaphthalene according to the method of Whitehurst.[2] Some observations upon this synthesis are pertinent.

(1) Abstracted from a thesis presented to the Graduate School, University of North Dakota, by Robert W. Bayer in partial fulfillment of the requirements for the Master of Science degree in chemistry.

(2) J. S. Whitehurst, *J. Chem. Soc.* 222 (1951).

EXPERIMENTAL

In this six-step process, the intermediate products were accumulated in several runs, in which the reaction conditions were varied in attempts to improve the yields. Only the significant departures from Whitehurst's work are given in any detail. The best experimental conditions are described.

A mixture[3] of 40 g. of 1,5-dinitronaphthalene (K and K Laboratories, reagent grade), 120 g. of iron powder, 12 g. of ferrous sulfate, and 400 ml. of water was put into a 1-liter 3-neck flask equipped with a mechanical stirrer, and refluxed for 5 hr., cooled in an ice water bath, and filtered. The residue was returned to the reaction flask and refluxed with 250 ml. of pyridine for about 5 min., treated with Norite A, and filtered hot. The residue was extracted twice more with pyridine. To the hot extracts 30 g. of *p*-toluenesulfonyl chloride was added, the mixture kept hot for 30 min., then cooled, and 250 ml. of water added. The crude 1,5-bis(*p*-toluenesulfonamido)naphthalene was recrystallized once more from pyridine-water. The yield was 30.4 g. (35.5%). A purer sample had a melting point of 325–327° (decomp., corr.; lit.: 318° C., uncorr.).

The 4,8-dibromo-1,5-bis(*p*-toluenesulfonamido)naphthalene was prepared from the above intermediate on a ten-gram scale according to the method of Whitehurst.[2] The crude product was washed with boiling ethanol (95%). The yield was 8.1 g. (60%) and the material had a melting point of 245–250° (decomp., corr.; lit. 248°, decomp., uncorr.).

The 1,5-dibromo-4,8-diiodonaphthalene was prepared[2] by hydrolyzing ten-gram quantities of the above intermediate in concentrated sulfuric acid for 36 hr., followed by tetrazotization and reaction with potassium iodide. The crude product was extracted with acetic acid. The yield in the best run after one such extraction was 2.0 g.

A solution of 4.2 g. of the crude 1,5-dibromo-4,8-diiodonaphthalene dissolved in a minimum quantity of a 7:1 by volume *n*-heptane/benzene mixture was placed upon a 67 × 2.2 cm. activated alumina column (Alcoa, F-20). This mixture was fractionated using *n*-heptane (Phillips 66, pure grade) as the eluant. The course of the process was followed by infrared spectrometry. The first 4750 ml. of eluant contained an impurity, compound I. The pure 1,5-dibromo-4,8-diiodonaphthalene was taken off the column with 350 ml. of benzene. The yield was 1.9 g. and the pure product had a melting point of 163.5–164.5° (corr.; lit. 148°, uncorr.).

Anal.: Calcd. for $C_{10}H_4Br_2I_2$: C, 22.33; H, 0.75; halogen, 76.92. Found: C, 22.37; H, 0.87 halogen, 76.15, 76.40.

The infrared spectrum possessed an intense absorption at 823 cm.$^{-1}$, and hence was consistent with that of a 1,4,5,8-tetrasubstituted naphthalene.

The impurity, compound I, had intense absorption bands at 823 and 796 cm.$^{-1}$, consistent with that of a 1,4,5-trisubstituted naphthalene. The melting point was 106–109°. Its ultimate analysis is given in Table I.

TABLE I

ANALYSIS OF COMPOUND I

	Sample 1[a]	Sample 2[a]		$C_{10}H_5BrI_2$	$C_{10}H_5Br_2I$
C	26.23	26.08	25.99	26.17	29.16
H	0.93	1.26	1.32	1.10	1.22
Br		12.79	13.32	17.42	38.80
I		59.63	59.68	55.31	30.81
Total halogen	69.55, 69.45	(72.42)[b]	(73.00)[b]	72.73	69.61
Total	96.71	99.96	100.31		

[a] 50 mg. samples. [b] Calculated quantities are in parentheses.

DISCUSSION

In the preparation of the diamine it was found that the yields could be improved almost twofold by increasing the reduction time from 3 to 5 hr., and by extracting the material with pyridine rather than with boiling alcohol. While the bromination of the 1,5-bis(*p*-toluenesulfonamido)naphthalene is evidently incomplete, it does not appear that it can be improved upon. The procedure involves a 100% excess of bromine; compare Whitehurst's discussion.[2] Attempts to purify the 4,8-dibromo-1,5-bis(*p*-toluenesulfonamido)naphthalene through recrystallization from nitrobenzene,[2] led only to a black residue.

The method used in the preparation of the 1,5-dibromo-4,8-diiodonaphthalene from the 4,8-dibromo-1,5 bis(*p*-toluenesulfonamido)naphthalene leaves a great deal to be desired. The best yield obtained from 10 grams of this starting material can be estimated to be approximately one gram of pure product (11%). Using the method of Whitehurst, our yields were less than those he reported. In attempting to improve these yields, the time of tetrazotization was varied. The best results were obtained when the entire tetrazotization and iodination were carried out as rapidly as possible. Increasing the time of tetrazotization over the 5 min. recommended by Whitehurst caused a substantial decrease in the yield.

Extreme precautions were taken to keep the temperature of the tetrazotization and iodination reaction below 0°. The amount of urea added to decompose the excess nitrous acid was varied from 0 to 4 grams. The acidity of the solution was doubled. These last two variations gave no significant improvement over Whitehurst's procedure. The difficulty in the last step would then appear to be in the long hydrolysis of the 4,8-dibromo-1,5-bis(*p*-toluenesulfonamido)naphthalene to obtain the 4,8-dibromo-1,5-diaminonaphthalene.

The impurity, compound I, in the 1,5-dibromo-4,8-diiodonaphthalene, had a negative qualitative test for nitrogen. While the ultimate analysis is far from conclusive, the constant agreement of the carbon and of the total halogen analysis (if it is assumed that the 3.3% error in sample one is an error in the halogen analysis) seems to indicate that it is primarily 4-bromo-1,5-diiodonaphthalene. This is the logical impurity since it was not possible to purify the 4,8-dibromo-1,5-bis(*p*-toluenesulfonamido)naphthalene. It was thought that the compound I may have been caused by the loss of iodine from the tetrahalide in an acid solution or under the influence of ultraviolet light, since the acetic acid solutions used for initial recrystallizations became colored. However, compound I was found in the infrared spectrum of the crude product before recrystallization. The infrared spectrum of a sample of Professor Whitehurst's 1,5-dibromo-4,8-diiodonaphthalene showed the presence of compound I.

The behavior of the 1,5-dibromo-4,8-diiodonaphthalene upon recrystallization from acetic acid is anomalous. While it is possible to obtain a spectroscopically pure sample in three recrystallizations, the melting point of the crystals is 90–145°.

Acknowledgment. We wish to acknowledge the assistance of Professor Whitehurst in supplying us with samples of his compounds and advice on the procedures.

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(3) H. H. Hodgson, J. S. Whitehurst, *J. Chem. Soc.*, 2, 202 (1945).

Studies in Chalcones and Related Compounds Derived from 2-Hydroxy-5-acetaminoacetophenone. III. Synthesis of 6-Amino-2-methylchromone and 6-Aminoflavone by the Claisen Reaction

A. A. Raval and N. M. Shah

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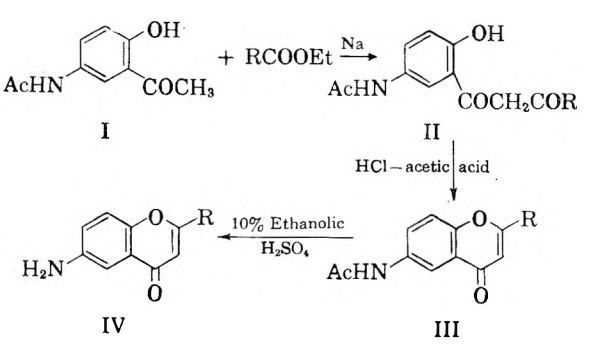
In earlier parts of this series,[1] the authors described several 6-acetaminoflavones obtained by selenium dioxide oxidation of different chalcones obtained from 2-hydroxy-5-acetaminoacetophenone.

This method could not be applied for obtaining the chromones. The Claisen condensation was therefore studied and the syntheses of 6-acetamino- and 6-amino-2-methylchromone and of 6-acetamino- and 6-aminoflavone are described in this paper.

2-Hydroxy-5-acetaminoacetophenone (I) was condensed with ethyl acetate under the conditions of the Claisen reaction to yield the β-diketone, 2-hydroxy-5-acetamino-ω-acetylacetophenone (II: R = CH_3), which on cyclization gave 6-acetamino-2-methylchromone (III: R = CH_3). The latter was then deacetylated to 6-amino-2-methylchromone (IV: R = CH_3). If 2-hydroxy-5-amino-acetophenone hydrochloride was used, 6-amino-2-methylchromone was formed directly; no β-diketone could be isolated.

The Claisen reaction of I with ethyl benzoate gave 2-hydroxy-5-acetamino-ω-benzoylacetophenone (II: R = Ph), which on cyclization with HI gave 6-aminoflavone (IV: R = Ph). When, however, a hydrochloric–acetic acid mixture was used for ring closure, 6-acetaminoflavone (III: R = Ph), identical with that obtained by selenium dioxide oxidation of chalcone, was obtained.



A study of the Kostanecki-Robinson acylation of 2-hydroxy-5-acetaminoacetophenone is in progress.

(1) (a) A. A. Raval and N. M. Shah, *J. Org. Chem.*, **21**, 1408 (1956); (b) *J. Org. Chem.*, **22**, 304 (1957).

EXPERIMENTAL

2-Hydroxy-5-acetamino-ω-acetylacetophenone (II: R = CH_3). A mixture of 2-hydroxy-5-acetaminoacetophenone[2] (1 g.), finely divided metallic sodium (1 g.) and ethyl acetate (25 ml.) was refluxed on a water bath for 6 hr.; the reaction mixture changed from pale green to deep yellow color. It was then cooled and methanol (5 ml.) was added to it to dissolve unreacted sodium.

The mixture was then diluted with ice cold water and acidified with glacial acetic acid. A pale yellow solid separated which was crystallized from dilute acetic acid as pale brown long needles, 0.75 g., m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: N, 5.95. Found: N, 6.10.

The compound is soluble in dilute alkali with the formation of a red color. It dissolves readily in ethanol, acetic acid, ethyl acetate, and methanol. It gives a red color with ethanolic ferric chloride.

6-Acetamino-2-methylchromone (III: R = CH_3). To 2-hydroxy-5-acetamino-ω-acetylacetophenone (0.5 g.) dissolved in glacial acetic acid (25 ml.), concentrated hydrochloric acid (2 ml.) was added and the solution was heated on a wire gauze at 110–112° for 15 min., when colorless shining plates started to separate. The mixture was then diluted with water to precipitate a pale yellow solid. It was filtered, washed with dilute alkali (5%), and crystallized from acetic acid as colorless shining plates, 0.4 g., m.p. 270–271°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: N, 6.45. Found: N, 6.36.

The compound is soluble in acetic acid and benzene, but less soluble in ethanol and ethyl acetate. It is insoluble in dilute alkali as well as dilute mineral acids. It does not give an ethanolic ferric chloride color test.

The *diacetyl derivative*, prepared by the acetic anhydride–sodium acetate method, crystallized from ethanol in the form of colorless shining needles, m.p. 278–279°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: N, 5.40. Found: N, 5.26.

6-Amino-2-methylchromone (IV: R = CH_3). (*a*) 6-Acetamino-2-methylchromone (0.2 g.) in ethanol (25 ml.) was treated with dilute sulfuric acid (10%; 30 ml.) to slight turbidity, which was removed by adding more ethanol (20 ml.). The clear solution was refluxed on a water bath for 5 hr. On removal of ethanol, a clear solution was obtained, which on treatment with ammonia gave a brown solid. It was collected and crystallized from ethanol from which the compound separated in the form of golden yellow shining needles, turning brown after 260° and melting at 275°.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8.00. Found: N, 7.80.

(*b*) A mixture of 2-hydroxy-5-aminoacetophenone hydrochloride (0.5 g.), finely divided sodium metal (0.5 g.), and ethyl acetate (15 ml.) was refluxed on a water bath for 6 hr. as before. On working it up similarly, a yellowish brown solid separated, which was collected. It crystallized from ethanol, separating as golden yellow shining needles, turning brown after 260° and melting at 275°. The yield was 0.2 g.

The product is insoluble in dilute alkali, but dissolves readily in dilute mineral acids. It is also soluble in common organic solvents. It does not give an ethanolic ferric chloride color test.

The *diacetyl derivative*, prepared by the acetic anhydride–sodium acetate method, was identical with the diacetyl derivative described earlier.

2-Hydroxy-5-acetamino-ω-benzoylacetophenone (II: R = Ph). 2-Hydroxy-5-acetaminoacetophenone (1 g.), finely divided sodium metal (1 g.), and ethyl benzoate (20 ml.) were refluxed on an oil bath at 180–200° for 6 hr. The cold reaction mixture, washed as before and acidified with acetic acid, was then subjected to steam distillation; a yellow solution was obtained. It was extracted with ether, and the ethereal extract dried with anhydrous calcium chloride. After removal of ether, the solid obtained was twice crys-

(2) F. Kunckell, Ber., **34**, 125 (1901); Julia and Baillarge, *Bull. soc. chim. France*, 639 (1952); *Chem. Abstr.*, **47**, 3815 (1953) [*cf.* ref. 1a.]

tallized from ethanol to give 0.8 g. of pale yellow needles, m.p. 117–118°.

Anal. Calcd. for $C_{17}H_{15}NO_4$: N, 4.71. Found: N, 4.58.

It is soluble in ethanol, acetic acid, ethyl acetate, and acetone. It gives a reddish brown color with an ethanolic ferric chloride. It is soluble in dilute alkali, but insoluble in dilute mineral acids.

6-Acetamino-flavone (III: R = Ph). 2-Hydroxy-5-acetamino-ω-benzoylacetophenone (0.5 g.) in a mixture of acetic acid (15 ml.) and concentrated hydrochloric acid (3 ml.) was heated at 118–120° for 0.5 hr. On diluting with ice cold water, a brown solid separated; it was collected, washed with dilute alkali (5%) and crystallized from ethanol to give yellowish brown needles, m.p. 174°; the mixed melting point with an authentic sample was undepressed.

The *diacetyl derivative* prepared by the acetic anhydride–pyridine method, crystallized from ethanol in form of brown granules, m.p. 256–258°, mixed melting point with an authentic sample remaining undepressed.

6-Aminoflavone (IV: R = Ph). 2-Hydroxy-5-acetamino-ω-benzoylacetophenone (0.5 g.) and concentrated hydriodic acid (10 ml.) were refluxed on an oil bath at 140° for 3 hr. The reaction mixture was poured into ice cold water containing sodium bisulfite. The clear solution on treatment with ammonia gave a pale brown solid; it was collected and washed with dilute alkali and crystallized from ethanol to give brown needles, m.p. 192°, mixed melting point with an authentic sample remaining undepressed.

The *diacetyl derivative*, prepared as before, crystallized from ethanol in form of brown granules, m.p. 256–258°; the mixed melting point with the sample obtained earlier was undepressed.

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9,10-Dimethyl-3,4-benzpyrene[1,2]

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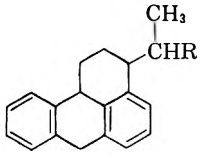
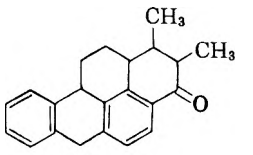
Received October 18, 1957

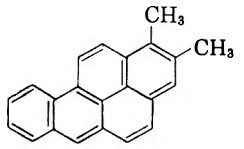
The synthesis of 9,10-dimethyl-3,4-benzpyrene (IV) has been accomplished *via* α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionic acid (I), an intermediate available from previously reported research.[4] The Wilds modification of the Arndt-Eistert synthesis with diazoethane[5] converted α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionyl chloride to α-methyl-β-(1,2,3,-11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)butyric acid (II) in 80% yield. Cyclization of II with anhydrous hydrogen fluoride produced 8-keto-9,10-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (III). Reduction of the ketone III with aluminum isopropoxide in toluene gave a carbinol which was directly dehydrated and dehydrogenated over palladium-charcoal to provide 9,10-dimethyl-3,4-benzpyrene (IV) in 20% yield from III.



I, R = COOH
II, R = CH(CH₃)COOH



III



IV

The acid II, the ketone III, and its *p*-nitrophenylhydrazone were isolated as oily mixtures of diastereoisomers which could not be crystallized. Precedence for this reaction sequence was established by the synthesis of 9-methyl-3,4-benzpyrene described previously.[6]

The hydrocarbon IV formed an unstable purple picrate derivative and gave an ultraviolet absorption spectrum characteristic of 3,4-benzpyrene. The hydrocarbon has been submitted to Northwestern University Medical School for carcinogenic testing.

EXPERIMENTAL[7]

8-Keto-9,10-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (III). This ketone (3.5 g.) was obtained as a viscous yellow oily mixture of isomers from 5.8 g. (0.020 mole) of α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionic acid (I) via the acid II using previously published procedures.[6]

9,10-Dimethyl-3,4-benzpyrene (IV). Reduction of 3.15 g. (0.0104 mole) of the oily ketone III was carried out with 5.0 g. (0.0245 mole) of aluminum isopropoxide and 50 ml. of C.P. toluene. After 50 hr. of intermittent distillation using a Hahn condenser, the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The reaction mixture was worked up in the usual manner[6] and the crude alcohol thus obtained was directly dehydrated and dehydrogenated at 240–345° over 0.5 g. of 10% palladium-charcoal for 1.5 hr. After cooling, the hard cake was dissolved in benzene and the solution was filtered. This solution was chromatographed over alumina to give an initial fraction containing an oil which did not give a darkly colored solution with picric acid. Further elution of the column with benzene yielded fractions containing an orange solid which was decolorized with Norit and crystallized twice from ethyl acetate producing 0.57 g. (11% over-all yield from I) of 9,10-dimethyl-3,4-benzpyrene (IV) as small yellow needles, m.p. 174–175.5°.

(1) From the dissertation presented by Jules L. Adelfang to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) This investigation was supported in part by a research grant (C-1595) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Graduate Research Assistant, February 1956 to August 1957.

(4) J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **77**, 3297 (1955).

(5) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

(6) J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **79**, 1751 (1957).

(7) All melting points are uncorrected.

An analytical sample, m.p. 174.5–175.5°, was prepared by crystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.25; H, 5.75. Found: C, 94.45; H, 5.64.

The hydrocarbon IV gave an unstable, purple picrate, m.p. 182–184°.

Ultraviolet absorption spectrum. The ultraviolet absorption spectrum of 9,10-dimethyl-3,4-benzpyrene in 95% ethanol was measured with a Model DU Beckman spectrophotometer. Maxima and (log ϵ) values are: 260 mμ (4.59), 268 mμ (4.70), 288 mμ (4.63), 300 mμ (4.70), 372 mμ (4.40), and 392 mμ (4.48).

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Vinyl-Alkali Metal Compounds[1]

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Reaction of vinyl chloride with alkali metals in tetrahydrofuran has yielded the vinyl-alkali metal compounds, as might be expected from recent success in making the vinyl-Grignard reagent in that solvent.[2] The simplicity of the procedure makes it preferable to the exchange reaction through which vinylsodium was first made.[3] Propenyllithium and several other alkenyllithium compounds have been made directly from the bromides in diethyl ether or petroleum ether,[4] but all attempts to similarly prepare vinyl compounds have failed.

The example given below concerns vinylpotassium prepared from liquid 90% potassium-sodium alloy,[5] but small-scale qualitative observations have shown that potassium, sodium, and lithium will each react.

Though the Grignard reagent is as easily made, vinylsodium or vinylpotassium may offer advantage on those occasions where the solid organometallic compound is needed, since they have little solubility and can be made solvent-free without decomposition by removal of solvent under reduced pressure. This operation leads to decomposition of the vinyl Grignard reagent.[2]

As an example the reaction of vinyl Grignard solution with diethyl bromoborane gave only triethylborane, no trivinylborane, and evidence of polymers was seen. In contrast reaction of solid vinylpotassium gave some polymer, but trivinylborane and a mixture of ethylvinylboranes were obtained also.

The solvent should be removed from vinylpotassium (and presumably vinylsodium) as soon as possible because the solid reacts with the tetrahydrofuran. Were the solvent removed at once, the yield would probably be comparable with the best obtained by the exchange method.

EXPERIMENTAL

The vinyl chloride solution (95 g. in 405 g. tetrahydrofuran) was prepared by passing the gas through sodium hydroxide solution and a drying train into the solvent cooled to 0°. This was added slowly to 50 g. 90% potassium-sodium alloy covered with 350 g. tetrahydrofuran cooled to 0° C. in a 3-neck flask fitted with a Hershberg stirrer. A blue precipitate formed which reached a viscous gel-like consistency as the reaction proceeded.

A day after completion the preparation was assayed using a 3/808 g. aliquot from the well stirred slurry. Treatment with isopropyl alcohol in the vacuum apparatus gave 1.8 mmoles of ethylene with the correct vapor pressure, corresponding to a total vinylpotassium content of 485 mmoles or a yield of 32%. Five days later the solvent was removed under reduced pressure, and a similar assay of a 1.81/90 g. aliquot of dry powder gave a yield of 7.4%. Apparently reaction with the solvent had occurred.

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Reaction of Isocyanates with Tris(hydroxymethyl)aminomethane

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During the course of an investigation of certain urea derivatives it was necessary to prepare a series of 1-substituted-3-tris(hydroxymethyl)methylureas. Pierce *et al.*[2] described aromatic compounds of this type in which the substituents were phenyl, *o*- and *p*-tolyl, and 1- and 2-naphthyl. These compounds were prepared by reaction of equimolar quantities of isocyanate with tris(hydroxymethyl)aminomethane (I) in chloroform solution, but this method was disadvantageous in that I was insoluble in chloroform.

In addition to the phenyl and 1-naphthyl derivatives, made by the method of Pierce, a series of new derivatives has been prepared. It was found

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF 18(600)-1541. Reproduction in whole or in part is permitted for any purpose of the United States Government.

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(1) For reprints: 3267 57th Avenue S. W., Seattle 16, Wash.

(2) J. S. Pierce, C. D. Lunsford, R. W. Raiford, J. L. Rush, and D. W. Riley, *J. Am. Chem. Soc.*, 73, 2595 (1951).

that reactions proceed more smoothly and in better yield when conducted in dilute isopropyl alcohol in which I was soluble. Reaction of the amino group of I with isocyanate was very rapid, and carbamate formation by reaction with solvent or the hydroxymethyl groups of I was negligible.[3] The urea derivatives listed in Table I ranged from colorless crystals in the case of the short-chain members to white waxy solids in the case of the long-chain compounds.

TABLE I

1-SUBSTITUTED-3-TRIS(HYDROXYMETHYL)METHYLUREAS
$RNHCONHC(CH_2OH)_3$

R	Yield, %	M.P.,[4] °C.	Analysis % N Calcd.	Analysis % N Found
Allyl	79	140	13.72	13.45
Isopropyl	75	165	13.59	13.49
n-Butyl	82	145	12.72	12.21
n-Amyl	81	162	11.96	11.77
Phenyl	85	196	11.66	11.86
Cyclohexyl	82	189	11.38	11.26
n-Octyl	79	140	10.14	9.87
1-Naphthyl	96	215	9.65	9.90
n-Dodecyl	89	141	8.43	8.37
2-Biphenylyl	95	188	8.86	8.43
n-Octadecyl	97	64	6.73	6.38

EXPERIMENTAL

Materials. Isocyanates were supplied by the Monsanto Chemical Co., Anniston, Ala., and St. Louis, Mo. Tris(hydroxymethyl)aminomethane was obtained from the Commercial Solvents Corp., New York, N. Y.

Anal. Calcd. for $C_4H_{11}NO_3$: N, 11.57. Found: N, 11.63.

Synthesis of 1-substituted-3-tris(hydroxymethyl)methylureas. General procedure. Isopropyl alcohol (35 ml.) was added to a hot solution of tris(hydroxymethyl)aminomethane (I) (12.1 g., 0.10 mole) in water (25 ml.) and the mixture heated to gentle reflux. The isocyanate (0.10 mole), followed by isopropyl alcohol (15 ml.), was then added dropwise during a two-minute period and the mixture was refluxed for ten minutes. On cooling, the urea derivative was filtered and recrystallized twice from isopropyl alcohol.

Tolylene-2,4-bis[3'-tris(hydroxymethyl)methylurea]. This compound was prepared in 96% yield by the method described above, using tolylene-2,4-diisocyanate (17.5 g., 0.10 mole) and I (24.2 g., 0.20 mole) in isopropyl alcohol (75 ml.). Recrystallization twice from the same solvent yielded white needle-like crystals, m.p. 207–208°.

Anal. Calcd. for $C_{17}H_{28}N_4O_8$: N, 13.46. Found: N, 13.27.

4,4'-Bis[3'-tris(hydroxymethyl)methylureido]diphenylmethane. One-gram increments of diphenylmethane-4,4'-diisocyanate (25.0 g., 0.10 mole) were slowly added to I (24.2 g., 0.20 mole) dissolved in a hot mixture of water (20 ml.) and isopropyl alcohol (75 ml.). After the initial strongly exothermic reaction had subsided the mixture was refluxed for 15 min., then set aside to cool. White crystals, yield, 48.2 g. (98%). Two recrystallizations from isopropyl alcohol gave a product of m.p. 188°.

Anal. Calcd. for $C_{23}H_{32}N_4O_8$: N, 11.38. Found: N, 11.30.

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(3) The amino group of I is much more basic than are the hydroxyl groups. The basic dissociation constant, pK_b 5.97, has been determined by S. Glasstone and A. F. Schram, *J. Am. Chem. Soc.*, 69, 1213 (1947). When I is treated with RNCO the amino group apparently reacts at a greater rate than the hydroxyl groups.

(4) Melting points are uncorrected.

Intramolecular Hydrogen Bonding Involving π-Electrons in Phenethyl Alcohols

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Received October 22, 1957

That aromatic hydrocarbons can participate as weak electron donors in hydrogen bond formation has been shown conclusively in recent publications.[1–3] Of special interest is the intramolecular hydrogen bonding in a series of vinyl alcohols reported by Rodebush.[4] Evidence is presented here for the presence of intramolecular hydrogen bonding in a series of phenethyl alcohols.

During the course of a spectral examination of phenethyl alcohol (I) (0.5% in carbon tetrachloride) it was observed that the first overtone of the fundamental stretching vibration of the hydroxyl group[5] was not a single, sharp peak as would have been expected for a non-bonded hydroxyl group, but was a doublet with a strong peak at 1.4084 μ and a weaker peak at 1.4209 μ. The ratio of the intensities of these two peaks (as measured at maximum absorption) was independent of concentration at several low concentrations. Under the same conditions benzyl alcohol (II) and 3-phenyl-1-propanol (III) showed only sharp singlets at 1.4155 μ and 1.4067 μ, respectively.

From an examination of molecular models of I, II, and III it was apparent that the peak at 1.4209 μ in the spectrum of I could have resulted from an intramolecular hydrogen bond between the hydroxyl group and the π-electrons at the 1-position of

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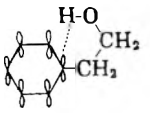
the aromatic nucleus in those molecules having the conformation shown:



I

This interesting possibility was confirmed by examining the spectra of *p*-methoxyphenethyl alcohol (IV) and *p*-nitrophenethyl alcohol (V): IV showed the expected doublet; V showed only a singlet.[6] Since compounds I to V all showed only one peak in the 1.417 to 1.424 μ region when the spectra were run in *benzene* solution, the peak at longer wave length for each doublet is assigned to the first overtone of the fundamental stretching vibration of the bonded hydroxyl group. The expected doublets were also observed in the spectra of 1,2-diphenyl ethanol (VI) and 1-phenyl-2-propanol (VII). All spectra are recorded in Table I.

TABLE I

ABSORPTION BANDS IN THE 1.4 μ REGION[7]

	0.5% CCl_4 Soln.	Δ[8]	0.5% Benzene Soln.
Phenethyl alcohol (I)	1.4084, 1.4209	0.0125	1.4235
Benzyl alcohol (II)	1.4155		1.4193
3-Phenyl-1-propanol (III)	1.4067		1.4170
p-Methoxyphenethyl alcohol (IV)	1.4085, 1.4223	0.0138	1.4220
p-Nitrophenethyl alcohol (V)	1.4088[9]		1.4220
1,2-Diphenyl ethanol (VI)	1.4161, 1.425[10]		
1-Phenyl-2-Propanol (VII)	1.4129, 1.4229		

That the above spectral data are compatible with the postulated intramolecular hydrogen bonding at the 1-position rather than at the 2,6-positions is shown by comparison of the Δ values above. The order $\Delta_{IV} > \Delta_I$ would be expected on the basis of Hammett's σ constants[11] for interaction at the 1-position. If, on the other hand, the interaction were at the 2,6-positions the reverse order $\Delta_I > \Delta_{IV}$ should have been observed.

(6) The absence of a second peak at longer wave length in the spectrum of V is attributed to the powerful electron-withdrawing ability of the *p*-nitro group.

(7) Spectra were measured on a Cary recording spectrophotometer, Model 14. Wave lengths, in microns, are accurate to ± 0.0003 micron.

(8) Δ = distance in microns between the peaks for I and IV.

(9) 0.15% solution.

(10) Shoulder.

(11) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 188.

Using the value of 70 cm^{-1} for each kcal/mole of bond energy[12] the strengths of the hydrogen bonds in compounds I and IV are determined to be 0.88 and 0.98 kcal/mole, respectively.

EXPERIMENTAL

The phenethyl alcohol (Dow Chem. Co.) was purified by fractional distillation, n_D^{20} 1.5325 (lit.[13] n_D^{20} 1.5310–1.5330). *p*-Methoxyphenylacetic acid (Aldrich Chem. Co.), m.p. 86–88° (lit.[14] m.p. 85–87°), was reduced with lithium aluminum hydride to give IV, semicrystalline at 25° (lit.[15] m.p. 24°). Nitration of I according to the published procedure[16] yielded V, m.p. 61.5–62.5° (lit.[16] m.p. 62°). A commercial sample of 1,2-diphenyl ethanol (VI), m.p. 66–67° (Eastman), was used without further purification. 1-Phenyl-2-propanone (Eastman) was reduced with lithium aluminum hydride to give VII, n_D^{20} 1.5217 (lit.[17] $n_D^{14.5}$ 1.5243).

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Carbonyl Reactions. III. The Formation of Aromatic Semicarbazones. A Nonlinear Rho-Sigma Correlation[1]

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The formation of semicarbazones represents one of the important examples of general acid catalysis.[2-4] The effect of structure upon reactivity has been studied by Price and Hammett[3] who point out that the relative entropy of activation fluctuates in a series of aliphatic compounds. Cross and Fugassi[5] have reported a satisfactory Hammett-type correlation for a limited number of *p*-substituted acetophenones. On the other hand, the report of

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Vavon and Montheard[6] indicates that simple rho-sigma correlation may not obtain with aromatic aldehydes in the formation of phenylhydrazones and oximes.

Since the formation of semicarbazones, phenylhydrazones, and oximes almost certainly proceeds by the same general mechanism, and since the details of semicarbazone formation have been the most thoroughly investigated, we have carried out a study of the rate of reaction of a representative series of aromatic aldehydes with semicarbazide.

EXPERIMENTAL

Reagents. The aromatic aldehydes were crystallized or distilled under nitrogen as appropriate. The physical constants were concordant with those in the literature. Other reagents were of reagent grade.

The kinetic runs were carried out in 75% ethanol by volume. Solutions of semicarbazide hydrochloride were made up in 60% ethanol and of 1:1 sodium acetate–acetic acid (0.04*M*) in 75% ethanol. Solutions of the aldehydes were made up in 95% ethanol. The *p*H of the sodium acetate–acetic acid buffer is calculated to be 6.5 from the data of Grunwald and Berkowitz.[7]

Procedure. One hundred milliliters of the sodium acetate–acetic acid buffer solution was pipetted into a 250-ml. glass stoppered flask, and to this was added 20 ml. of 0.05*M* aldehyde solution. At the start of the reaction 20 ml. of 0.05*M* semicarbazide hydrochloride solution was added, and the mixture made up to volume. The rate of reaction was followed by iodimetric titration, essentially as described by Bartlett.[8] Reactions were followed to better than 50% completion.

RESULTS AND DISCUSSION

The kinetic results are summarized in Table I. It is apparent that, under the conditions of our experiments, a simple linear rho-sigma relationship is not obtained. Such failure has been observed in other situations. The reactions of benzyl nitrate with bromide ion,[9] benzyl fluoride with sodium ethoxide,[10] benzyl chloride with trimethylamine,[11] and the copolymerization of methyl methacrylate with substituted styrenes[12] are examples in which the rho-sigma plots are generally concave upward. In the case of the formation of Schiff's bases from substituted benzaldehydes and butylamine[13] Santerre, Hansrote, and Crowell have observed results in which the rho-sigma plot is concave downward. Jaffé[14] and Branch and Calvin[15] have also commented on the possible reasons for failure to obtain simple rho-sigma correlations.

TABLE I

RATE OF FORMATION OF SEMICARBAZONES OF SUBSTITUTED BENZALDEHYDES

Substituent	σ[a]	k_2 (Liter Mole^{-1} Sec.$^{-1}$) $\times 10^2$[b]
p-$(C_2H_5)_2N$	−0.600	0.21[c]
p-CH_3O	−0.268	1.93, 2.10, 1.93[d]
p-CH_3	−0.170	4.58, 4.57
m-CH_3	−0.069	5.76
H	0.000	6.18, 6.02, 6.30, 5.80[d]
m-CH_3O	0.115	5.23
p-Cl	0.227	5.40, 5.42
m-Cl	0.373	5.00
m-NO_2	0.710	3.42, 3.42, 3.25[d]
p-NO_2	0.778	4.45, 4.32

[a] Ref. 14, p. 222. [b] ± 4% unless otherwise noted. [c] ± 8%. [d] Followed spectrophotometrically under pseudo first order conditions with semicarbazide in 50-fold excess. Initial aldehyde concentration, $3 \times 10^{-4} M$.

Our view at the present time is that the most likely cause of failure to obtain a linear rho-sigma correlation with substituted benzaldehydes is that the addition and dehydration steps in the reaction sequence[16] have rate constants such that addition and dehydration are comparable.[17] Willi and Robertson[18] have considered the hydrolysis of Schiff bases from this point of view. On this basis it is also explicable that a more straightforward correlation is obtained with ketones; the rate of addition will be slower, and the rate of dehydration appreciably faster, and the rate controlling step is more simply the rate of addition to the carbonyl group.

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(17) By using the steady state approximation it can be shown for the general case

$$A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B \xrightarrow{k_3} C$$

that the observed rate $k_r = k_1k_3/(k_2 + k_3)$ and that the equation for the relative observed rate is of the form

$$\log (k_r/k_0) = (\rho_1 + \rho_3 - \rho_2)\sigma - \log\left[\frac{1 + \frac{k_3^0}{k_2^0}\,10^{(\rho_3 - \rho_2)\sigma}}{1 + \frac{k_3^0}{k_2^0}}\right]$$

This function is not linear in σ, and may be shown to pass through a maximum by successive differentiation.

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Nitrofuraldoximes. Separation of Isomers by Urea Complex Formation

GABRIEL GEVER

Received November 1, 1957

The separation of various types of isomers by complex formation with urea is a rapidly expanding field of investigation. Most of the work to date has been in the separation of straight chain aliphatic compounds from branched chain compounds.[1] The separation of isomers of aromatic and heterocyclic compounds has also been reported.[2] The examples of separation of stereoisomers are quite rare. Priewe[3] reported the separation of the *cis*-trans isomers of estradiol, and the separation of oleic acid from elaidic acid has been carried out utilizing urea complex formation.[4]

It is the purpose of this paper to report the separation of the *syn* and *anti* forms of 5-nitro-2-furaldoxime by means of urea complex formation. The two isomeric oximes were first reported by Gilman,[5] the *syn* form melting at 121° and the *anti* at 153°. Raffauf[6] reported the melting points as 121° and 159–161°, respectively.

When 5-nitro-2-furaldehyde diacetate was reacted with hydroxylammonium sulfate in the presence of sulfuric acid, a mixture of the isomeric oximes was obtained. Since the *anti* form is much less soluble in methanol than the *syn* it was not difficult to isolate the former from the mixture by recrystallization. Also, the mixture could be completely converted to the *anti* form by treatment of the hydrochlorides of the mixture of oximes with sodium carbonate.[5]

In order to isolate the *syn* form, the applicability of urea complex formation was investigated. An available sample of relatively pure *syn* oxime was treated with urea in methanolic solution and found to form a (1:1) complex. Under identical conditions the *anti* isomer did not form a complex. Decomposition of the *syn* oxime-urea complex with cold water regenerated the pure *syn* oxime.

Taking advantage of the above findings, it was found that a mixture of the two forms could be separated into its two components. Treatment of a 60:40 (*syn*:*anti*) mixture with urea and methanol resulted in a 77% recovery of the pure *syn* form and a 53% recovery of the pure anti form.

The physical constants for the syn oxime were significantly different from those previously reported.[5,6] The melting point was found to be 129–130° compared to 121° and the ultraviolet absorption data in water showed ϵ values of 13,400 and 13,200 at 232.5 mμ and 349 mμ, respectively, compared to 11,900 and 12,500 at 230 mμ and 345 mμ reported by Raffauf.[6]

A melting point curve[7] of varying mixtures (in 10% increments) of the two pure isomers revealed that mixtures containing from 10% to 70% of the *syn* form had a melting point range of about 118–150°. However, mixtures containing 80% or 90% of the *syn* form were completely melted at 119–123° and 119–124°, respectively.

EXPERIMENTAL[8]

syn-5-Nitro-2-furaldoxime-urea Complex (I). To a solution of 98 g. of 5-nitro-2-furaldoxime (m.p. 117–118°) in 400 cc. of methanol was added 60 g. of urea. The mixture was stirred for one hour at 25° and the resulting precipitate filtered and air dried to yield 66.7 g. of yellow crystals, m.p. 123–125°.

Anal. Calcd. for $C_6H_8N_4O_5$: C, 33.34; H, 3.73; N, 25.92. Found: C, 33.45; H, 3.84; N, 25.97.

Attempted preparation of anti-5-nitro-2-furaldoxime (II)–*urea complex.* A mixture of 10 g. of *anti*-5-nitro-2-furaldoxime, 40 cc. of methanol, and 6 g. of urea was stirred at 25° for 15 hr. No complex formed.

Regeneration of syn-5-nitro-2-furaldoxime (III) *from its urea complex.* A suspension of 30 g. of I in 750 cc. of water was stirred for 2 hr. The mixture was filtered and the solid washed with two 50-cc. portions of water. After drying there was obtained 18.6 g., 85%, of III, m.p. 129–130°.

Anal. Calcd. for $C_5H_4N_2O_4$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.6; H, 2.44; N, 17.59.

Conversion of this material to the urea complex, followed by regeneration of the oxime, gave no further change in properties.

Separation of syn and anti forms of 5-nitro-2-furaldoxime. A solution of 100 g. of a mixture of the isomers of 5-nitro-2-furaldehyde oximes (m.p. 118–145°, ϵ = 11,600 at 232.5 mμ) in 500 cc. of methanol was stirred with 75 g. of urea for one hour at 25°. The mixture was filtered to yield 43 g. of the complex (I). The filtrate was evaporated to dryness and the residue slurried with 300 cc. of water to yield 65 g. of a mixture of II and III. This mixture was recrystallized from 250 cc. of methanol (cooling only to 20°) to yield 11.6 g. of II, m.p. 157–160°. The methanolic filtrate was then stirred with 35 g. of urea for one hour at 25° to yield 18.7 g. of I. The filtrate was evaporated to dryness and the above procedure repeated. A total of 71.7 g. of I, 21.3 g. of II, and 14 g. of unseparated material was obtained. The 71.7 g. of I were stirred with 400 cc. of water for one hour. The solid was removed by filtration, washed with cold water, and dried at 60° to yield 46.2 g. of pure III.

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(1) Two review articles which discuss this aspect and contain many references to the literature are F. Cramer, *Rev. Pure and Appl. Chem.* (*Australia*), **5**, 143 (1955); and K. Kobe and W. Domask, *Petroleum Refiner*, **31**, No. 3, 106 (1952).

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(7) I am indebted to Mr. B. Stevenson for preparing a pure sample of *anti*-5-nitro-2-furaldoxime and obtaining these melting point data.

(8) Microanalyses were carried out by Messrs. G. Ginther and A. Mayer of these laboratories. The ultraviolet absorption data were obtained by Mr. C. Eaton using a Beckman DU spectrophotometer. Melting points were taken on the Fisher-Johns apparatus and are corrected.

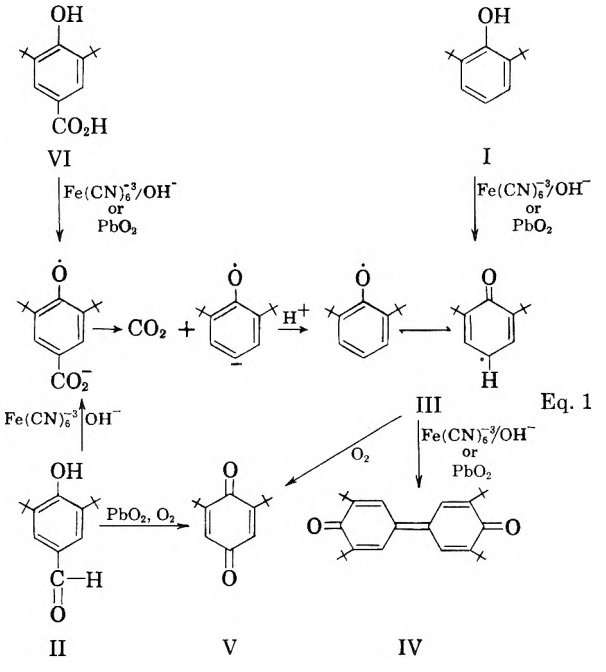
Oxidation of Hindered Phenols. VI. Oxidative Decarboxylation of 3,5-Di-*t*-butyl-4-hydroxybenzoic Acid

CLINTON D. COOK, EDWIN S. ENGLISH, AND BARBARA JOHNSON WILSON

Received November 1, 1957

A recent paper by Yohe and co-workers[1] describes the formation of 2,6-di-*t*-butylquinone upon the oxidation of 2,6-di-*t*-butyl-4-methylphenol and 3,5-di-*t*-butyl-4-hydroxybenzaldehyde with molecular oxygen under alkaline conditions. Since work done in these laboratories has some bearing on this subject, we are led to the publication of this note.

We have found that oxidation of 2,6-di-*t*-butylphenol (I), 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (II), and 3,5-di-*t*-butyl-4-hydroxybenzoic acid (VI) by alkaline ferricyanide in the absence of molecular oxygen produces 3,5,3′,5′-tetra-*t*-butyldiphenoquinone (IV) in essentially quantitative yield. If oxygen is present, moderate yields of 2,6-di-*t*-butylbenzoquinone (V) are also produced from the aldehyde. Under the latter conditions, 2,6-di-*t*-butylphenol gives small yields of the benzoquinone and 3,5-di-*t*-4-hydroxybenzoic acid forms only the diphenoquinone. When lead dioxide is used as the oxidizing agent, 2,6-di-*t*-butylphenol and 3,5-di-*t*-butyl-4-hydroxybenzoic acid both produce the diphenoquinone in excellent yield. In the presence of oxygen, lead dioxide reacts with the aldehyde to give some 2,6-di-*t*-butylbenzoquinone but no diphenoquinone is produced.



These facts are consistent with an oxidatively induced decarboxylation of 3,5-di-*t*-butyl-4-hydroxybenzoic acid, presumably *via* the corresponding phenoxy radical (III). The failure of lead dioxide to produce diphenoquinone by reaction with the aldehyde is undoubtedly due to the inability of lead dioxide to oxidize the aldehyde to the acid. In this case the benzoquinone may perhaps be formed *via* an unstable peroxide. High molecular weight tars were also produced in this case. The proposed reaction scheme is outlined in Equation 1.

Since the acid does not decarboxylate in the absence of the oxidizing agents and since these oxidizing agents are known to react with phenolic hydroxyl groups to produce phenoxy radicals,[2] the proposed ion-radial (or, perhaps, an uncharged radical) is an attractive intermediate. The situation seems not unlike the alkaline decarboxylation of those acids which produce stable anions upon decarboxylation.[3] In the present case, the oxidative removal of the phenolic hydrogen permits the formation of a resonance-stabilized intermediate. A very intense green color during the initial stage of the oxidation of the aldehyde also suggests the incursion of a radical at this point. The variations in the ratio of benzoquinone to diphenoquinone are probably due to variations in the momentary concentration of phenoxy radical at the interface. Thus it is to be noted that maintaining a high dilution (dropwise addition) of the sparingly base-soluble aldehyde markedly increased the yield of the benzoquinone on oxidation with alkaline ferricyanide. This is the expected result since increasing the concentration should increase the rate of dimerization. Similarly, only the dimeric diphenoquinone was formed on oxidation of the acid which, of course, would tend to concentrate at the interface.

EXPERIMENTAL

Materials. The method of Coppinger and Campbell,[4] oxidation of 2,6-di-*t*-butyl-4-methylphenol with bromine in *t*-butyl alcohol, was used to prepare 3,5-di-*t*-butyl-4-hydroxybenzaldehyde. A Cannizzaro reaction on the aldehyde according to the method of Yohe *et al.*,[1] gave 3,5-di-*t*-butyl-4-hydroxybenzoic acid. The Ethyl Corporation generously supplied the 2,6-di-*t*-butylphenol.

Oxidation and identification of products. The solution of the aldehyde, phenol, or acid (.35*M* in benzene) was vigorously stirred with the oxidizing agent while nitrogen or oxygen was bubbled through the system. When ferricyanide was the oxidant, sufficient stock solution (175 g. potassium ferricyanide, 100 g. potassium hydroxide, 1 liter of water) was used to provide five moles of ferricyanide per mole of the reductant; with lead dioxide ten moles of oxidant per mole of reductant was used. The amount of reductant was between 1 and 5 grams in all runs. For the high-dilution runs, the reductant was dissolved in one half the solvent and added

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(3) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, (1956), pp. 283–284.

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TABLE I

Substrate	Oxidant	Temp., °C.	Atm.	Rate of Addn.	Total Time, Hr.	Dipheno-quinone	Benzo-quinone	Remarks
Phenol	Ferricyanide	25 ± 2	N_2	Immediate	4	98%[a]	Trace[c]	
			O_2	Dropwise	43	71%[b]	7%	
	Lead dioxide		O_2	Immediate	12	96%[a]	None	
Aldehyde	Ferricyanide		N_2	Dropwise	48	95%[a]	Trace[c]	
			O_2	Immediate	17	98%[a]	Trace[c]	
			O_2	Dropwise	36		30%	Remainder dipheno-quinone
		0	O_2		48		58%	
	Lead dioxide	25 ± 2	O_2	Immediate	96	None	39%	Remainder tar
	Moist lead dioxide		O_2		72	None	26%	
Acid	Ferricyanide		N_2	Dropwise	24	97%[a]	None	
			O_2		44	96%	None	
	Lead dioxide		O_2	Immediate	2	95%[a]	None	
Diphenoquinone	Ferricyanide		O_2	Immediate	48			No reaction
Aldehyde	$H_2O + O_2$		O_2		75			
	$H_2O/NaOH/O_2$		O_2		72			

[a] Before recrystallization. [b] Loss in handling during recrystallization. [c] Less than 0.1%.

to the reaction mix containing the remainder of the solvent by means of a capillary dropping funnel. After reaction, the benzene layer was evaporated to dryness and the 2,6-di-*t*-butylbenzoquinone separated by sublimation at 65°. The diphenoquinone was recrystallized from ethanol, m.p. 240–241° (uncorr.), reported 245–247°,[5,6] and identified by the identity of the mixture melting point and ultraviolet spectrum with those of an authentic sample.[7]

In those cases where no benzoquinone was formed, the crude diphenoquinone melted within two degrees of the purified product.

Anal. Calcd. for $C_{28}H_{40}O_2$: C, 82.30; H, 9.87. Found: C, 82.35; H, 9.77.

The 2,6-di-*t*-butylbenzoquinone was recrystallized from methanol-water, m.p. 65–66°, reported 65–66°,[8] 67.5–68.5°.[9] A mixture melting point with a known sample showed no depression.

In several runs using the aldehyde, the aqueous layer was strongly acidified. Essentially quantitative (98%) evolution of carbon dioxide resulted.

Acknowledgments. We are indebted to the Research Corp. and the National Science Foundation for grants under which this work was done. The completion of this work was made possible by Dr. Yohe, who provided instructions for the preparation of 3,5-di-*t*-butyl-4-hydroxybenzoic acid prior to their publication. We are also indebted to Dr. Cheves Walling for a very helpful discussion.

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Application of a Silicic Acid Chromatostrip Technique for Observing the Sequential Methylation of β-Resorcylic Acid and Related Reactions

R. L. Lyman,[1] A. L. Livingston, E. M. Bickoff, and A. N. Booth

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During recent work on the characterization of the naturally occurring estrogen, coumestrol,[2] it became necessary to prepare the 2,4-dimethoxy and 2-hydroxy-4-methoxybenzoic acids. We found that these acids, together with their methyl esters, form sequentially as discrete products during the methylation of β-resorcylic acid in alkaline solution. Utilization of a fluorescent silicic acid chromatostrip technique[3] permitted us to observe under ultraviolet light the sequence of formation of each intermediate compound during methylation. As a result, it was possible to stop the reaction at any time in order to obtain the desired derivative. Thus, from one methylation reaction mixture all the methylated derivatives of β-resorcylic acid could be readily isolated.

The chromatostrip technique used to follow the chemical reactions was originally developed by Kirchner *et al.*[3] and Miller and Kirchner[4] and has

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(2) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and F. DeEds, *Science*, **126**, 969 (1957).

(3) J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951).

been successfully applied to a variety of isolations from natural materials.[5–7]

This communication describes a further application of the chromatostrip for following and maintaining control of the methylation of a polyhydroxybenzoic acid. The simplicity of its use suggests that the method may be advantageously employed to follow a variety of reactions involving other types of aromatic compounds.

Table I summarizes the R_f values of a variety of hydroxy aromatic compounds and related derivatives. All could be identified under ultraviolet light either as a fluorescing spot or as a dark spot resulting from absorption of the ultraviolet rays.

From the R_f values in Table I, it may be seen that a mixture of nearly all of the compounds shown could be resolved using only the 3 solvent systems described. In addition to its high resolution, the chromatostrip is suitable for following slow chemical reactions because a separation may be completed in 15 min. or less, permitting reasonably close control of the reaction. Also detection of compounds which fluoresce or absorb ultraviolet light may be made instantaneously without resorting to further manipulations. If necessary for detection, however, it is possible to carry out a number of color tests or other chemical reactions directly on the glass strip.

In the procedure described the termination of a reaction was made at a time when only a single component of the system was present. This made it very easy to isolate the compound in high yield. However, it may not always be possible to obtain single intermediate compounds. Thus, when phloroglucinol was methylated with methyl sulfate and potassium hydroxide, the monomethoxyl, dimethoxyl, and trimethoxyl derivatives formed in an overlapping manner with all 3 being present after 1 hr. Further methylation resulted in the gradual disappearance of first the monomethoxyl, then the dimethoxyl derivatives, leaving finally the trimethoxylated compound. Whether the conditions of the reaction might have been altered to produce any desired intermediate was not investigated.

TABLE I

R_f VALUES OF A VARIETY OF POLYHYDROXY AROMATIC COMPOUNDS WHEN DEVELOPED ON SILICIC ACID CHROMATOSTRIPS

	Ether: Skelly-solve B (7:3)	Ethyl Acetate: Skelly-solve B (3:1)	Acetone: Skelly-solve B (1:3)	Appearance of Spot under Ultraviolet Wave Length
	R_f[a]	R_f[a]	R_f[a]	2540 Å
Resorcinol	0.49	0.78	0.19	Dark purple
Hydroquinone	0.45	0.78	0.17	Purple fluor.
Catechol	0.65	0.89	0.41	Black
Phloroglucinol	0.18	0.52	0.0	Black (faint)
Pyrogallol	0.39	0.72	0.17	Black (faint)
α-Resorcylic acid	0.21	0.61	0.73	Purple
β-Resorcylic acid	0.57	0.85	0.19	Blue fluor.
γ-Resorcylic acid	0.10	0.15	0.10	Purple
Salicylic acid	0.72	0.88	0.48	Blue fluor.
Protocatechuic acid	0.32	0.55	0.10	Purple
Gentisic acid	0.35	0.65	0.17	Blue fluor.
2,4,6-Trihydroxybenzoic acid	0.15	0.50	0.10	Black (faint)
p-Hydroxyphenylacetic acid	0.35	0.72	0.14	Purple
2,5-Dihydroxyphenylacetic acid	0.67	0.85	0.43	Black
m-Hydroxyphenylacetic acid	0.32	0.65	0.19	Purple
p-Hydroxyacetophenone	0.48	0.83	0.40	Purple
o-Hydroxyacetophenone	0.85	1.0	0.72	Purple
2,6-Dihydroxyacetophenone	0.71	1.0	0.54	Purple
Orcinol	0.49	0.81	0.27	Black (faint)
3,5-Dimethoxybenzoic acid	0.64	0.86	0.36	Blue-purple
p-Methoxybenzoic acid	0.63	0.92	0.39	Blue-purple
4-Hydroxy-3-methoxybenzoic acid	0.46	0.76	0.29	Blue-purple
3,4,5-Trimethoxybenzoic acid	0.43	0.75	0.31	Purple
Ferulic acid	0.42	0.76	0.16	Blue
Syringic acid	0.33	0.57	0.16	Blue-purple
2,4-Dimethoxyphenylacetonitrile	0.77	1.0	0.56	Purple

[a] The R_f's are only relative and will vary somewhat between different batches of chromatostrips. Each strip was spotted with 10–20 gamma of material and the solvent front allowed to travel 10–11 cm.

EXPERIMENTAL

Chromatographic procedure. The chromatostrips, having the dimensions of about 0.5 inch by 5.5 inches were prepared from 1/16-inch window glass. The strips were coated on one side with a paste made up of silicic acid, starch, and inorganic fluorescing materials as described by Kirchner *et al.*[3] and Miller and Kirchner.[4] The inorganic fluorescing agent[8] allows detection of compounds that do not fluoresce, but do absorb under ultraviolet light in the wavelength range of 230–390 mμ. The silicic acid–starch paste was applied by spreading it on a glass strip and drawing the strip

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under a straight-edged object adjusted to give a coating about 0.5 mm. thick. It was found advantageous to dry the chromatostrips at 105° for 30 min. and to store them over potassium hydroxide in a desiccator until used.

For chromatography, a small spot of the solution to be developed was placed one centimeter above one end of a strip. The strip was immersed in the appropriate developing solution contained in a test tube. About 1.5 ml. of solvent in the tube is sufficient for development. Three solvent mixtures that we have found to be particularly useful are ether–Skellysolve B (7:3); ethyl acetate–Skellysolve B (3:1); and acetone–Skellysolve B (1:3).[9a]

For following the methylation of β-resorcylic acid, the ether: Skellysolve B (7:3) mixture was employed as the developer. The methoxy derivatives were observed on the strip as dark absorption spots when viewed under an ultraviolet lamp having a peak emission wave length at 2540 Å. At 15-min. intervals, samples were removed from the reaction mixture by means of a micropipet, acidified, and chromatographed. In this way, formation of the new methoxy compound and the disappearance of the reactant were simultaneously observed.

Methyl 2,4-dihydroxybenzoate. To 10 g. of β-resorcylic acid dissolved in acetone was added 10 g. of sodium carbonate, and while the mixture was boiling on a steam bath dimethyl sulfate and 10% methanolic potassium hydroxide were alternately added dropwise to maintain the *p*H at 7–8. The original spot representing β-resorcylic acid (R_f = 0.57) gradually changed during 1.5 hr. to a faster-moving spot (R_f = 0.73). After acidification of the reaction mixture and removal of acetone, the compound was extracted from the mixture with ether and crystallized from methanol to give colorless needles, producing a positive ferric chloride reaction, m.p. 117°.[9b] Hydrolysis of this compound with 10% methanolic potassium hydroxide for 0.5 hr. on the steam bath gave the original β-resorcylic acid. Therefore, the first product formed was the methyl 2,4-dihydroxybenzoate.

Anal. Calcd. for $C_8H_8O_4$: C, 57.1; H, 4.77; OMe, 18.4. Found: C, 57.1; H, 4.85; OMe, 18.4.

Rangaswami[9] described the preparation of the methyl-β-resorcylate by means of methanol and hydrochloric acid. The completely dried compound melted at 119°.

Methyl 2-hydroxy-4-methoxybenzoate. Continued heating of the solution of methyl ester and maintenance of the *p*H at 7–8 for 2.5 additional hours produced another compound which gave a single spot (R_f = 0.86). This material crystallized in the refrigerator from methanol and water as white needles, m.p. 46°. Mauthner[10] gave 48° as the melting point for this compound. The compound was the methyl 2-hydroxy-4-methoxy-benzoate.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.3; H, 5.49; OMe, 34.1. Found: C, 59.4; H, 5.62; OMe, 33.8.

2-Hydroxy-4-methoxybenzoic acid. Saponification of the acetone solution of methyl 2-hydroxy-4-methoxybenzoate for 4 hr. on the steam bath with 10% methanolic potassium hydroxide resulted in another pure compound as shown by a single blue fluorescent spot (R_f = 0.67). The isolated material, after removal of acetone and extraction into ether, was crystallized from methanol as colorless needles, m.p. 158°. The compound gave a positive ferric chloride test and was soluble in 5% sodium carbonate solution.

Calcd. for $C_8H_8O_4$: C, 57.1; H, 4.77; OMe, 18.4. Found: C, 57.1; H, 4.77; OMe, 18.8.

Mauthner[10] indicated158° as the melting point for 2-hydroxy-4-methoxybenzoic acid.

Methyl 2,4-dimethoxybenzoate. The methyl dimethoxybenzoate was conveniently formed by the alternate additions of dimethyl sulfate and 10% potassium hydroxide to a boiling acetone solution of β-resorcylic acid so as to maintain the *p*H at 11–12. The reaction went *via* the same methyl ester intermediates described above, but at the higher *p*H, the reaction was completed within 2 hr. and the chromatostrip showed only a single spot (R_f = 0.63). The material isolated was an amber-colored liquid at room temperature. It was further purified to a colorless liquid by distillation at 120° and 0.75 mm. It boiled at 293–296° under atmospheric pressure. No ferric chloride reaction was observed and the compound was not extracted from ether by 5% sodium carbonate.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.12; OMe, 47.5. Found: C, 60.9; H, 6.44; OMe, 45.0.

Perkin and Schiess[11] had previously described the preparation of this compound with a boiling point of 294–296° at atmospheric pressure.

2,4-Dimethoxybenzoic acid. Saponification of the methyl 2,4-dimethoxybenzoate with 10% methanolic potassium hydroxide for 2 hr. on the steam bath resulted in formation of a compound giving a new dark spot on the chromatostrip (R_f = 0.27), which when isolated crystallized from water as colorless needles, m.p. 108°. The material gave no ferric chloride reaction and was soluble in sodium carbonate.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.1; H, 5.49; OMe, 34.1. Found: C, 59.4; H, 5.54; OMe, 34.4.

Karrer *et al.*[12] have described the dimethoxybenzoic acid as having a melting point of 107°.

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N,N-Bis(cyanomethyl)carboxamic Acids

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In a previous note[1] the synthesis of a series of *N,N*-bis(2-cyanoethyl)carboxamic acids was reported. This note describes the synthesis and properties of several analogous compounds, *N,N*-bis(cyanomethyl)carboxamic acids, which were prepared by the reaction of iminodiacetonitrile with cyclic anhydrides in an inert solvent.

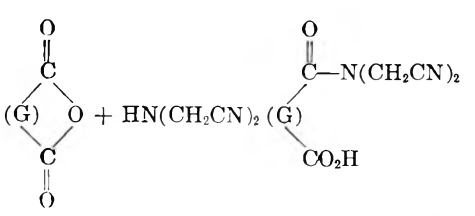

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TABLE I

N,N-BIS(CYANOMETHYL)CARBOXAMIC ACIDS: $HO_2C—(G)—CON(CH_2CN)_2$

(G)	Formula	Yield, %	M.P.,[2] °C.	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
—CH=CH—	$C_8H_7N_3O_3$	70	132–5	49.70	49.74	3.63	3.81	21.80	21.95
—CH=CCl—	$C_8H_6ClN_3O_3$	80	139–42	42.21	42.59	2.64	3.0	18.45	18.42
—CH(C_8H_{15})CH_2—	$C_{16}H_{23}N_3O_3$	95	Part. solid	63.0	61.8	7.54	7.60	13.76	12.34
	$C_{12}H_{13}N_3O_3$	70	147–9	58.3	58.0	5.26	5.50	17.0	16.6
	$C_{13}H_{13}N_3O_3$	68	128–32	60.2	60.4	5.02	5.26	16.2	16.18
	$C_{12}H_9N_3O_3$	90	168–70	59.2	59.2	3.71	3.90	17.3	17.54

Physical properties, analyses and yields of the products are given in Table I.

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(2) All temperatures are uncorrected.

Preparation of Phenyldiazomethane[1,2]

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Phenyldiazomethane has been prepared previously either by the action of concentrated aqueous base on the *N*-nitroso derivatives of benzylurethan,[4] benzylurea,[5] or benzylnitroguanidine,[6] or by the oxidation of benzaldehyde hydrazone with mercuric oxide.[7] Gutsche and Jason[8] have recently compared these methods and concluded that the oxidative method was preferable. However, this method gave only an 80% yield (based on benzaldehyde) of crude phenyldiazomethane of *ca.* 40% purity.

As a result of our studies on the reaction of diazoketones with base[9] we have developed a novel and convenient method for the preparation of phenyldiazomethane in ethereal solution from azibenzil in *ca.* 70% yield. The azibenzil in ethereal solution was treated with an aqueous-methanolic solution of eight molar equivalents of sodium hydroxide; by suitable choice of the relative proportions of the three solvents a homogeneous solution was obtained which deposited only a trace of solid material during the course of the reaction. The solution was left to stand for eight hours at room temperature and then diluted with aqueous sodium hydroxide; the ethereal phenyldiazomethane layer was separated, washed, and dried. The identity and yield of the product were determined by reaction with *p*-nitrobenzoic acid and mandelic acid, which gave benzyl *p*-nitrobenzoate and benzyl mandelate in yields of 71 and 70%, respectively. Since azibenzil is readily prepared in high yield from benzil monohydrazone[10] and, when pure, may be stored in the cold for several months without deterioration, this is an attractive method for the preparation of ethereal phenyldiazomethane.

Acidification of the aqueous basic layer gave a mixture of benzoic acid (90%) and diphenylacetic acid (6%). Thus *under these conditions* the major path of reaction may be formulated as:

$$C_6H_5CN_2COC_6H_5 + NaOH \longrightarrow C_6H_5CHN_2 + C_6H_5CO_2Na.$$

This mode of cleavage of an aliphatic diazo compound has previously been suggested by Wilds and Meader[11] to account for the formation of *p*-chlorobenzoic acid from the action of warm aqueous-methanolic potassium hydroxide on *p*-chlorophenyl-*a*-diazopropiophenone; in this case, the other fragment was not identified.

A preliminary attempt was made to extend this method to the preparation of *p*-chlorophenyldiazomethane from 4,4′-dichloroazibenzil. However, although *p*-chlorobenzoic acid was obtained in high yield, the major neutral product was *p*-chlorobenzyl alcohol; this presumably arises from further reaction of the *p*-chlorophenyldiazomethane with the aqueous basic medium, the reaction being favored

(1) Aliphatic Diazo Compounds. IV.

(2) Work supported by an institutional research grant from the American Cancer Society to Harvard University.

(3) Shell Foundation Fellow, 1955–1956.

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(11) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

in this case by the presence of an electron-withdrawing substituent on the phenyl ring.

EXPERIMENTAL[12]

Azibenzil. Azibenzil was prepared from benzil monohydrazone[13] by the method of Nenitzescu and Solomonica[10] with the following minor modifications: (*i*) the reaction mixture was cooled slightly before addition of the cold, alcoholic potassium hydroxide in order to minimize the frothing which accompanies the initial reaction; (*ii*) the crude azibenzil was dissolved in ether at room temperature and the solution was allowed to stand at room temperature for 1–2 hours, decanted from traces of mercury which otherwise always contaminated the product, and cooled at −20° overnight to effect crystallization. Pure azibenzil remained unchanged after storage at 0° in a dark, evacuated desiccator for several months.

Phenyldiazomethane. A solution of sodium hydroxide (8 g., 0.2 mole) in a mixture of water (15 ml.) and methanol (100 ml.) was added to a solution of azibenzil (5.56 g., 0.025 mole) in ether (125 ml.). The container was loosely stoppered and the mixture was allowed to stand at room temperature for 8 hr. Occasionally a small amount of white solid, possibly sodium benzoate, came out of solution early in the reaction, but homogeneity was restored by addition of small amounts of alcohol and/or water.[14] At the end of the reaction time a very small amount of pale yellow solid had been deposited (probably benzilazine[9]); this was removed by filtration and the clear, red solution was treated with 10% aqueous sodium hydroxide (100 ml.). The ethereal layer was washed with 10% aqueous sodium hydroxide (four 25-ml. portions) and dried over sodium sulfate, $\lambda_{max}^{CCl_4}$ 4.91 μ.

This ethereal solution of phenyldiazomethane was treated with *p*-nitrobenzoic acid in small amounts at a time until the solution was very pale yellow and further additions no longer caused gas evolution. The solution was washed with 5% aqueous sodium bicarbonate and with water, dried, and evaporated *in vacuo* to give benzyl *p*-nitrobenzoate (4.27 g., corresponding to a 71% yield of phenyldiazomethane); the infrared spectrum of the crude product showed only the bands of benzyl *p*-nitrobenzoate and one recrystallization from 95% ethanol gave the ester as shining plates, m.p. 82–82.5° (rec.[15] m.p. 83.5–84.5°) undepressed on admixture with an authentic sample. In another run, mandelic acid was used in a similar manner giving a yield of benzyl mandelate corresponding to a 70% yield of phenyldiazomethane; one recrystallization from ethanol gave material, m.p. 92.5–93.5° (rec.[16] m.p. 93°).

The aqueous basic layer and washings from the cleavage reaction were combined, cooled to 0°, acidified with dilute sulfuric acid, and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated *in vacuo* to give a dirty white solid (3.00 g.). An aliquot of the solid was sublimed for 8 hr. at a bath temperature of 60° and a pressure of 0.5 mm. to give a sublimate of benzoic acid and a residue of diphenylacetic acid, each identified by its infrared spectrum, m.p., and mixed m.p. The yields of benzoic and diphenylacetic acid were 90 and 6%, respectively.

4,4′-Dichlorobenzil monohydrazone. A solution of 95+ % hydrazine (3.5 g., 0.1 mole) in absolute ethanol (20 ml.) was added to a stirred, refluxing suspension of 4,4′-dichlorobenzil[17] (27.9 g.: 0.1 mole) in absolute ethanol (650 ml.). With the addition of the hydrazine, the ketone went into solution. The solution was refluxed for 30 min. and then distilled with continuous slow addition of water until approximately 350 ml. of distillate had been collected; the hydrazone began to separate after the removal of about 200 ml. of ethanol. The mixture was cooled in an ice bath and filtered: the hydrazone was washed with water and dried to constant weight *in vacuo* at 80°; yield, 28.1 g. (96%), m.p. 143–147° dec. Five crystallizations from absolute ethanol gave the hydrazone as fluffy, white crystals, m.p. 149.5–151.5° dec., $\lambda_{max}^{CH_2Cl_2}$ 2.92, 3.05, 6.08 μ.

Anal. Calcd. for $C_{14}H_{10}N_2OCl_2$: C, 57.36; H, 3.44; N, 9.56. Found: C, 57.60; H, 3.36; N, 9.68.

4,4′-Dichloroazibenzil. A suspension of 4,4′-dichlorobenzil monohydrazone (11.73 g., 0.04 mole), yellow mercuric oxide (30 g.: 0.14 mole) and anhydrous sodium sulfate (10 g.) in ether (150 ml.) was cooled to *ca.* 10° and treated with a few drops of cold, saturated ethanolic potassium hydroxide. A dark precipitate of mercury and mercury salts began to form immediately and the solution became dark orange-red. The suspension was shaken for 45 min. and then allowed to settle. The ethereal solution was decanted and the residual sludge was washed with ether by decantation until the washings were no longer colored. The combined solution and washings were allowed to stand for *ca.* 2 hr. to permit further separation of finely divided mercury, filtered, dried, and evaporated to a volume of about 100 ml. The solution was cooled at 0° overnight to give the diazoketone as shiny, orange spikes, m.p. 77–80° dec.; yield, 6.31 g. (54%); a small additional yield could be obtained by concentration of the mother liquors. Five recrystallizations from ether gave material, m.p. 91–92° dec., $\lambda_{max}^{CH_2Cl_2}$ 4.85, 6.14, 7.47 μ.

Anal. Calcd. for $C_{14}H_8N_2OCl$: C, 57.75; H, 2.77; N, 9.63. Found: C, 57.57; H, 2.82; N, 9.69.

Basic cleavage of 4,4′-dichloroazibenzil. The reaction of 4,4′-dichloroazibenzil with sodium hydroxide in ethereal-aqueous-methanolic solution was carried out exactly in the fashion used for the basic cleavage of azibenzil. Treatment of the orange-red, ethereal solution of the neutral product with benzoic acid and a few drops of boron trifluoride etherate gave a poor yield (*ca.* 50%) of a mixture of *p*-chlorobenzyl alcohol and *p*-chlorobenzyl benzoate (identified on the basis of the infrared spectrum). Acidification of the aqueous basic solution gave a 91% yield of *p*-chlorobenzoic acid, identified by infrared spectrum, m.p., and mixed m.p.

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(12) Melting points are uncorrected.

(13) L. I. Smith and H. H. Hoehn, *Org. Syntheses*, Coll. Vol. III, 357 (1955).

(14) Maintenance of homogeneity was found to be essential, since separation into two phases, leading to deposition of solid, drastically reduced the yield of phenyldiazomethane.

(15) R. Kothe, *Ann.*, 266, 313 (1891).

(16) D. Base, *J. Am. Pharm. Assoc.*, 12, 7 (1923).

(17) M. Gomberg and F. J. Van Natta, *J. Am. Chem. Soc.*, 51, 2238 (1929).

Some Polyaryl Derivatives of Metals and Metalloids as Liquid Scintillator Solutes

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In previous surveys[1] of compounds screened as liquid scintillator solutes, an attempt has been made

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

to derive some generalizations regarding the effect exerted on their efficiency by various aromatic systems, position of attachment of polyaryls, heteroatoms, and various functional groups. In order to investigate any unusual effects caused by incorporating some less common heteroelements, a variety of polyaryl derivatives of various metals and metalloids (silicon, germanium, tin, lead, phosphorus, arsenic, antimony, and iron) were examined, and the results are listed in Table I. The compounds are generally inefficient scintillator solutes, and some are even mild quenchers.[1d]

In all of the compounds screened the aromatic rings are separated from each other by the heteroatom, so that in no case are there more than two benzene rings joined directly (although Compounds 9 and 10 each contain eight benzene rings). The fact that Compound 10 has a marked relative pulse height while Compound 9 does not is further evidence of a previous observation, concerning the effect of position on these values, in the instance of the three terphenyls,[1a] *i.e.*, a *para* linkage<< *meta*<*ortho*. This effect was one of many which led to postulation of continuous resonance throughout the system[1b] as an important criterion in a scintillator solute. Obviously continuous resonance in *o*-terphenyls is prevented by lack of coplanarity, and in *m*-terphenyls by odd atoms, separating the terminal rings.

Included in the table are a variety of dimethylaminophenyl and methoxyphenyl derivatives (3, 4, 14, 18, 19, and 20), but even these groups, which have been shown to be beneficial to poor scintillator molecules in other instances,[1e,1f,1h,2] do not impart a measurable response to any of these compounds. Nor does the secondary amine function[1h] in hexaphenyldisilazane have any observable effect.

The failure to observe any values for the Group Vb elements is disappointing in view of the interesting results obtained with the corresponding nitrogen compounds. For example, although triphenylamine and diphenylamine gave very poor responses,[1a] tris(4-biphenylyl)amine (0.58) and bis(4-biphenylyl)amine (0.95) proved to be quite efficient solutes.[1g] The failure of the biphenylylphosphine, -arsine, and -stibine compounds to scintillate, coupled with the quenching properties of the tetraphenyl derivatives of Group IVb metals, leads to the preliminary conclusion that elements beyond the first period of the periodic table are detrimental in scintillator molecules. This conclusion seems to hold for the halogens and for sulfur compounds in general.[1b] Perhaps incorporation of some of these elements in molecules which are otherwise good solutes would afford a more specific impression of the magnitude and reliability of this detriment.

The values reported in Table I were measured in the pulse height analyzer previously described,[1b] and all were measured at a concentration of 3 g./l.

TABLE I

PRIMARY-SOLUTE RELATIVE PULSE HEIGHTS

No.	Compound	Relative Pulse Heights	Ref.
1	Tetraphenylmethane	<0.10	[a]
2	Tetraphenylsilane	<0.10	[b]
3	Tris(*p*-dimethylaminophenyl)-(*p*-methoxyphenyl)silane	<0.10	[c]
4	Tetrakis(*p*-dimethylaminophenyl)-silane	<0.10	[c]
5	1,1,1,3,3,3-Hexaphenyldisilazane	<0.10	[d]
6	1-Naphthyltriphenylsilane	<0.10	[e]
7	2-Naphthyltriphenylsilane	0.14	[f]
8	Ethoxytri-1-naphthylsilane	<0.10	[e]
9	Tetra-3-biphenylylsilane	<0.10	[g]
10	Tetra-4-biphenylylsilane	0.29	[h]
11	*p*-Phenylenebis[triphenylsilane]	<0.10	[i]
12	Tetraphenylgermane	<0.10	[j]
13	Tetraphenyltin	<0.10	[k]
14	(*p*-Dimethylaminophenyl)triphenyltin	<0.10	[l]
15	1-Indenyltriphenyltin	<0.10	[m]
16	p-Phenylenebis[triphenyltin]	<0.10	[i]
17	Tetraphenyllead	<0.10	[n]
18	Tetrakis-(*p*-methoxyphenyl)lead	<0.10	[o]
19	Bis(*p*-dimethylaminophenyl)-diphenyllead	<0.10	[p]
20	Tetrakis(*p*-dimethylaminophenyl)-lead	<0.10	[p]
21	Triphenylphosphine	<0.10	[k]
22	Triphenylphosphine oxide	<0.10	[q]
23	Tris(2-biphenylyl)phosphine	<0.10	[r]
24	Tris(4-biphenylyl)phosphine	<0.10	[s]
25	Tris(2-biphenylyl)arsine	<0.10	[r]
26	Tris(4-biphenylyl)arsine	<0.10	[t]
27	Tris(2-biphenylyl)stibine	<0.10	[r]
28	Tris(4-biphenylyl)stibine	<0.10	[u]
29	Ferrocene	<0.10	[v]

[a] M. Gomberg and L. H. Cone, *Ber.*, **39**, 1463 (1906). [b] A. Polis, *Ber.*, **19**, 1013 (1886). [c] H. Gilman and M. A. Plunkett, *J. Am. Chem. Soc.*, **73**, 1686 (1951). [d] H. H. Reynolds, L. A. Bigelow, and C. A. Kraus, *J. Am. Chem. Soc.*, **51**, 3067 (1929). [e] H. Gilman and C. G. Brannen, *J. Am. Chem. Soc.*, **73**, 4640 (1951). [f] H. Gilman, C. G. Brannen, and R. K. Ingham, *J. Am. Chem. Soc.*, **77**, 3917 (1955). [g] H. Gilman and G. D. Lichtenwalter, *J. Org. Chem.*, **21**, 1307 (1956). [h] W. C. Schumb, J. Ackerman, and C. M. Saffer, *J. Am. Chem. Soc.*, **60**, 2486 (1938). [i] H. Zimmer and H. G. Mosle, *Ber.*, **87**, 1255 (1954). [j] D. L. Tabern, W. R. Orndorff, and L. M. Dennis, *J. Am. Chem. Soc.*, **47**, 2039 (1925). [k] Commercially available. [l] H. Gilman and C. E. Arntzen, *J. Org. Chem.*, **15**, 994 (1950). [m] H. Gilman and L. A. Gist, *J. Org. Chem.*, **22**, 250 (1957). [n] H. Gilman and J. Robinson, *J. Am. Chem. Soc.*, **49**, 2315 (1927). [o] H. Gilman and J. C. Bailie, *J. Am. Chem. Soc.*, **61**, 731 (1939). [p] P. R. Austin, *J. Am. Chem. Soc.*, **54**, 3726 (1932). [q] A. Michaelis and H. v. Sodern, *Ann.*, **229**, 306 (1885). [r] D. E. Worrall, *J. Am. Chem. Soc.*, **62**, 2514 (1940). [s] D. E. Worrall, *J. Am. Chem. Soc.*, **52**, 2933 (1930). [t] D. E. Worrall, *J. Am. Chem. Soc.*, **52**, 664 (1930). [u] D. E. Worrall, *J. Am. Chem. Soc.*, **52**, 2046 (1930). [v] T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

Isotopes, **1**, 284 (1957); (*e*) H. Gilman, E. A. Weipert, T. Soddy, and F. N. Hayes, *J. Org. Chem.*, **22**, 1169 (1957); (*f*) H. Gilman, E. A. Weipert, J. J. Dietrich, and F. N. Hayes, *J. Org. Chem.*, **23**, 361 (1958); (*g*) H. Gilman, E. A. Weipert, R. O. Ranck, and F. N. Hayes, *J. Org. Chem.*, in press; (*h*) H. Gilman, E. A. Weipert, and F. N. Hayes, *J. Org. Chem.*, in press.

(2) J. R. Arnold, *Science*, **122**, 1139 (1955).

in toluene, except 19 and 20, which, due to limited solubility, were measured as saturated solutions. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

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The Constituents of *Casimiroa Edulis* Llave *et* Lex. IV.[1] Identification of Edulein with 7-Methoxy-1-methyl-2-phenyl-4-quinolone

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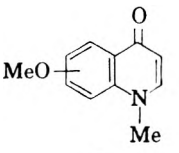
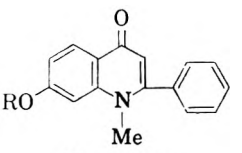
The isolation of the three new alkaloids edulein, edulitine, and edulinine from the bark of the tree *Casimiroa edulis* Llave *et* Lex, was reported in a previous paper of this series.[2] We now describe the elucidation of the structure of edulein through its identification with an alkaloid of known structure which was reported since our original paper was written.

Edulein, $C_{17}H_{15}NO_2$, m.p. 201°, was previously shown to contain one methoxyl and one *N*-methyl group.[2] It was suggested that edulein contained an amide grouping since it was essentially neutral and the amide must have been tertiary in view of the absence of active hydrogen. Boiling edulein with potassium hydroxide in ethylene glycol has now given demethyledulein, $C_{16}H_{13}NO_2$, m.p. 324°, which no longer contains the methoxyl function. The substance is derived from edulein by cleavage of the methoxyl group to hydroxyl since methylation with diazomethane regenerated edulein. Boiling edulein with hydriodic acid likewise yielded demethyledulein and the alkaloid, like casimiroin,[1] is therefore very stable under both acidic and basic conditions.

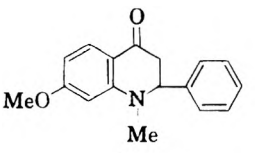
The reduction of edulein with lithium aluminum hydride gave dihydroedulein, $C_{17}H_{17}NO_2$, m.p. 130°. The formation of this substance made the presence of an amide in edulein unlikely, since amides are generally reduced to the amines (involving loss of an oxygen atom) with lithium aluminum hydride.[3] The presence of a vinylogous tertiary amide of type I in edulein was indicated, since this would still account for the essentially non-basic character of the alkaloid and also for its reduction to a dihydro derivative. Such a formulation moreover lacks only a phenyl group to make up the complete structure of edulein.



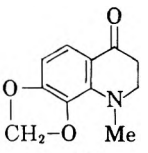
I



IIa, R = Me
b, R = H



III



IV

At this stage of the investigation we were made aware through an interesting discussion with Dr. Sidney Goodwin (National Heart Institute, National Institutes of Health, Bethesda, Md.) of the similarity between edulein and an alkaloid isolated from the bark of *Lunasia amara* by Dr. J. R. Price *et al.* (Commonwealth Scientific and Industrial Research Organization, Melbourne, Australia) and from the leaves by Dr. Goodwin *et al.* This alkaloid, which has been found to be 7-methoxy-1-methyl-2-phenyl-4-quinolone (IIa),[4] was shown by us by direct comparison to be completely identical with edulein. A difference seemed to lie in the picrates, since edulein picrate has been reported to have m.p. 192°[2] whereas the picrate of IIa has m.p. 220°.[5] The lower melting point of edulein picrate must have been due to polymorphism, since a new preparation showed the same melting point as the picrate of IIa and there was no depression on admixture. Edulein is therefore 7-methoxy-1-methyl-2-phenyl-4-quinoline (IIa) and demethyledulein is 7-hydroxy-1-methyl-2-phenyl-4-quinolone (IIb).

Dihydroedulein is comparatively non-polar, is not extracted from ether solution with mineral acids, and shows strong carbonyl absorption in the infrared (λ_{max} 6.01, 6.20, and 6.37 μ). It is most probably 7-methoxy-1-methyl-2-phenyl-4-keto-1,2,3,4-tetrahydroquinoline (III), derived from edu-

(1) Part III, A. Meisels and F. Sondheimer, *J. Am. Chem. Soc.*, **79**, 6328 (1957).

(2) J. Iriarte, F. A. Kincl, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 4170 (1956).

(3) *Cf.* W. G. Brown, *Org. Reactions*, Vol. 6, Chapter 10, pp. 479–480 (1951); N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers Inc., New York, 1956, pp. 544–592.

(4) J. R. Price, *Fortschr. Chem. org. Naturstoffe*, **13**, 310 (1956).

(5) J. R. Price, private communication.

lein (IIa) by 1,4-addition of hydrogen. This structure, which still represents a vinylogous amide, accounts for the non-basic properties of the reduced substance. Support for the correctness of this formulation is provided by the similarity of the infrared spectrum of dihydroedulein in the carbonyl region with that of the similarly constituted 1-methyl-4-keto-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline (IV) (λ_{max} 5.99, 6.17, and 6.34 μ), the lithium aluminum hydride reduction product of casimiroin.[1]

EXPERIMENTAL[6]

Demethyledulein (7-hydroxy-1-methyl-2-phenyl-4-quinolone) (IIb). A mixture of 90 mg. of edulein, 1 g. of potassium hydroxide, and 10 cc. of ethylene glycol was boiled under reflux for 24 hr. Water was added, the solution was filtered, the filtrate was acidified with dilute hydrochloric acid, and the precipitate was collected. Crystallization from ethanol gave 74 mg. of demethyledulein as needles, m.p. 322–324° (dec.). The substance gave a red color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.25; H, 5.36.

The same substance was obtained by boiling edulein (90 mg.) with hydriodic acid (3 cc.; d 1.7) for 1 hr.

Treatment of demethyledulein in ether suspension with ethereal diazomethane at 5° for 24 hr. regenerated edulein in almost quantitative yield.

Dihydroedulein (7-methoxy-1-methyl-2-phenyl-4-keto-1,2,3,4-tetrahydroquinoline (III). Edulein (150 mg.) dissolved in 25 cc. of dry tetrahydrofuran was added dropwise to a solution of 500 mg. of lithium aluminum hydride in 15 cc. of tetrahydrofuran and the mixture was boiled under reflux for 7 hr. It was then cooled, poured into ice cold dilute sulfuric acid, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. Chromatography of the residue on 3.5 g. of alumina and crystallization of the fractions eluted with pentane-benzene (1:1) from ether-pentane gave 105 mg. of dihydroedulein, m.p. 129–130°, λ_{max} 238, 255, 283, and 375 mμ (log ϵ 4.21, 4.37, 3.96, and 3.70, respectively), λ_{max} 6.01, 6.20 and 6.37 μ, no hydroxyl band.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.19; N, 5.25.

Identification of edulein with 7-methoxy-1-methyl-2-phenyl-4-quinoline (IIa). A sample of edulein, m.p. 200–201°, gave no melting point depression on admixture with a sample of IIa (m.p. 199–200°) obtained by Dr. J. R. Price from the bark of *Lunasia amara*. The infrared spectrum of edulein was re-determined ($\lambda_{max.}$ 6.15, 6.19, 6.24, 6.33, and 6.39 μ) and was found to be completely identical with the spectrum of IIa.

Edulein picrate was prepared again and after crystallization from methanol formed yellow needles, m.p. 220–221°. There was no depression on admixture with a sample of the picrate of IIa, m.p. 220–221°, kindly supplied by Dr. Price.

Acknowledgment. We are indebted to Drs. F. A. Kincl and G. Rosenkranz (Syntex S. A., Mexico City) for the edulein used in this investigation, to Dr. Sidney Goodwin for interesting discussions and correspondence, and to Dr. J. R. Price for samples of the alkaloid IIa and its picrate.

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(6) Melting points are uncorrected. The ultraviolet spectrum was measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer and the infrared spectra in chloroform solution on a Baird double-beam recording spectrophotometer. The analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

Spiroisoindolinium Salts

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During an investigation of various types of quaternary ammonium salts, seven new spiroisoindolinium compounds were prepared for pharmacological evaluation (Table I). These derivatives resulted from the reaction of cyclic secondary amines and various *o*-xylylene halides in the manner generally described by other investigators.[2–5] While most of the intermediates used have been previously described, improved preparations of some of them are reported in the experimental part.

The isoindolinium salts were pressor agents in dogs. No other marked pharmacological activity was noted.

EXPERIMENTAL[6]

General procedure. The isoindolinium salts were prepared by heating under reflux a mixture of 0.1 mole of an *o*-xylylene halide and 0.1 mole of a cyclic secondary amine in 600 ml. of isopropyl alcohol containing 0.1 mole of sodium hydroxide and 10 ml. of water. After 6 to 18 hr. the solution was filtered, then concentrated to a volume of 50 to 150 ml. and filtered again to remove inorganic material. The product was obtained by diluting the filtrate with anhydrous ether and refrigerating the mixture.

Crude yields of 60 to 90% were obtained. The products were recrystallized and dried *in vacuo* before analysis.

Secondary amines. Hexamethyleneimine was obtained from a commercial source; 2- and 4-methyl hexamethyleneimine were prepared by the method of Blicke and Doorenbos.[7]

Intermediates. 1,2-Bis(α-bromoethyl)benzene. A mixture of 5.0 g. (0.03 mole) of 1,2-bis(α-hydroxyethyl) benzene[8] and 100 ml. of 65% aqueous hydrobromic acid was stirred for 48 hr. at room temperature, then poured into a mixture of 250 g. of ice and 250 ml. of water. The solid was separated by filtration, washed well with water and air-dried to give 8.4 g. (96%) of pure product, m.p. 88–91°.[9]

(1) Present address: The Upjohn Company, Research Division, Kalamazoo, Mich., (1) (a) Present address: Cutter Laboratories, Berkeley, Calif.

(2) M. Scholtz, *Ber.*, **31**, 414 (1898).

(3) J. von Braun, *Ber.*, **49**, 2640 (1916).

(4) J. von Braun and Z. Köhler, *Ber.*, **51**, 263 (1918).

(5) F. F. Blicke and E. B. Hotelling, *J. Am. Chem. Soc.*, **76**, 5099 (1954).

(6) All melting and boiling points as uncorrected.

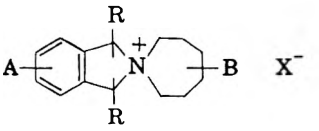
(7) F. F. Blicke and N. J. Doorenbos, *J. Am. Chem. Soc.*, **76**, 2317 (1954).

(8) M. Deluchat, *Compt. rend.*, **190**, 438 (1930).

(9) M. Deluchat, *Compt. rend.*, **192**, 1387 (1931), m.p. 91°.

TABLE I

SPIROISOINDOLINIUM SALTS[a]



No.	A	R	B	X	Formula	M.P., °C.	Analysis C Calcd.	C Found	H Calcd.	H Found	X Calcd.	X Found
1	...	H	2-CH_3	Br	$C_{15}H_{22}BrN$	237–239[b]	60.80	60.62	7.49	7.36	26.98	26.77
2	...	H	4-CH_3	Br	$C_{15}H_{22}BrN$	216–218	60.80	60.44	7.49	7.50	26.98	26.90
3	...	CH_3	...	Br	$C_{16}H_{24}BrN$	246–247[c]	61.93	61.52	7.80	7.73	25.76	26.30
4	4-CH_3O—	H	...	Cl	$C_{15}H_{22}ClNO$	237–238[c]	67.26	67.13	8.28	8.32	13.24	13.16
5	5,6-di-CH_3O—	H	...	Cl	$C_{16}H_{24}ClNO_2$	218–219[c]	64.51	64.09	8.12	8.05	11.91	11.60
6	4,5,6,7-tetra-Cl	H	...	Br	$C_{14}H_{16}BrCl_4N$	287[c]	40.03	40.26	3.84	3.99	19.03	18.84
7	hexahydro	H	...	Br	$C_{14}H_{26}BrN$	289–291[c]	58.33	58.45	9.09	9.12	27.72	27.51

[a] All compounds were dried at 100° over P_2O_5 *in vacuo* for several hours before analysis. Compounds 2, 3, 4, 5, and 7 were recrystallized from isopropyl alcohol; 6 from 95% ethanol and 1 from absolute ethanol–dry ether. [b] Possible decomposition. [c] Decomposition.

Anal. Calcd. for $C_{10}H_{12}Br_2$: C, 41.13; H, 4.14; Br, 54.73. *Found:* C, 41.25; H, 4.37; Br, 54.46.

3-Methoxyphthalic anhydride. Oxidation of 3-methoxy-*o*-xylene[10] with potassium permanganate using the method of Grewe[11] gave a 49% yield of 3-methoxyphthalic anhydride, m.p. 159–160° after recrystallization from toluene. This melting point agrees well with published values for the same compound prepared in other ways.[12]

3-Methoxy-o-phthalyl alcohol. A Soxhlet apparatus containing 19.4 g. (0.11 mole) of 3-methoxyphthalic anhydride was attached to a flask containing a solution of 8.3 g. (0.22 mole) of lithium aluminum hydride in 600 ml. of anhydrous ether. After 48 hr. of refluxing, 17.4 g. (0.098 mole) of anhydride had been extracted. The stirred complex was decomposed by carefully adding 20 g. of ethyl acetate, then 40 ml. of water. After filtration, the solution was evaporated to dryness. Recrystallization of the residue from petroleum ether (75–90°) gave 4.3 g. (26%) of pure product, m.p. 95–96°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.36.

3-Methoxy-o-xylene chloride. A mixture of 4.0 g. (0.024 mole) of 3-methoxy-*o*-phthalyl alcohol, 28 g. (0.24 mole) of thionyl chloride and 50 ml. of dry benzene was heated at reflux temperature for one hour, then evaporated under reduced pressure. The residue was diluted with 50 ml. of dry benzene and again evaporated.

The residual brown oil was not purified, but was used directly to prepare Compound 4 (Table I).

4,5-Dimethoxy-o-xylylene chloride. This intermediate, used to prepare Compound 5 (Table I), was synthesized by the method of Wood and co-workers.[13]

3,4,5,6-Tetrachloro-o-phthalyl alcohol. The addition of a benzene solution of tetrachlorophthalic anhydride to an excess of lithium aluminum hydride in anhydrous ether followed by the usual isolation procedure gave 20 to 26% yields of 3,4,5,6-tetrachloro-*o*-phthalyl alcohol; m.p. 224–226°, after recrystallization from methanol.

Anal. Calcd. for $C_8H_6Cl_4O_2$: C, 34.82; H, 2.19; Cl, 51.40. Found: C, 35.14; H, 2.41; Cl, 50.85.

The same melting point has been reported for this compound prepared by another method.[14]

3,4,5,6-Tetrachloro-o-xylylene bromide. A mixture of 14 g. (0.051 mole) of 3,4,5,6-tetrachloro-*o*-phthalyl alcohol and 300 ml. of 65% aqueous hydrobromic acid was stirred for 12 hr. at room temperature, then for 3 hr. at 100°. The material was poured into a mixture of ice and water and the crude solid was separated and air-dried to give 18.3 g. (89%), m.p. 108–114°. An analytical sample recrystallized from isopropyl alcohol melted at 117–118°.

Anal. Calcd. for $C_8H_4Br_2Cl_4$: C, 23.91; H, 1.00; Halogen, 75.08. Found: C, 24.01; H, 1.24; Halogen, 75.10.

When prepared by bromination of 3,4,5,6-tetrachloro-*o*-xylene, the reported melting point was 114–117°.[14,15]

Hexahydro-o-xylene bromide. A mixture of 13 g. (0.09 mole) of *cis-d*-hexahydrophthalyl alcohol[16] prepared by lithium aluminum hydride reduction of hexahydrophthalic anhydride, and 150 ml. of 65% aqueous hydrobromic acid was stirred overnight at room temperature then for 4 hr. at 90°. The mixture was poured into a slurry of ice and water, and the product was extracted with several portions of ether. After the combined ether extracts were washed with water, solvent was removed and the residue was distilled to give 18.5 g. (76%) of pure product; b.p. 143–146° (14 mm.); n_D^{25}, 1.5410.

Anal. Calcd. for $C_8H_{14}Br_2$: C, 35.58; H, 5.23; Br, 59.19. Found: C, 36.39; H, 5.46; Br, 59.10.

Birch and co-workers[16] prepared this compound in a different manner.

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(12) W. H. Bentley, R. Robinson, and C. Weizmann, *J. Chem. Soc.*, 91, 104 (1907); A. Girardet, *Helv. Chim. Acta*, **14**, 504 (1931), m.p. 160–161°.

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(14) S. D. Ross and M. Markarian, U.S. Patent **2,631,168** (March 10, 1953).

(15) S. D. Ross and M. Markarian, U. S. Patent **2,600,691** (Aug. 14, 1951).

(16) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, **1953**, 389; W. H. Bailey and H. R. Golden, *J. Am. Chem. Soc.*, **75**, 4780 (1953); S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, 19, 1449 (1954).

Gas Phase Synthesis of 2-Trifluoromethylpyridines[1]

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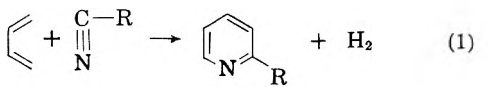
The gas phase cyclization of nitriles with dienes at moderately high temperatures, with loss of hydrogen to yield substituted pyridines:



(1)

has been reported by Janz and co-workers.[2] The reaction has been found to be an example of the Diels-Alder type synthesis, in which the (C≡N) group exhibits dienophilic properties, and in which the dihydro-cyclic adduct loses hydrogen spontaneously at the elevated temperatures to form the pyridinic products. Trifluoroacetonitrile, like cyanogen, cyclizes with butadiene at 350°–520° without the aid of a catalyst.[2e] The present communication describes the results of some studies at relatively long reaction periods, extending the experiments with trifluoroacetonitrile to pentadiene and isoprene, as well as butadiene.

EXPERIMENTAL

Chemicals. Trifluoroacetonitrile (Columbia Organic) and *butadiene* (Matheson) were purified by low temperature distillation and degassed under vacuum prior to use. *Isoprene* (Matheson) was redistilled at atmospheric pressure just prior to use. The *pentadiene* was a research sample from Phillips Petroleum containing 91% of predominantly *cis*-1,3-pentadiene, and 9% of cyclopentenes and hexenes. Prior to an experiment, it was also redistilled at atmospheric pressure.

Apparatus and procedure: The continuous flow reaction system was similar to that used previously,[2e] but with a 5.38-l. flask as the reaction zone to achieve longer contact times at lower flow rates. The reaction conditions, material balances, and yields are summarized in Table I. The loss of material in the experiments with butadiene and isoprene is attributed to volatilization in the final weighings rather than pyrolysis, and the yields were corrected accordingly. These could undoubtedly be minimized with improved low temperature gas transfer techniques. After each flow experiment was completed, the product separation was achieved by low temperature fractionation for the diene and nitrile recoveries, and the pyridinic compound, by fractional distillation through a Podbielniak semi-micro analyzer. The physical properties found for the pyridinic products are given in Table II. The trifluoromethylpyridines were found to be essentially non-basic, *i.e.* attempts to prepare picrate derivatives were unsuccessful, and they could not be titrated as bases in the conventional manner.

TABLE I

REACTION CONDITIONS, MATERIAL BALANCE AND YIELDS

	Butadiene	Pentadiene	Isoprene
Reaction Conditions			
Contact time (sec.)	2490	1568	1760
Total time (hr.)	2.88	8.71	7.17
Temp. (°C.)	400	401	400
Ratio, RCN/diene (mole)	0.67	0.49	0.52
Diene input (moles)	0.244	1.303	0.95
Nitrile input (mole)	0.162	0.637	0.495
Material balance (wt. %)	91	99	95
Conversions			
Nitrile conv. (mole)	0.093	0.356	0.343
Diene conv. (mole)	0.171	0.629	0.629
Yields of Pyridinic Product			
Pyridinic prod. (mole)	0.094	0.350	0.339
Yield (%, diene)	55	56	54
Yield (%, CF_3CN)	100	98	100

TABLE II

PHYSICAL PROPERTIES OF TRIFLUOROMETHYLPYRIDINES

Diene	Butadiene	Pentadiene	Isoprene
Pyridine-	2-Trifluoromethyl-	6-Methyl-2-trifluoromethyl-	4-Methyl-2-trifluoromethyl-
n_D^{25}	1.4155	1.4262	1.4380
B.p. (°C.)	143 (745 mm.)	153 (756 mm.)	171 (760 mm.)
M.p. (°C.)	...	12.5	...
Infrared spectra	(Ref. 2)	This work	This work

A Perkin-Elmer model 21 double-beam recording spectrometer equipped with NaCl and LiF optics was used to obtain the spectra for these pyridines as liquids.

2-Trifluoromethylpyridine. The infrared spectrum, vibrational assignment of the ring fundamentals and CF_3 modes, and product identification have been described in an earlier communication,[2d] and need no further comment.

6-Methyl-2-trifluoromethylpyridine. Infrared frequencies ($cm.^{-1}$) and intensities:[3] 3477 (m); 3027 (w), 2488 (w), 2262 (w), 2124 (v.w.), 1987 (s), 1902 (s), 1881 (v.w.), 1821 (w), 1779 (v.w.), 1728 (w), 1672 (v.w.), 1608 (v.s.), 1581 (v.w.), 1466 (v.s.), 1426 (v.s.), 1378 (v.s.), 1338 (v.s.), 1290 (s), 1261 (v.s.), 1245 (v.s.), 1183 (s), 1171 (s), 1157 (s), 1139 (m.s.), 1103 (s), 1093 (s), 1075 (w), 1042 (s), 999 (v.s.), 990 (w), 911 (s), 878 (v.s.), 847 (v.w.), 805 (v.s.), 746 (v.s.), 658 (s); LiF resolution: 3022 (s), 3019 (s), 2956 (s), 2930 (s), 2872 (s). Inspection of the generalized cyclization-dehydrogenation reaction (1) leaves little doubt as to the identity of this pyridinic product since 6-methyl-2-trifluoromethylpyridine is the only isomeric pyridine feasible with pentadiene and CF_3CN as reactants. The vibrational assignment (below) confirms the identity of this product through the empirical recognition of these structural units.

Anal. Calculated for $C_7H_6NF_3$: N, 8.69. Found; N, 9.02.

4-Methyl-2-trifluoromethylpyridine. Infrared frequencies ($cm.^{-1}$) and intensities: 3442 (m), 3017 (w), 2950 (v.s.), 2495 (w), 2197 (v.w.), 2092 (w), 1989 (m), 1895 (m), 1741

(1) Part XII in the series, The Reaction of Cyanogen and Related Nitriles With 1,3-Dienes.

(2) (a) G. J. Janz, R. G. Ascah, and A. G. Keenan, *Can. J. Res.* B25, 272, 283 (1947); (b) G. J. Janz and S. C. Wait, Jr., *J. Am. Chem. Soc.*, **76**, 6377 (1954); (c) G. J. Janz and W. J. McCulloch, *J. Am. Chem. Soc.*, **77**, 3014, 3143 (1955); (d) G. J. Janz, J. M. S. Jarrie, and W. E. Fitzgerald, *J. Am. Chem. Soc.*, **78**, 978 (1956); (e) G. J. Janz and J. M. S. Jarrie, *J. Phys. Chem.*, **60**, 1430 (1956).

(3) Filed with the Catalog of Infrared Spectral Data, A.P.I. Project 44, Petroleum Research Laboratory, Carnegie Institute of Technology.

(m), 1674 (v.w.), 1614 (v.s.), 1586 (m), 1570 (w), 1509 (w), 1493 (w), 1441 (w), 1421 (v.s.), 1379 (s), 1327 (v.s.), 1299 (w), 1250 (s), 1209 (s), 1176 (s), 1135 (s), 1117 (s), 1088 (s), 1044 (s), 1031 (s), 998 (v.s.), 977 (w), 948 (v.w.), 896 (s), 876 (v.s.), 836 (v.s.), 800 (v.w.), 757 (v.s.), 749 (s), 719 (s), 686 (v.s.), 654 (m), 645 (s); LiF resolution: 3702 (s), 3062 (s), 3027 (s), 2971 (s), 2932 (s), 2873 (s).

Two trifluoromethylpyridines, *i.e.* the 4-methyl-and 5-methyl-isomers, may be conceived as products in this reaction (1) with isoprene and CF_3CN as reactants. The identity of the product as the 4-methyl-2-trifluoromethyl isomer rather than the 5-methyl-2-trifluoromethyl isomer or a mixture of the two is in accord with previous syntheses using isoprene and CH_3CN, C_6H_5CN, and $(CN)_2$ as nitriles, respectively.[2c] The 4-methyl-substituted pyridine was the only product found in each case. Comparison of the observed boiling point (171°, Table I) with the values predicted for 4-methyl-2-trifluoromethyl pyridine (172°) and 5-methyl-2-trifluoromethylpyridine (176°), and the vibrational assignment (below) leave little doubt as to the product identity.

The values for the boiling points were estimated from those of 2-trifluoromethylpyridine (Table I, 143°), 2-picoline[4] (128°), 2,3-lutidene[5] (161°), and 2,4-lutidene (157°), assuming that the non-bonded interactions account for the additive properties[6] in the isomeric trifluoromethylpyridines as in the lutidene series.

Anal. Calculated for $C_7H_6NF_3$: N, 8.69. Found; N, 8.40.

Vibrational assignment: The infrared absorption frequencies generally used to characterize pyridines are those suggested by Cannon and Sutherland:[7] 3020, 1600 to 1590, 1500 (s) or lower, near 1200 (s), 1100 to 1000 (s), 900 to 650—two strong bands. The observed frequencies at 3027, 1600, 1466, 1245, 1103, 878, 805, and 3017, 1596, 1421, 1209, 1117, 896, 757 for the 6-methyl-and the 4-methyl-2-trifluoromethyl pyridines respectively, are in accord with the pyridinic ring assignments. The corresponding vibrations in 2-trifluoromethylpyridine were 3040, 1596, 1445, 1250, 1100, 795, and 745. For the CF_3 group Randle and Whiffen[8] reported the mean values for the C—F stretching modes of aromatic trifluoromethyl compounds to be: 1321 ± 9, 1179 ± 7, and 1140 ± 9 (cm.$^{-1}$). Inspection of the observed spectra reveals these characteristic absorptions at 1338, 1183, 1139 and 1327, 1176, 1135 for the 6-methyl- and the 4-methyl-substituted pyridines, respectively. An investigation[9] of a series of benzotrifluorides resulted in the assignment of a CF_2 deformation frequency at 658–665 cm.$^{-1}$ The 6-methyl and the 4-methyl compounds show strong absorptions at 658 and 686 (cm.$^{-1}$), respectively. Symmetrical deformation frequencies occur at 760 in CF_3Br and 741 (cm.$^{-1}$) in CF_3I. Strong absorption frequencies in the spectra of the 6-methyl and the 4-methyl substituted pyridines occur at 746 and 749 cm.$^{-1}$, respectively. The C—H stretching frequencies of the CH_3 group in a series of hydrocarbons assigned by Fox and Martin[10] in the region of 3000 cm.$^{-1}$ (LiF resolution) are 2962, 2934, 2912, and 2872 (cm.$^{-1}$). 6-Methyl-2-trifluoromethylpyridine has bands at 2956, 2930, and 2872; 4-methyl-2-trifluoromethylpyridine, at 2971, 2932, and 2873 (cm.$^{-1}$).

(4) I. G. Heap, W. J. Jones, and J. B. Speakman, *J. Am. Chem. Soc.*, **43**, 1936 (1921).

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DISCUSSION

The high reactivity in this Diels-Alder synthesis of trifluoroacetonitrile undoubtedly may be attributed to the polarization of the (C≡N) link by the proximity of the CF_3 group with its strong electrophilic properties. In preliminary experiments with trifluoroacetonitrile alone, this compound proved thermally very stable, showing no trace of pyrolysis or self-polymerization in the region 350°–500°. Inspection of the results in Table I shows clearly that the reacted nitrile may be accounted for entirely by the Diels-Alder process, *i.e.* the yield of pyridinic product is 100 mole percent, within experimental limits of accuracy, based on trifluoroacetonitrile.

The lower yields, based on the dienes, may be attributed to the fact that two different dienophilic groups, *i.e.* the C=C and the C≡N groups, are competing for the diene. Thus for butadiene, 3-vinylcyclohexene as well as 2-trifluoromethylpyridine was confirmed in the product analyses. No effort was made in the present phase of the work to estimate such products quantitatively. Inspection of the data in Table I shows that 44–46 mole percent of the diene that has been converted per pass may be accounted for in this manner. With CF_3CN in large excess, the effect of this competing process would undoubtedly be minimized.

The results in Table I are of further interest to ascertain whether kinetic or thermodynamic control is operative at these long reaction times. In the study of gaseous reactions in continuous flow systems, providing the operating conditions are comparable, the concept of space-time-yield (S.T.Y.) offers a direct insight[11] on kinetic control since it is directly proportional to the rate constant. From the definition of S.T.Y., *i.e.* moles of product/unit time/unit reaction volume, it follows in the present case, that:

$$\text{S.T.Y.} = \left(\frac{\text{moles pyridinic product}}{\text{volume of reaction vessel}}\right) = k_2\left(\frac{N_D N_T}{V_0}\right) \quad (2)$$

where N_D, N_T are the moles of diene and nitrile, V_0 is the velocity of flow of the entering mixture, and k_2 the rate constant. The relation strictly applies only at low conversions, but has been used as a first approximation to calculate the space-time-yields in the present instance.

Diene	Butadiene	Pentadiene	Isoprene
S.T.Y.[a]	6.1×10^{-4}	7.8×10^{-4}	8.8×10^{-4}

[a] Units, moles/hr./100 cc. reaction zone.

It follows from Equation 2 that the values of the space-time-yield should directly reflect the relative reactivities of the three dienes if the reactions are subject to kinetic control. The values of the S.T.Y. (above) are all the same order of magnitude, no significance being attributable to the small dif-

(11) G. J. Janz and S. C. Wait, Jr., *J. Chem. Phys.*, **23**, 1550 (1955).

ference to the variation in the pre-exponential factor. The closely similar diene conversions (Table I) are also in accord with the possibility that these yields reflect equilibrium rather than rate values.

By the method of statistical thermodynamic functions, the free energy change for the butadiene-trifluoroacetonitrile reaction was calculated. Using the precise values[12,13] for butadiene, hydrogen, and trifluoroacetonitrile, and the methods[14] of group equations and group increments to estimate the functions for trifluoromethylpyridine and the heats of formation for CF_3CN and the latter, it was found that ΔF° was negative over the entire temperature range 300°–1000° K., being −9 kcal./mole at the upper limit. It is sufficient for the present discussion to refer only to the result at 400°. The standard free energy change, and the equilibrium S.T.Y. calculated from the well known equation:

$$\Delta F^\circ = -RT \ln K_p \qquad (3)$$

at 400° were thus found to be −14 kcal./mole and 13×10^{-4} moles/hr./100 cc. reaction volume.

Comparison of the thermodynamically predicted value with the experimental S.T.Y., 6.1×10^{-4}, confirms that the present yields should be recognized as equilibrium yields, *i.e.* that thermodynamic control rather than kinetic control operates. It should be noted that the preceding results should be interpreted only qualitatively rather than giving a quantitative estimate of the nearness to equilibrium conditions in these experiments.

Extension of these studies is in progress at very short reaction times as well as very long periods, to evaluate the relative reactivities of the dienes and the reaction equilibria in the homogeneous gas phase at moderately high temperatures.

Acknowledgment. Grateful acknowledgment is made to the Monsanto Chemical Co. for a grant-in-aid to support this work, and to the Phillips Petroleum Co. for a gift of chemicals. The authors are indebted to J. M. S. Jarvie for the thermodynamic estimates and stimulating discussions.

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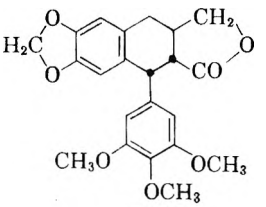
Methyl Desoxypodophyllate and Its Methyl Ether

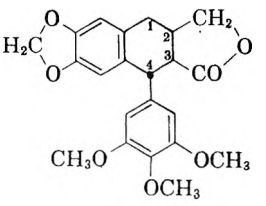
ANTHONY W. SCHRECKER AND MARY M. TRAIL

Received December 2, 1957

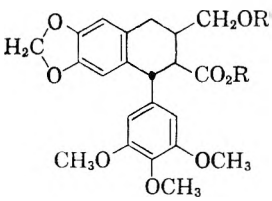
In a previous paper from this laboratory,[1] it was shown that anthricin (isolated by Noguchi and Kawanami[2] from *Anthriscus sylvestris* Hoffm.), hernandion (isolated by Hata[3] from *Hernandia ovigera* L.), and silicicolin [isolated by Hartwell, Johnson, Fitzgerald, and Belkin[4] from *Juniperus silicicola* (Small) Bailey] are all identical with desoxypodophyllotoxin (I),[5,6] a compound also obtained[7] from *Podophyllum peltatum* L. Base-catalyzed epimerization of I (at C_3) produces the *cis*-(2:3)-*trans*-(3:4) desoxypicropodophyllin (II),[5,6] which is identical[1] with isohernandion,[3] with silicicolin-B,[5] and also with cicutin (isolated by Marion[8] from *Cicuta maculata* L.[9]). Both I and II are saponified to the same hydroxy acid, desoxypodophyllic acid (IIIa), which in turn is lactonized to II.[5] Noguchi's isoanthricin[2] was probably[1] a mixture of this acid with some II.



I



II



IIIa: R = R′ = H
IIIb: R = CH_3; R′ = H
IIIc: R = H; R′ = CH_3
IIId: R = R′ = CH_3

In view of the identity of the various lactones with I or II, it is difficult to understand certain apparent discrepancies with regard to their reactions. Thus, Noguchi and Kawanami[2] reported that treat-

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(2) K. Noguchi and M. Kawanami, *J. Pharm. Soc. Japan*, **60**, 629 (1940); *Chem. Abstr.*, **47**, 6386*a* (1953).

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(6) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953).

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(8) L. Marion, *Can. J. Research*, **20B**, 157 (1942).

(9) Cicutin is probably[1] an artifact, produced by epimerization of desoxypodophyllotoxin during its isolation, which included treatment with methanolic sodium hydroxide.

ment of isoanthricin with dimethyl sulfate in cold alkali yielded "isoanthricinic acid methyl ester" [*i.e.*, methyl desoxypodophyllate (IIIb)], $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 173°, $[\alpha]_D$ −43.6° (chloroform), which was saponified to "isoanthricinic acid" [*i.e.*, desoxypodophyllic acid (IIIa)], $C_{19}H_{15}O_5(OCH_3)_3$, m.p. 205°, and which was regenerated from this acid with diazomethane. Hata[3] reported that reaction of silver desoxypodophyllate (prepared from isohernandion) with methyl iodide afforded a methyl ester, also $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 173°, which thus appeared to be identical with Noguchi's ester.

Noguchi's results disagree with the observation[6] that desoxypodophyllic acid fails to form a methyl ester when treated with diazomethane, but is lactonized to II, even at 0°, in contrast to isodesoxypodophyllic acid[6] [IIIa, but *trans*-(2:3)-*trans*-(3:4)], which does yield the corresponding methyl ester. Moreover, Marion[8] reported that treatment of cicutin with dimethyl sulfate in hot alkali, followed by acidification, afforded an acid, $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 194–195°, evidently desoxypodophyllic acid methyl ether (IIIc).

These contradictory findings could be reconciled only by the assumption that Noguchi's ester, m.p. 173°, was actually methyl dexoxypodophyllate methyl ether (IIId), which on saponification would yield IIIc, identical with Marion's acid. To determine whether this assumption was correct, potassium desoxypodophyllate (prepared from I) was methylated under conditions similar to those reported[2] by Noguchi. The neutral fraction was separated by chromatography into desoxypicropodophyllin (II) and methyl desoxypodophyllate methyl ether (IIId), $C_{19}H_{13}O_3(OCH_3)_5$, m.p. 173–174°, $[\alpha]_D$ −70° (chloroform). This compound depressed the melting point of methyl desoxypodophyllate (IIIb), m.p. 175–176°, $[\alpha]_D$ −66° (chloroform), prepared by Hata's[3] procedure. None of the latter ester could be isolated from the reaction with dimethyl sulfate. Methylation of desoxypicropodophyllin according to Marion[8] (*i.e.*, in hot alkali) yielded IIIc, m.p. 180–184° (foaming), in addition to unmethylated IIIa. Although the melting (or, rather, decomposition) point of IIIc was much lower than that reported by Marion, the substance was found to be analytically pure. Variable decomposition points of different samples have also been observed in the case of IIIa[5] and may be caused by the presence of trace impurities.

In summary, it appears that Noguchi's "isoanthricinic acid methyl ester" was actually methyl desoxypodophyllate methyl ether (IIId) and that his "isoanthricinic acid" was desoxypodophyllic acid methyl ether (IIIc).

EXPERIMENTAL[10,11]

Methyl desoxypodophyllate (IIIb). Silver desoxypodophyllate (0.9 g.), prepared from desoxypicropodophyllin[5] by Hata's procedure,[3] was stirred and refluxed with 7 ml. of methyl iodide for 1 hr. The mixture was extracted with hot ethanol and the filtrate concentrated. The solid thus obtained (0.57 g., m.p. 163–164°) afforded, after four recrystallizations from ethanol, small colorless needles, m.p. 175–176°, $[\alpha]_D^{22}$ −65.9° (*c* 0.99, chloroform), $[\alpha]_D^{22}$ −138° (*c* 0.50, pyridine), infrared maximum (in chloroform) at 1735 cm.$^{-1}$ (ester group). Prolonged heating with piperidine in ethanol caused partial conversion to II.

Anal. Calcd. for $C_{19}H_{14}O_4(OCH_3)_4$: C, 64.17; H, 6.09; OCH_3, 28.84. Found: C, 63.82; H, 5.92; OCH_3, 28.91.

Desoxypodophyllic acid methyl ether (IIIc). A hot solution of desoxypicropodophyllin in 3% sodium hydroxide was treated with dimethyl sulfate and 10% sodium hydroxide according to Marion's procedure.[8] The precipitate obtained after acidification was dissolved in sodium bicarbonate solution, which was then extracted with chloroform and reacidified at 0°. The gelatinous material, when recrystallized from methanol, formed tiny needles, m.p. 180–184° (foaming) (reported[8] m.p. 194–195°).

Anal. Calcd. for $C_{19}H_{14}O_4(OCH_3)_4$: C, 64.17; H, 6.09; OCH_3, 28.84. Found: C, 64.26; H, 6.02; OCH_3, 28.56.

The methanolic mother liquor, when diluted with water, yielded desoxypodophyllic acid (IIIa), m.p. 164–165° (foaming), which had an infrared spectrum (Nujol mull) identical with that of an authentic sample.[5]

Methyl desoxypodophyllate methyl ether (IIId). Following essentially Noguchi's procedure,[2] a chilled solution of 916 mg. of desoxypodophyllotoxin (I)[5] in 48 ml. of 40% potassium hydroxide was stirred magnetically and treated dropwise with 24.7 ml. (33.4 g.) of dimethyl sulfate during 15 min. It was then stirred at room temperature (with occasional immersion in cold water) for 3 hr., treated dropwise with another 18.7 ml. (25.3 g.) of dimethyl sulfate, and stirred for 3 more hr. The still alkaline mixture was then exhausted with ether in a continuous extractor. The extract was evaporated, the residue dissolved in chloroform, and the solution was washed with sodium bicarbonate solution and water, dried, and evaporated. The crude product was chromatographed on 18 g. of alumina (Alcoa, F-20) and eluted with 100 ml. of 1:1 benzene-chloroform, with 50 ml. of chloroform, and with 100 ml. of 9:1 chloroform-methanol. The last eluate left almost no evaporation residue.

The material eluted with benzene-chloroform was rechromatographed on neutral alumina (Woelm). Elution with 4:1 benzene-chloroform, followed by recrystallization from benzene-pentane provided rosettes of colorless needles, yield 50 mg., m.p. 173–174°, $[\alpha]_D^{26}$ −69.8° (*c* 0.84, chloroform), infrared maximum (in chloroform) at 1735 cm.$^{-1}$ (ester group). The compound and IIIb gave a mixed melting point depression and different infrared spectra.

Anal. Calcd. for $C_{19}H_{13}O_3(OCH_3)_5$: C, 64.85; H, 6.35; OCH_3, 34.91. Found: C, 65.00; H, 6.42; OCH_3, 35.05.

The material that was eluted with chloroform (113 mg.) crystallized from ethanol as electrified needles, m.p. 172–173°, $[\alpha]_D^{26}$ +35.8° (*c* 0.93, chloroform) (lit.[5,6] m.p. 172–173°, average $[\alpha]_D$ +34°). It was identified as desoxypicropodophyllin by the mixed melting point and infrared spectrum (lactone band in chloroform at 1770 cm.$^{-1}$).

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(10) Melting points are corrected and were determined in Pyrex capillaries with the Hershberg apparatus. Samples were dried for analysis at 78° and 0.01 mm. overnight. Optical rotations were measured in 10-dm. tubes.

(11) Microanalyses by Mrs. Evelyn Peake and Miss Paula M. Parisius in Dr. W. C. Alford's laboratory.

(12) National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

Preparation of Several New Phosphonic and Phosphinic Acids

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Received December 4, 1957

A previous paper[1] reported that bis(*p*-nitrophenyl)phosphinic acid possesses considerable activity *in vitro* against *Treponema pallidum*, the causative agent of syphilis. This finding has prompted us to investigate the activity of a large number of phosphonic and phosphinic acids which were available in this laboratory. The results of this investigation are being published elsewhere.[2] Among the compounds tested are four which have not been described in the literature. The present note describes the preparation and chemical properties of these compounds.

(*o*-Carboxyphenyl)phenylphosphinic acid and *o*-phenoxyphenylphosphonic acid were originally prepared as possible intermediates for the synthesis of heterocyclic phosphinic acids. 5-Chloro-2-methoxyphenylphosphonic acid was synthesized during the course of some studies on the demethylation of methoxyphenylphosphonic acids. (*o*-Nitrophenyl)phenylphosphinic acid was prepared in low yield from *o*-nitrobenzenediazonium fluoborate and phenyldichlorophosphine after a number of unsuccessful attempts to prepare *o*-nitrophenylphosphonic acid by the diazo reaction.[3]

EXPERIMENTAL

o-Phenoxyphenylphosphonic acid. An intimate mixture of 10.0 g. of *o*-bromophenylphosphonic acid, 20 ml. of redistilled phenol, 10.0 g. of anhydrous potassium carbonate, and 0.2 g. of copper powder was heated under reflux for a period of 16 hr. The reaction mixture was then diluted with about 35 ml. of water, and the excess phenol removed by steam distillation. The residual liquid from the steam distillation was treated with Darco and filtered.[4] The filtrate was evaporated on the steam bath to about 70 ml. and then acidified to Congo red with concentrated hydrochloric acid. The mixture was cooled and the precipitate removed by filtration. Recrystallization from a mixture of one volume of alcohol to 5 volumes of 6*N* hydrochloric acid yielded 6.6 g. (63%) of pure *o*-phenoxyphenylphosphonic acid as long white needles, m.p. 200–202°.

Anal. Calcd. for $C_{12}H_{11}O_4P$: P, 12.38; neut. equiv. (for one ionizable hydrogen per molecule), 250.2. Found: P, 12.39; neut. equiv. (to *p*H 4.3) 254.3.

When the neutral equivalent was determined with thymolphthalein in the usual manner, a sharp end-point was not obtained. This fact suggests that the second dissociation constant of *o*-phenoxyphenylphosphonic acid is abnormally low.[5]

5-Chloro-2-methoxyphenylphosphonic acid. 5-Chloro-2-methoxyaniline (Eastman P 4202) was converted to the corresponding diazonium fluoborate by the method designated by Roe as II A.[6] The diazonium salt, after being dried in a vacuum desiccator, was suspended in dry ethyl acetate and treated with phosphorus trichloride and cuprous bromide in the usual manner.[3a] After steam-distillation of the reaction mixture, the residual liquid was filtered. A small amount of the diarylphosphinic acid remained on the filter but could not be readily purified. The filtrate was evaporated on the steam bath to incipient crystallization, cooled, and filtered. The resulting crude phosphonic acid was dissolved in an excess of 7% sodium hydroxide solution and treated with Darco. The charcoal was removed by filtration and the filtrate acidified to Congo red with concentrated hydrochloric acid. The precipitate obtained was recrystallized from a mixture of one volume of alcohol to 2 volumes of 3*N* hydrochloric acid. The yield was 27%; m.p. 222.5–225°.

Anal. Calcd. for $C_7H_8ClO_4P$: Cl, 15.93; P, 13.92; neut. equiv., 111.3. Found: Cl, 16.01; P, 13.67; neut. equiv., 113.3.

(o-Nitrophenyl)phenylphosphinic acid. This compound was prepared from *o*-nitrobenzenediazonium fluoborate and phenyldichlorophosphine by the general method described previously.[3b] After the reaction mixture was steam-distilled, the residual liquid in the distilling flask was transferred to a beaker and cooled. The crude phosphinic acid was removed by filtration and dissolved in 10% sodium carbonate solution. The alkaline solution was treated with Darco, filtered, and the acid precipitated by the addition of concentrated hydrochloric acid. Further purification was effected by dissolving the phosphinic acid in 95% ethanol (70 ml. per 0.2 mole of diazonium salt used) and adding 15 volumes of ether. The gummy material which separated on cooling was removed by filtration and discarded. The filtrate was evaporated on the steam bath to incipient crystallization and then cooled in a deep-freeze at −25°. The yield of yellow crystals thus obtained was 5%, m.p. 229–232°.

Anal. Calcd. for $C_{12}H_{10}NO_4P$: N, 5.32; P, 11.77; neut. equiv., 263.2. Found: N, 5.27; P, 11.68; neut. equiv., 265.6.

(o-Carboxyphenyl)phenylphosphinic acid was prepared from *o*-carbomethoxybenzenediazonium fluoborate and phenyldichlorophosphine by the general method described previously[3b] and was recrystallized from aqueous acetone. Obviously, the ester was cleaved to the free carboxy group during the course of the reaction. The yield was 55%; m.p. 161–164°.

Anal. Calcd. for $C_{13}H_{11}O_4P$: P, 11.82; neut. equiv., 131.1. Found: P, 11.76; neut. equiv., 131.9.

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Kinetics of the Acid-Catalyzed Condensation of Formaldehyde with *N,N*-Dimethyl-*m*-toluidine

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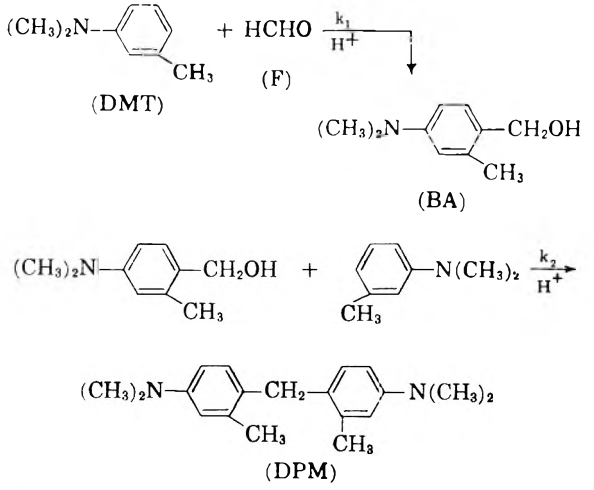
The acid-catalyzed reaction of an aldehyde with an aromatic tertiary amine to form a di- or triphenylmethane derivative is a familiar preparative process which has indeed been a mainstay of the commercial production of triphenylmethane dyes. In a preliminary kinetic investigation of this reaction which we are not now able to continue, we employed the reaction of dimethyl-*m*-toluidine with formaldehyde in a dioxane-water medium. From previous work, we expected the reaction to occur in two steps, of which the first would be rate-



determining under conditions of moderate acidity.[1-4] The possibility of isolating the substituted benzyl alcohol (BA) under conditions of high acidity[5] suggested, however, that there is an inversion of relative specific rates k_1/k_2 as the acidity of the medium is increased. The earlier work indicated that in the absence of excessive concentrations of formaldehyde the reaction is uncomplicated by further additions, condensation, or polymerization, or by ortho addition. Our experiments have, however, led to the entirely unexpected conclusion that the rate of the reaction is markedly accelerated by oxygen, the major product remaining the diphenylmethane derivative (DPM). The evidence follows.

The extent of reaction at equal time (16 min.) of a series of reaction mixtures at 55° in solutions approximately $0.14M$ in formaldehyde, $0.20M$ in DMT, and $1.2M$ in pyridine, in a solvent approximately 65% dioxane by volume, revealed a dependence upon standing time before initiation of the reaction by addition of the formaldehyde. Pyridine was present as a buffer to prevent changes in acidity as the reaction progressed. The acidity was varied among the runs by addition of varying amounts of perchloric acid. Table I summarizes some typical results. The acidity is given as the ratio of the concentration of added perchloric acid to the sum of the initial concentration of DMT and the concentration of pyridine. No attempts were made in any but the last set of data to exclude atmospheric oxygen from the reaction mixtures, both before and during the reaction. Each of the groups in the table consists of runs made with the same solution. Reproducibility under identical conditions was reasonably good, as illustrated by the data of one of these groups.

TABLE I

DEPENDENCE OF CONVERSION OF FORMALDEHYDE UPON STANDING TIME OF DMT-PYRIDINE-DIOXANE-WATER SOLUTION BEFORE REACTION

$(HClO_4)$ / $(DMT)_0 + [P]$	Oxygen Excluded	Standing Time Before Reaction	% Conversion of F
0.00	No	20 Min.	0.0
0.14	No	20 Min.	5.7
0.43	No	20 Min.	11.3
0.43	No	20 Hr.	20.5
0.45	No	20 Min.	21.0
0.45	No	4 Hr.	26.8
0.46	No	20 Min.	27.4
0.46	No	6 Hr.	38.0
0.50	No	20 Min.	13.2
0.50	No	16 Hr.	24.4
0.51	No	20 Min.	14.0
0.51	No	20 Min.	14.2
0.44	Yes	15 Min.	3.4
0.44	Yes	5 Hr.	3.8
0.44	Yes	22 Hr.	3.6

Qualitatively similar results were obtained by a comparison of runs made in unbuffered reaction mixtures. This fact seems to eliminate the possibility of a role of pyridine in the reaction. Further work was undertaken to prepare the diphenylmethane base end product[2] under atmospheres of both nitrogen and oxygen. Results in both cases were quantitative yields, thus precluding the possibility of different reaction products when carried out in an atmosphere of oxygen. The reaction was considerably faster, however, in the oxygen environment.

The above results indicate an accelerative role of oxygen in the condensation reaction and suggest that the maximum reactivity occurs when there are appreciable amounts of both basic DMT and

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its conjugate acid in solution. The latter conclusion is of only qualitative value, however, in view of the marked oxygen effect.

EXPERIMENTAL

N,N-Dimethyl-*m*-toluidine was obtained from Eastman Kodak Co. and was purified by drying with magnesium sulfate and distillation through a 25-cm. vacuum-jacketed Vigreux column under an atmosphere of nitrogen. The boiling point was 211–212° at 760-mm. pressure, and the refractive index, n_D^{20}, was 1.5490. The amine was stored in sealed ampoules after distillation.

Pyridine was of reagent grade and was used without further purification. Commercial dioxane was purified and stored in the method given by Fieser.[6] Perchloric acid was of reagent grade.

Aqueous formaldehyde solutions were prepared by hydrolysis of paraformaldehyde in dilute phosphoric acid with subsequent distillation.

Analytical. The analysis of formaldehyde was carried out according to the method of de Jong[7] by addition to the reaction mixture of an excess of KCN followed by back titration of excess cyanide with mercuric nitrate using diphenyl carbazone as indicator. Mercuric nitrate solutions were prepared using triply distilled mercury as a primary standard,[8] and KCN solutions were checked against these. The reaction mixtures were quenched prior to analysis by addition of an excess of base. Reaction vessels were simple volumetric flasks.

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Reactions of (1-Nitrocyclohexyl)methanol

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Although (1-nitrocyclohexyl)methanol has been known for some time,[1] it appears to have been subjected to only one reaction, namely, catalytic reduction to the corresponding amino alcohol.[2–4] This paucity of published information regarding its chemical properties prompted the present investigation.

Attempts to prepare (1-nitrocyclohexyl)methyl bromide from (1-nitrocyclohexyl)methanol by treatment in the usual manner with phosphorus tribromide were unsuccessful as were attempts to prepare (1-nitrocyclohexyl)methyl iodide from the *p*-toluenesulfonate derivative of the alcohol by treatment with iodide ions. Failure of these nucleophilic displacement reactions to take place can be accounted for on the basis of the neopentyl-type structure of this primary alcohol.[5] However, (1-nitrocyclohexyl)methyl bromide was prepared by reaction of the alcohol with phosphorus tribromide in the presence of quinoline according to the method of Sommer *et al*,[6] for the successful conversion of neopentyl alcohol to the corresponding bromide.

Oxidation of (1-nitrocyclohexyl)methanol with nitrogen dioxide in chloroform under reaction conditions similar to those reported for converting primary alcohols to aldehydes[7,8] gave, instead, 1-nitrocyclohexanecarboxylic acid. The structure of this acid was established by the elemental and infrared analyses. The infrared spectrum has typical carboxyl absorption at 3.87 to 5.80μ as well as nitro absorption at 6.45 and 7.42μ.[9] The crystalline nitro acid was stable when stored at 0° but was unstable at room temperature, slowly decomposing with the evolution of gas. Attempts to obtain the nitro aldehyde by an Oppenhauer oxidation of the nitro alcohol in the presence of either acetone or cyclohexanone were unsuccessful as were attempts to prepare the nitro aldehyde by the reaction of the nitro alcohol with *N*-bromosuccinimide in carbon tetrachloride.[10]

Attempts to prepare the symmetrical ether, bis[(1-nitrocyclohexyl)methyl] ether, from (1-nitrocyclohexyl)methanol by dehydration under acidic conditions (sulfuric acid or *p*-toluenesulfonyl chloride[11]) and by the classical Williamson synthesis utilizing the potassium alcoholate and the nitro bromide were unsuccessful.

EXPERIMENTAL

(1-Nitrocyclohexyl)methanol. This compound, prepared according to Newman and Edwards[2] by the base-catalyzed condensation of nitrocyclohexane with paraformaldehyde, was purified by distillation; b.p. 100–102° (1 mm.), n_D^{25} 1.4846. This nitro alcohol is reported[3] to boil at 136–137° (5.5 mm.) with n_D^{25} 1.4853.

(1-Nitrocyclohexyl)methyl p-toluenesulfonate. A solution of 120 g. (0.75 mole) of (1-nitrocyclohexyl)methanol, and 150 g. (0.79 mole) of *p*-toluenesulfonyl chloride in 600 ml. of pyridine was kept at 10° for 3 days. The mixture was poured into water, and the white solid which formed was washed with dilute hydrochloric acid followed by water and then recrystallized from ethanol to give 220 g. (94% yield) of (1-nitrocyclohexyl)methyl *p*-toluenesulfonate, m.p. 57–58°,

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Anal. Calcd. for $C_{14}H_{19}NO_5S$: C, 53.67; H, 6.07; N, 4.47. Found: C, 53.86; H, 6.01; N, 4.30.

(1-Nitrocyclohexyl)methyl bromide. To a cool (0°) mixture of 15.9 g. (0.1 mole) of (1-nitrocyclohexyl)methanol and 16.8 g. (0.13 mole) of quinoline in 500 ml. of bromobenzene was added slowly 20.3 g. (0.075 mole) of phosphorus tribromide. The mixture was heated at 150° for 5 hr. and then allowed to stand at room temperature for several days. The bromobenzene solution was poured into cold water, separated, and dried over magnesium sulfate. The residue obtained after removal of the solvent *in vacuo* was distilled to give 12.5 g. (0.056 mole) of nitro bromide, b.p. 94.5–95° (1 mm.), $n_D^{23.5}$ 1.5100.

Anal. Calcd. for $C_7H_{12}BrNO_2$: C, 37.86; H, 5.45; Br, 35.98; N, 6.30. Found: C, 38.07; H, 5.37; Br, 36.14; N, 5.93.

1-Nitrocyclohexanecarboxylic acid. A mixture of 80 g. (0.5 mole) of (1-nitrocyclohexyl)methanol and 80 ml. of dinitrogen tetroxide in 640 ml. of chloroform was allowed to stand at room temperature for one week, during which time a water layer formed slowly. The chloroform layer was separated and then concentrated *in vacuo* to give a white, waxy solid. Recrystallization of this material by dissolution in ether-cyclohexane mixture and then pumping off the ether gave 62 g. (72% yield) of product which melted at 83–84°, with decomposition, to first a blue and then a brown liquid. The nitro acid dissolved readily in 2% aqueous sodium hydroxide solution. Acidification of the basic solution at room temperature caused the evolution of carbon dioxide.

Anal. Calcd. for $C_7H_{11}NO_4$: C, 48.55; H, 6.36; N, 8.09. Found: C, 48.94; H, 6.62; N, 8.05.

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Identity of Mevalonic and Hiochic Acids

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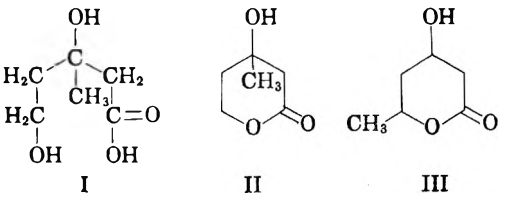
A new acetate-replacing and growth factor for *Lactobacillus acidophilus*, ATCC 4963, was reported recently.[1,2] The structure of this compound was proved to be 3,5-dihydroxy-3-methylpentanoic acid (I),[3,4] and it was given the generic name, mevalonic acid (and corresponding lactone, II). This compound was found to be utilized in the biosynthesis of cholesterol by rat liver homogenates.[5]

A new growth factor, designated hiochic acid, indispensable for the growth of "true Hiochi bacteria" (*Lactobacillus homohiochi* and *Lactobacillus heterohiochi*) was reported to be present in Japanese rice wine (Sake), and also in the culture broth of several organisms such as *Aspergillus*, *Penicillium*, *Monilia*, and *Lactobacillus*.[6] This factor was produced from the broth in which *Aspergillus oryzae* was grown. The studies on the factor revealed four structures which were compatible with the observations. Structure III seemed to be the most probable on the basis of a distinctly positive iodoform test. The negative iodoform test[3] on mevalonic acid,



when reexamined, gave a trace of iodoform, but when the test was compared with companion positive and negative control compounds, the test with mevalonic acid was considered again to be negative. The yield of iodoform with the positive control compounds was nearly quantitative. It is considered possible that mevalonic acid might be degraded to methyl β-hydroxyethyl ketone in trace amounts under the iodoform test conditions and this compound would be converted to iodoform.

The published infrared spectrum[6] of hiochic acid and that of mevalonic acid are identical. Samples (*N,N'*-dibenzylethylenediammonium bis-DL-mevalonate and hiochic acid quinine salt) were exchanged for comparison. The DL-mevalonic acid was found to have one half the microbiological activity for *Lactobacillus heterohiochi* as compared with hiochic acid, and the hiochic acid was found to have the same activity for *Lactobacillus acidophilus*, ATCC 4963 as mevalonic acid.

Since the infrared spectra of mevalonic acid and hiochic acid are identical, and they have the same microbiological activities for the microorganisms tested, it appears evident that hiochic acid is identical with mevalonic acid and is, therefore, 3,5-dihydroxy-3-methylpentanoic acid (I).[7]

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RAHWAY, N. J.

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Synthesis of a Silicone Derivative of Sucrose

CLARENCE D. CHANG[1] AND H. B. HASS[2]

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We wish to report the synthesis of a silicone derivative of sucrose. The compound, the octakis(trimethylsilyl) ether of sucrose, was prepared by treating sucrose in pyridine solution with trimethylchlorosilane (General Electric Silicone SC-01). Schwarz, Baronetsky, and Schoeller[3] have reported the preparation of glucose derivatives.

The sucrose used was commercial grade material which was purified by recrystallization from aqueous ethanol and dried *in vacuo;* the silylating agent, assaying 85% minimum trimethylchlorosilane, was used without preliminary purification.

Trimethylchlorosilane (250 g., 2.3 mole) was added dropwise into a mechanically stirred solution of 85.6 g. (0.25 mole) sucrose in 1.5 l. of anhydrous pyridine, after which the reaction mixture was heated at 80°–85° for two hours. Upon completion of the reaction the excess pyridine was distilled off *in vacuo* and the residual slurry extracted thoroughly with petroleum ether. The ether extract was concentrated *in vacuo* and the viscous concentrate distilled in a Hickman alembic still at 0.02–0.05 mm. at 190°–200°.

The product was a clear, almost colorless oil with high viscosity, soluble in benzene, methanol, acetone, petroleum ether, diethyl ether, and chlorinated hydrocarbons, and insoluble in water. $[\alpha]_D^{20}$ +3.47° (50 wt. % in benzene); n_D^{20} 1.4434.

Anal.: Calcd. for $C_{36}H_{86}O_{11}S_8$: mol. wt., 918. Found: Si, 23.3; mol. wt. (Rast), 933.

The data suggest that the compound may be a mixture containing some hepta or lower silicated derivatives. However, it is believed that these very possibly have higher boiling points or even would tend to polymerize without distillation.

The compound exhibited a marked tendency to hydrolyze in the presence of water. A sample, refluxed with water and chromatographed, showed a single spot which was identified as sucrose. Since the compound is volatile and can readily be hydrolyzed, yielding sucrose, it offers a good means for the analytical separation of sucrose by vapor phase chromatography and its identification.

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NEW YORK, N. Y.

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Reduction of Chlorobenzene at the Dropping Mercury Electrode

FRANK L. LAMBERT AND KUNIO KOBAYASHI

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Although there have been several attempts to reduce chlorobenzene and its derivatives at the dropping mercury electrode,[1-3] they were not successful, ostensibly because of the extreme potentials involved. We wish to report the reduction of chlorobenzene and to suggest that other difficultly reducible organic substances will be accessible by the technique employed. Because our work lies primarily in the area of aliphatic halogen compounds, we do not intend to pursue further investigations of chlorobenzenes or unsaturated compounds which might now be reducible by others according to the procedure described herein.

Tetrabutylammonium iodide (TBI) has been shown to be the supporting electrolyte with the most negative decomposition potential of the substances tested in dioxane-water.[4] Kolthoff and Coetzee[5] found that several supporting electrolytes had the same decomposition potential in anhydrous acetonitrile. As might be expected, our work in anhydrous *N,N*-dimethylformamide (DMF) has shown that 0.05*M* TBI has an apparent decomposition potential of approximately −2.85 volts *vs.* the saturated calomel electrode (S.C.E.) and 0.05*M* tetraethylammonium bromide (TEB) "discharges" at −2.76 volts. Yet, contrary to obvious deduction, chlorobenzene in DMF solution with TBI as the supporting electrolyte yields only a marked rise in current just prior to the cathodic discharge, whereas with TEB as the supporting electrolyte chlorobenzene gives a clear wave with a flat plateau. The half-wave potential in 0.05*M* TEB is −2.58 volts *vs.* the S.C.E.

The reduction of chlorobenzene is influenced by the cation of the supporting electrolyte because no polarographic wave is observed when tetrabutylammonium bromide (or TBI) is used but waves are present with 0.05*M* tetraethylammonium iodide or perchlorate (or TEB) as supporting electrolytes. (The half-wave potentials are −2.58 for chlorobenzene in tetraethylammonium iodide and −2.60 in tetraethylammonium perchlorate.) With tetramethylammonium bromide a rise in current is discernible before cathodic discharge but the wave

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is not at all clear because of the high resistance of the solution.

Lothe and Rogers[6] have thoroughly investigated the effect of supporting electrolytes on the reduction of carbon tetrachloride in methanol (and aqueous methanol) solutions. They detected a shift of 0.06 volt in the half-wave potential toward more positive values in changing from TBI to TEB as the supporting electrolyte. The average $E_{1/2}$ for carbon tetrachloride with these electrolytes in methanol is -0.85 volt. This would be in proportion to a shift from the hypothetical $E_{1/2}$ for the chlorobenzene with TBI in DMF of -2.8 volts (*i.e.* near the discharge potential) and the $E_{1/2}$ for chlorobenzene with TEB in DMF of -2.6 volts, a difference of 0.2 volt in 2.7 volts.

A possible explanation for such a shift at very negative potentials is given by the work of Laitenen and Nyman[7] wherein it was shown that the cathodic discharge in liquid ammonia with TBI as the supporting electrolyte involved direct dissolution of electrons. With TEB in liquid ammonia, they found that a combination of both direct electron dissolution and amalgamation of the tetraethylammonium cation probably occurred at the discharge potential. In the present work the tetraethylammonium ions may be acting as intermediaries in the transfer of electrons from the cathode to the difficultly reducible chlorobenzene. When TBI is the supporting electrolyte, the tetrabutylammonium ions do not readily accept and then transfer electrons to the chlorobenzene; thus no reduction occurs until the electron dissolution process begins. This hypothesis is supported by our finding that mere addition of TEB to a solution of chlorobenzene in DMF already containing TBI allows the characteristic reduction wave for chlorobenzene to appear.

The chlorobenzene wave is diffusion controlled and has a slope of 0.09 volt. In a useful range of concentrations for analytical purposes, from 0.2 to $1 \times 10^{-3}M$ chlorobenzene with $0.05M$ TEB in DMF, the best value of the diffusion current is 4.5 microamperes per millimole. The diffusion current constant is subject to some error because of the rapid drop rate at extremely negative potentials but is of the order of 2.6 if a correction factor of 0.87[8] is applied to the fraction $i_d/m^{2/3}t^{1/6}$.

Attempts were made to reduce vinyl chloride and acetylene, both previously reported as unattacked at the dropping mercury electrode,[1] and a distinct rise in current just prior to the cathodic discharge was detected. However, no half-wave potential could be measured. Ethylene does not produce an increase in current before the discharge potential of TEB.

EXPERIMENTAL

A Pecsok-Juvet[9] cell thermostated at 25° ± 0.1° was used in conjunction with a Leeds and Northrup Type E Electrochemograph for the initial work. The cell resistance (with $0.05M$ TEB) was 6000 ohms. Later experiments employed a cylindrical cell with a fine sintered-glass disk sealed in a side arm located near the bottom of the cell similar to that of Kolthoff and Coetzee.[5] A saturated calomel cell fitted with a side tube closed by an agar plug could be inserted in the side arm of the polarographic cell. The capillary and nitrogen inlet tube were introduced through a standard taper joint in the top of the polarographic cell. The resistance of this cell was of the order of 3000 ohms with $0.05M$ TEB. All half-wave potentials reported have been corrected for IR drop. Matheson, Coleman, and Bell reagent chlorobenzene (n_D^{25} 1.5242), redistilled Eastman White Label DMF, Eastman White Label TEB and tetramethylammonium bromide, and Southwestern Analytical Chemicals TBI, tetrabutylammonium bromide, and tetraethylammonium iodide were employed. The tetraethylammonium perchlorate was synthesized according to Kolthoff and Coetzee.[5] The electrode characteristics were: m = 1.20 mg./sec. and t = 4.9 sec. for h = 66.1 cm., open circuit in $0.05M$ TEB in DMF. The diffusion currents were measured and the half-wave potentials determined by the "third method" described by Müller.[10]

Acknowledgment. We are greatly indebted to the Research Corp. for a Frederick Gardner Cottrell grant which initiated this work on the polarography of halogen compounds. The research here reported was completed while the senior author (F. L. L.) was a National Science Foundation Science Faculty Fellow at the California Institute of Technology.

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Reaction of Hexamine and Hexamine Dinitrate with Nitric Acid and Trifluoroacetic Anhydride in Liquid Sulfur Dioxide

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The action of nitric acid or mixtures of nitric acid and acetic or trifluoroacetic anhydride upon hexamine[1-3] or hexamine dinitrate[3-7] has been studied. However, the action of mixtures of nitric acid and trifluoroacetic anhydride upon hexamine (I) dissolved in sulfur dioxide has not been investigated. Liquid sulfur dioxide was found to dissolve large quantities of I; treatment of this solution with a mixture of nitric acid and trifluoroacetic anhydride resulted in the formation of 1-trifluoroacetyl-3,5-dinitro-1,3,5-triazacyclohexane (II) in good yield. This nitramine has not been previously reported and apparently is not formed when hexamine is treated with nitric acid-trifluoroacetic anhydride mixtures.[8] The structure of the trifluoroacetyl derivative (II) was confirmed by its formation from 3,5-dinitro-3,5-diazapiperidinium nitrate (PCX) and trifluoroacetic anhydride as well as by the titration of II with 0.1*N* alkali. Three moles of sodium hydroxide were consumed per mole of II with the formation of one mole each of disodium methylenedinitramine and sodium trifluoroacetate and, presumably, two moles of formaldehyde although the latter was not determined in a quantitative manner. The trifluoroacetyl compound (II) was inert to a mixture of nitric acid and trifluoroacetic anhydride although II "fumed-off" after being boiled in 99% nitric acid for ten minutes; ammonium nitrate was the only product isolated.

The action of trifluoroacetic anhydride upon a suspension of hexamethylenetetraammonium dinitrate (HADN) in liquid sulfur dioxide at −30° resulted in the formation of a pasty material (III) which was unstable and could not be obtained as a solid. However, when III was treated with methyl or ethyl alcohols there was obtained the 1-methoxymethyl- (IV) and 1-ethoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (V), respectively, as well as small quantities of 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX) and of II. The same products were obtained when the solvent sulfur dioxide was omitted in the nitrolyses but the subsequent isolation of IV and V was difficult because of the presence of pasty, amorphous solids. These compounds had been reported by Dunning and Dunning[9] to result from the action of the alcohols upon the unstable oil which they obtained by allowing nitric acid to react with hexamine at low temperatures. Wright and co-workers[3] obtained the ethoxy derivative V by the action of ethanol upon 1-acetoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VI) (see below).

In the present work it was found that hot alcoholic solutions of IV and V produced 3,7-dinitro-1,3,5,7-tetraazabicyclo[3,3,1]nonane (DPT).[2] The other products of this rearrangement have not been determined. A mixture of trifluoroacetic acid and trifluoroacetic anhydride which contained a small amount of nitric acid converted the methyl derivative IV to the 1-trifluoroacetoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VII), a crystalline solid which, however, slowly evolved trifluoroacetic acid upon standing. Aqueous sodium hydroxide rapidly degraded VII with the formation of disodium methylenedinitramine, sodium trifluoroacetate, and formaldehyde. The ester VII was also isolated when a sulfur dioxide suspension of HADN was treated with a mixture of trifluoroacetic anhydride, nitric and trifluoroacetic acids. Methanol rapidly transformed the ester VII to the unstable 1-hydroxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VIII), which was reconverted to VII by the action of trifluoroacetic anhydride. When a 2:1 mixture of nitric acid and trifluoroacetic anhydride was allowed to react with VII, there was isolated 1-nitroxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (IX), a crystalline solid which slowly decomposed on storage; IX is a sensitive and brisant explosive. Sodium acetate in acetic acid readily converted IX to the acetate VI which Wright[3] had prepared by the acetolysis of methylene-bis-1-[3,5-dinitro-1,3,5-triazacyclohexane].

The formation of only a small amount of the trifluoroacetyl derivative II in the nitrolysis of HADN may be due to the reluctance of this salt to undergo trifluoroacetylation as compared to hexamine. The nitrogen-trifluoroacetyl linkage once formed is not nitrolyzed (as was demonstrated by the inertness of II to nitric acid-trifluoroacetic anhydride mixtures) and would therefore be expected in the product. Liquid sulfur dioxide has also been employed successfully in other nitrolyses.[10]

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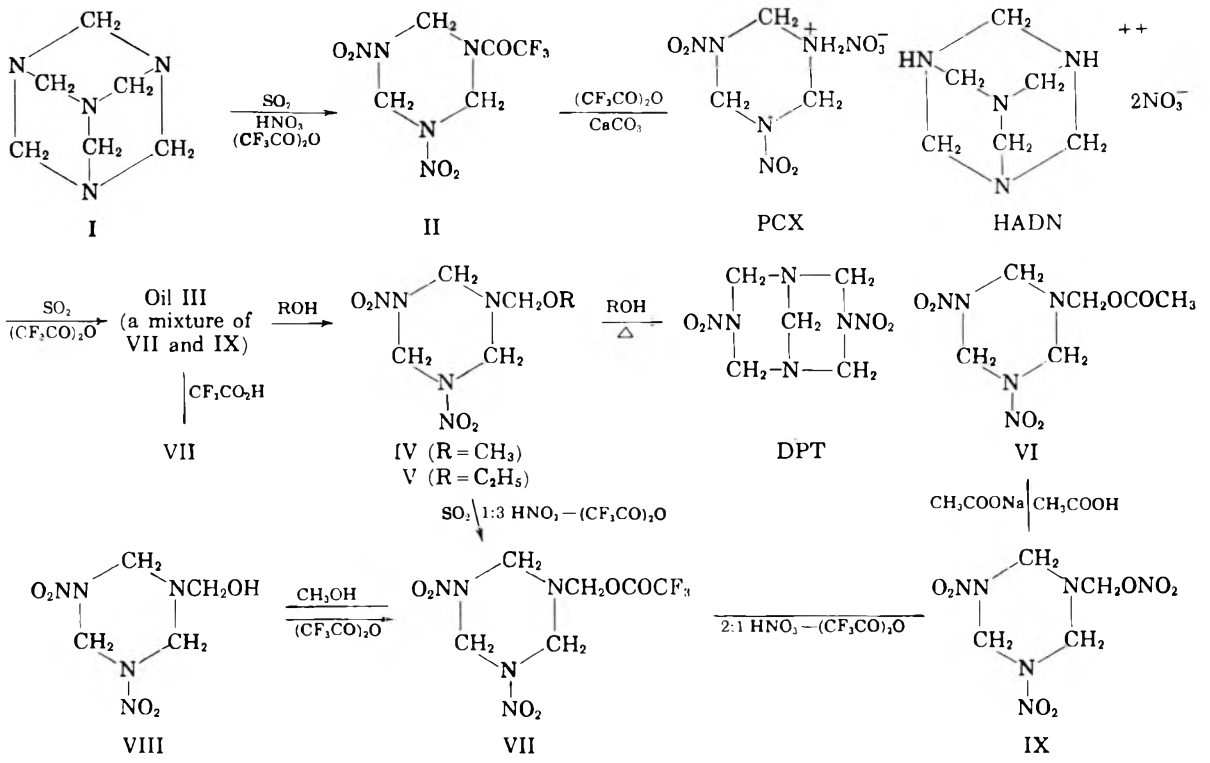
REACTIONS OF THE NITROLYSIS PRODUCTS



EXPERIMENTAL[11]

1-Trifluoroacetyl-3,5-dinitro-1,3,5-triazacyclohexane (II). A solution containing 8.00 g. (0.0572 mole) of hexamine and 43 ml. (0.311 mole) of trifluoroacetic anhydride in 150 ml. of sulfur dioxide maintained at −50° was treated with 15 ml. (0.357 mole) of colorless 99.7% nitric acid. After standing 30 min. at −50°, the sulfur dioxide was removed under reduced pressure leaving a clear colorless oil. The oil was poured into 100 ml. of ice water to produce II as a sticky solid which was dissolved in acetone and the solution slowly poured onto ice to yield 13.3 g. (85%)[12] of II as an easily filterable solid, m.p. 129–131°. Recrystallization from ethylene chloride gave 11.1 g., m.p. 130–131°; the slow addition of water to a solution of recrystallized II in 99% nitric acid produced fine needles, m.p. 131–132°.

Anal. Calcd. for $C_6H_6F_3N_5O_5$: C, 21.99; H, 2.21; N, 25.64. Found: C, 22.21; H, 2.45; N, 25.59.

An acetone solution of II was titrated with 0.1*N* standard sodium hydroxide using a Beckman Model H2 *p*H meter. The end point occurred at a *p*H of 11.1 (in 50% by volume aqueous acetone); neut. equiv. 91 (calcd. 91.0 for 3 equiv. per mole of II). The titrated solution was evaporated and then extracted with ether; evaporation of the ether left crystalline sodium trifluoroacetate, identified by a comparison of its X-ray powder pattern with that of an authentic sample. The residue of the titrated solution was acidified with *N* hydrochloric acid and shaken with 25 ml. of ether; evaporation of the ether gave crystals of methylenedinitramine, m.p. 101–102.5° (reported[13] 101°) identified by a comparison of the infrared spectrum with that of an authentic sample. When a solution of II in 99% nitric acid was boiled for 10–20 min. a fume-off occurred; ammonium nitrate was the sole product isolated from the nitric acid residue. Benzylamine and II gave a crystalline addition compound, m.p. 115° (gas evol.).

Anal. Calcd. for $C_{12}H_{15}F_3N_6O_5$: C, 37.90; H, 3.98; N, 22.10. Found: C, 37.77; H, 4.18; N, 22.05.

Recrystallization from warm 1:1 methylene chloride-ethylene chloride decomposed the compound and gave crystals of II, m.p. 125–127°.

Formation of 1-trifluoroacetyl-3,5-dinitro-1,3,5-triazacyclohexane (II) *from 3,5-dinitro-3,5-diazapiperidinium nitrate (PCX) and trifluoroacetic anhydride.* A mixture of 1.00 g. (0.00417 mole) of PCX,[14] 1.0 g. (0.010 mole) of calcium carbonate and 20 ml. of trifluoroacetic anhydride was refluxed for 20 hr. and filtered. Evaporation of the filtrate left 0.20 g. (18%) of crude II as a crystalline residue, m.p. 120–125°; recrystallization from 0.5 ml. of methanol yielded 0.13 g. of II, m.p. 130–131°, identified by a comparison of its infrared spectrum with that of II prepared from hexamine. Extraction of the calcium carbonate precipitate with 5.0 ml. of boiling acetone resulted in the isolation of 0.36 g. of crystalline 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX), m.p. 202–203° (dec.), identified by a comparison of its infrared spectrum with that of authentic material.

1-Methoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (IV). A suspension of 10.0 g. (0.0376 mole) of hexamethylenetetraammonium dinitrate in 75 ml. of sulfur dioxide maintained at −30° was treated with 40.0 g. (0.187 mole) of trifluoroacetic anhydride. After standing 3 min., the salt dissolved. The clear colorless solution was then evaporated at reduced pressure (water aspirator) to yield an oily residue which upon treatment with 30 ml. of methanol rapidly precipitated 5.05 g. (61%) of IV as fine needles, m.p. 136° (gas evol.); m.p. 137.5–138.0° (reported[9] 134°) after recrystallization from a large volume of ethyl ether. The mother liquor from crude IV was evaporated to a volume of 5.0 ml. and allowed to stand several days at 3°. There was deposited 1.03 g. (10%) of (II) m.p. 130–131°, identified by a com-

(11) All melting points are corrected. The combustion analyses were performed by Mr. Everett Bens of this laboratory.

(12) All yields were calculated upon the assumption that 1 mole of hexamine (I), or of HADN, produced 1 mole of product.

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parison of its infrared spectrum with that of the sample prepared from hexamine. The mixture melting point of II prepared from hexamine and that of II from HADN was not depressed.

When HADN was treated with a 20-molar excess of trifluoroacetic anhydride the salt slowly dissolved. After standing 2 hr. the clear solution was evaporated at reduced pressure to yield a colorless oil which did not become solid upon trituration with ether. The oil was dissolved in methanol and the solution was cooled to 0°. The 1-methoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (IV) soon crystallized; yield 63%.

A solution of 0.30 g. of IV in 99.5% nitric acid was poured onto ice to yield 0.20 g. (67%) of RDX, m.p. 201–202° (dec.).

When a solution of IV was refluxed in methanol or ethanol for 2 hr. and the solution allowed to stand 20 hr. at room temperature, there was produced a crystalline precipitate of 3,7-dinitro-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DPT) m.p. 207–208° (dec.) (reported[2] 208°) which was identified by a comparison of the infrared spectrum with authentic material.

1-Ethoxy-3,5-dinitro-1,3,5-triazacyclohexane (V) was prepared in the same manner as IV using absolute ethanol; yield 58%; m.p. 117–118° (after recrystallization from ethyl ether) (reported[3] 117°). The dropwise addition of water to an acetone solution of 1.0 g. (0.43 mole) of V precipitated 0.75 g. (81%) of crystalline DPT, m.p. 208° (dec.), which was identified by a comparison of the infrared spectrum and X-ray powder pattern with those of authentic material. Refluxing an ethanol solution of V for 3 hr. also gave DPT on cooling.

1-Trifluoroacetoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VII). To a suspension of 10.0 g. (0.376 mole) of HADN in a solution containing 150 ml. of liquid sulfur dioxide and 42.0 g. (0.20 mole) of trifluoroacetic anhydride which was maintained at −60° was added 3.16 ml. of colorless 99.7% nitric acid. The solution was warmed to −45°; after 3 min. all of the HADN had dissolved. The mixture was allowed to stand a total of 10 min. at −45° and then evaporated under reduced pressure. When the volume of liquid had been reduced by one half, crystals began to form. A small quantity of the solid was removed and identified as RDX by a comparison of its infrared spectrum with that of authentic material. Complete evaporation of the solvent left a crystalline solid, 11.7 g., m.p. 120–150° (dec.), which was dissolved in 100 ml. hot ethylene chloride to yield, on cooling, 2.14 g. (26%) of RDX, m.p. 203–204° (dec.). The mother liquor was evaporated to a volume of 20 ml. and cooled to 0° which caused the crystallization of 5.60 g. (49%) of crude VII, m.p. 132–140° (dec.); m.p. 153–154° (dec.) after five recrystallizations from ethylene dichloride containing 2% of trifluoroacetic acid. The infrared spectrum of VII exhibited absorption maxima at 5.60 (trifluoroacetate carbonyl), 6.25, 7.91 (nitramino), 8.8, 10.6, 11.96, 13.05 μ; the nitroxy absorption at 5.9–6.1 μ was absent.

Anal. Calcd. for $C_6H_8F_3N_6O_6$: C, 23.77; H, 2.66; N, 23.10. Found: C, 23.59; H, 2.71; N, 22.93.

The trifluoroacetyl derivative VII was obtained in 53% yield when the methoxy derivative IV was nitrolyzed as above.

The trifluoroacetate VII was insoluble in water but soluble in 50% aqueous acetone; the latter solution was acidic to Congo red test paper. Aqueous alkali rapidly attacked VII with the formation of the calculated amount of sodium trifluoroacetate and disodium methylenedinitramine (which upon acidification yielded methylenedinitramine in 75% yield. A solution of VII in 1:1 acetone-methanol was heated for 5 min. and then cooled to 0°. A crystalline precipitate of 1-hydroxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VIII) was obtained, m.p. 130–134° (dec.), which decomposed after standing several hours. VIII exhibited an absorption at 2.95 μ (OH) in the infrared. The m.p. was raised to 136–137° (dec.) after recrystallization from methylene chloride. Trifluoroacetic anhydride converted VIII to the trifluoroacetate VII in 30% yield.

1-Nitroxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (IX). To 15 ml. of 99.7% nitric acid at −10° was added 2.49 g. (0.0100 mole) of the trifluoroacetate (VII). The mixture was immediately poured into 100 ml. of ether, maintained at −70°, which resulted in the formation of a pasty solid that solidified upon scratching with a glass rod. Filtration gave 1.98 g. (79%) m.p. 120–130° of the crude nitrate ester IX. Four recrystallizations from methylene chloride raised the m.p. to 150–151° (violent dec.); prominent infrared absorption maxima: 5.95–6.00 (nitroxy), 6.25, 7.98–8.0 μ (nitramino). When IX was allowed to stand in cold water in which it was initially insoluble, there was formed after 3 days a gelatinous precipitate which could not be crystallized; the solution was acidic and gave a positive test for nitrate (nitron reagent).

Anal. Calcd. for $C_4H_8N_6O_7$: C, 19.05; H, 3.20; N, 33.33. Found: C, 19.30; H, 3.05; N, 33.71.

From the mother liquors of IX there was isolated a compound which was presumably the nitrate salt of IX, m.p. 145–147° (dec.). The salt was initially soluble in water to yield an acid solution; a gelatinous precipitate soon formed from which no pure substances were isolated. The solution gave a positive test for nitrate. A mixture m.p. of IX and the nitrate salt was depressed to 120–130° (dec.).

Anal. Calcd. for $C_4H_9N_7O_{10}$: C, 15.24; H, 2.88; N, 31.11. Found: C, 14.98; H, 2.80; N, 31.30.

1-Acetoxymethyl-3,5-dinitro-1,3,5-triazacyclohexane (VI). To a solution of 3.00 g. of fused sodium acetate in 10 ml. of acetic acid was added 2.52 g. (0.0100 mole) of the nitrate ester IX. After standing 16 hr., the solution had deposited large crystals. Filtration yielded 1.70 g. (68%) of the acetate VI, m.p. 149–150° (dec.); m.p. 151–152° (dec.) (reported[3] 143.7–144.7°) after two recrystallizations from methylene chloride; prominent infrared absorption maxima: 5.72 (acetate carbonyl), 6.35, 7.8–8.2 (nitramino), 8.43, 8.92, 9.84, 10.52, 10.77, 11.73, and 13.15 μ.

Anal. Calcd. for $C_6H_{11}N_5O_6$: C, 28.92; H, 4.45; N, 28.11. Found: C, 28.76; H, 4.38; N, 28.00.

RESEARCH DEPARTMENT, CHEMISTRY DIVISION
ORGANIC CHEMISTRY BRANCH
U. S. NAVAL ORDNANCE TEST STATION
CHINA LAKE, CALIF.

Communications TO THE EDITOR

A New Synthesis of 3,6-Dibromopyridazine

Sir:

A new method for the preparation of 3,6-dibromopyridazine makes it possible to employ this substance in the synthesis of 3-sulfanilamido-6-methoxypyridazine which has recently shown great promise as a drug. 3,6-Dibromopyridazine is much more reactive than the corresponding dichloropyridazine and may be used to advantage in the following reactions.

Phosphorus oxybromide (3 parts) reacted vigorously with 3,6-dioxohexahydropyridazine (1 part) at 70–80° for 2 hours; the OH groups were substituted by Br and the partially unsaturated ring became fully aromatized. The excess $POBr_3$ was removed *in vacuo* and the residue treated with water and made basic with ammonia. The product, 3,6-dibromopyridazine, separates on cooling; recrystallization from cyclohexane yields soft white needles, m.p. 118–119,° which is identical with material prepared from maleic hydrazide.[1] Yields higher than 50% may be obtained by operating in the presence of bromine (1.5 parts). In this case the reaction is violent at the beginning and requires cooling; short heating is then sufficient to complete the reaction. Phosphorus trichloride–bromine reacts similarly although with inferior yields.

An intimate mixture of 3,6-dibromopyridazine (1 part), potassium carbonate (1.1 parts) and sulfanilamide (1.4 parts) was heated in an oil bath (bath temp. 150–160°) until it began to melt and evolve carbon dioxide. Upon completion of gas evolution the mixture was extracted with hot water. Insoluble sulfanilamide was removed after cooling by filtration. Acidification of the filtrate with acetic acid yielded 3-sulfanilamido-6-bromopyridazine in yields exceeding 75%. A sample recrystallized from alcohol (yellow needles) became brown at 210° and melted at 243–244° (dec.).

Anal.: Calcd. for: $C_{10}H_9BrN_4O_2S$: Br, 24.31. Found: Br, 24.29; 24.60.

The replacement of bromine by alkoxyl may be accomplished easily by the Williamson reaction. A methanolic solution of 3-sulfanilamido-6-bromopyridazine (1 mole) was heated for 10 hours at 100–110° with 2.5 moles of sodium methoxide. The product, 3-sulfanilamido-6-methoxypyridazine, resulted in yields exceeding 85%.

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(1) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, **76**, 3225 (1954).

Trialkyl Phosphites as Reagents in a Novel Reductive *O*-Alkylation of Quinones[1]

Sir:

We have shown[2] that in the reaction of chloranil with either triphenylphosphine or triethyl phosphite, phosphorus-oxygen bonds are exclusively established, as in I and II. With triethyl phosphite, a subsequent group translocation takes place and yields an ether-phosphate V as the final product. The reaction of *p*-benzoquinone with triphenylphosphine, however, takes an entirely different course and yields a product in which a phosphorus-carbon bond has been established (VIII).[2a]

The purpose of this communication is to describe the interesting behavior of the *p*-benzoquinone-triethyl phosphite system. In this system, over 90% of diethyl(4-ethoxyphenyl)phosphate (VII) was formed, presumably *via* intermediate IV. The ether-phosphates V, VI (obtained from chloranil and trimethyl phosphite), and VII, were readily hydrolyzed to the corresponding quinol-monoalkylethers, namely, tetrachlorohydroquinone-monoethylether (IX), tetrachlorohydroquinone-monomethylether (X)[3] and hydroquinone-monoethylether (XI). Likewise, 2,5-dimethylhydroquinone-monomethylether was obtained from 2,5-dimethyl-*p*-benzoquinone and trimethyl phosphite. These reactions proceed in high yields under mild conditions. Thus, trialkyl phosphites become reagents in a facile method for the reductive *O*-alkylation of quinones and for the synthesis of monoalkylethers of hydroquinones.

The quinone and the trialkyl phosphite were allowed to react for several hours at room temperature in anhydrous benzene (or for shorter periods at reflux temperature). The products were isolated (after alkaline extraction of small amounts of acidic by-products) by distillation or recrystallization. Hydrolysis to the quinol-monoalkylethers (such as IX, X, and XI) was effected with 5% aqueous-alcoholic alkali (15–20 hours reflux).

If the trialkyl phosphite is slowly added to a solution of the quinone in benzene containing aqueous ethanol, the only products isolated are the

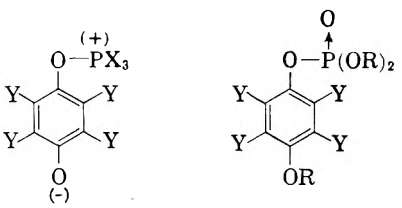
(1) The Structure of Quinone-Donor Adducts. III. Carried out under Public Health Service Grant CY-3250; we are also grateful to the Eli Lilly Research Grants Committee for initial financial support.

(2) (a) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, **78**, 5614 (1956); (b) *J. Org. Chem.*, **22**, 856 (1957).

(3) The naturally occurring antibiotic Drosophilin A has been identified as tetrachlorohydroquinone-monomethylether (X) [M. Anchel, *J. Am. Chem. Soc.*, **74**, 2943 (1952)].

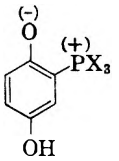
trialkyl phosphate and the unalkylated hydroquinone, in high yields. This is essentially the coupling of the two half-equations[4]: $X_3P + H_2O \rightleftarrows X_3PO + 2H^{(+)} + 2e$ and quinone $+ 2H^{(+)} + 2e \rightleftarrows$ hydroquinone, where X_3P is a tricovalent organophosphorous compound with phosphorous in the +3 oxidation state. In other words, trialkyl phosphites can be used, in the presence of water, to reduce quinones. Intermediates such as II, III, and IV (*cf.* isolation[2a] of I) would explain these processes. Evidently, the possibility of an irreversible group translocation (to V, VI, and VII) in the phosphorus compound, as well as the structural features of the quinone itself (oxidation potential, steric effects) can determine the over-all course of the reactions.[2]

The ether-phosphates, V,[2b] VI, and VII, exhibited the typical nonbonded phosphate P → O band at 7.85 μ and the expected ultraviolet spectra. VI had m.p. 94–95° (cyclohexane); found: C, 29.4; H, 2.7. VII had b.p. 139–140° (0.25 mm.), $n_D^{25°}$ 1.4829; found: C, 52.2; H, 6.0. The quinol-monoalkylethers (IX, m.p. 84–85°; X, m.p. 114–115°; XI, m.p. 66–67°) were characterized as such and as the corresponding well-known dialkyl ethers.[3,5]



I, Y = Cl, X = C_6H_5
II, Y = Cl, X = OC_2H_5
III, Y = Cl, X = OCH_3
IV, Y = H, X = OC_2H_5

V, Y = Cl, R = C_2H_5
VI, Y = Cl, R = CH_3
VII, Y = H, R = C_2H_5



VIII; X = C_6H_5

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(4) Standard potentials are known for half-equations involving certain phosphorus compounds with phosphorus in +1 and +3 oxidation states:

$H_3PO_2 + H_2O \rightleftarrows H_3PO_3 + 2H^{(+)} + 2e$, $E° = 0.50$ volt
$H_3PO_3 + H_2O \rightleftarrows H_3PO_4 + 2H^{(+)} + 2e$, $E° = 0.276$ volt

The expressions given for the hypophosphorus and phosphorus acids involve four atoms around the phosphorus. For a recent summary see: H. H. Sisler in M. C. Sneed and R. C. Brasted, *Comprehensive Inorganic Chemistry*, D. van Nostrand Co., Inc., N. Y., 1956; Vol. V, pp. 118, 126.

(5) (a) *Cf.* Beilstein's *Handbuch der organishen Chemie*, 4th Ed., **6**, 843 (I 416), (II 840), J. Springer, Berlin 1918; (b) A. Binz and C. Rath, *Ber.*, **58**, 309 (1925); (c) C. Graebe, *Ann.*, **146**, 20 (1868); (d) E. Banberger and J. Frei, *Ber.*, **40**, 1932 (1907), p. 1944.

Radiolysis of 1-Hexene[1]

Sir:

In order to investigate the mechanism of radiation-induced polymerization of simple olefins, we have irradiated 1-hexene with high energy electrons and gamma rays[2] at room temperature with exclusion of oxygen. Total doses varied from 12 to 40 × 10^{20} ev/g at rates between 6 × 10^{19} (gamma) and 6 × 10^{22} (electron) ev/g per hour. Gaseous products were analyzed mass spectrometrically and found to consist of hydrogen (G_{H_2} 0.8 ± 0.1) plus light hydrocarbons ($G_{L.H.}$ 0.12 ± 0.03). The recovered 1-hexene, analyzed by gas chromatography, was found to contain *n*-hexane ($G_{n\text{-}C_6H_{14}}$ 0.11 ± 0.02) and smaller amounts of other hexenes. The heavier materials consisted entirely of polymeric compounds, with $G<0.01$ for the total of compounds with carbon numbers not multiples of six. Yields determined by fractional distillation, with molecular weight confirmation by mass spectrometry, were G_{dimer} 0.98 ± 0.05, G_{trimer} 0.76 ± 0.05, $G_{tetramer}$ 0.22 ± 0.1 and $G_{pentamer}$ 0.35 ± 0.1 with overall $-G_{1\text{-hexene}}$ 10.5 ± 0.5. Unsaturation appeared to increase with molecular weight; the pentamer had as much diolefin as monoolefin.

The dimeric fraction by mass spectrometric analysis appeared to be approximately 90% monoolefin, with some saturated hydrocarbon and some diolefin. This is in contrast with the diolefinic dimer obtained from 1-octene by Kharasch, Schwartz, and Nudenberg,[3] who used free radicals from isopropyl bromide photolysis, and demonstrates that, in the present case, dimerization does not occur predominantly by combination of allyl-type radicals. The infrared spectrum of the dimer showed 27% terminal, 57% trans non-terminal and 3% vinylidene-type double bonds. Information on the location of the non-terminal double bonds was obtained by gas chromatographic analysis of methyl esters of the carboxylic acids obtained by oxidation of ozonolysis products. Methyl acetate, propionate, *n*-butyrate, *n*-valerate, hexanoate, 2-methylhexanoate, heptanoate, octanoate, nonanoate, and decanoate, plus the methyl esters of a branched C_{10} acid and a branched C_8 acid (not 2-methylheptanoate) were the only monocarboxylic esters found. Traces of dicarboxylic acids (from diolefins) and ketones (from vinylidene double bonds) were also products of ozonolysis. Identification of these compounds is in progress.

(1) This research was supported in part by the United States Air Force under Contract No. AF 33(616)-3875 monitored by Aeronautical Research Laboratory (WCRRC).

(2) The source of electrons was the 3 Mev. Van de Graaff accelerator at the Shell Development Company, Emeryville, Calif. The source of gamma rays was the High Level Gamma Irradiation Facility of the Argonne National Laboratory, Lemont, Ill.

(3) M. S. Kharasch, D. Schwartz, and W. Nudenberg, *J. Org. Chem.*, 18, 337 (1953).

Examination by mass spectrometry of the dimeric material that resisted ozonolysis disclosed a ratio of ion intensity at m/q = 170 to that at m/q = 168 of 0.60. This ratio is very much lower than the corresponding ratio for any of the octanes and indicates a substantial yield of cyclane relative to paraffin (mass spectra of all octanes, but no similar set of isomeric hydrocarbons of higher molecular weight, are available for comparison). Cyclization has not been reported heretofore in radiolysis of simple olefins or paraffins, but has been reported in thermal reactions of olefins.[4]

The very low yield of compounds other than polymers indicates that radical production by carbon-carbon scission of 1-hexene is not important in chain initiation. Moreover, the extent of unsaturation in the dimer, the location of its double bond, and the nature of its skeleton suggest that the initiating radical is formed by hydrogen atom transfer to the double bond. We suggest an ion-molecule reaction of the sort[5]

$$C_nH_{2n}^+ + C_nH_{2n} \longrightarrow C_nH_{2n+1}^+ + \cdot C_nH_{2n-1}$$

as an important initiating event.

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(4) V. Mark and H. Pines, *J. Am. Chem. Soc.*, 78, 5946 (1956).

(5) D. O. Schissler and D. P. Stevenson, *J. Chem. Phys.*, 24, 926 (1956).

(6) Deceased.

Specificity of Phenyllithium Addition Reactions

Sir:

It is generally well known that the addition of lithium aryls to aromatic heterocyclic compounds containing an azomethine linkage proceeds to give substitution adjacent to the nitrogen atom in this group.[1] In connection with our work on the synthesis and characterization of pyridine analogs of ter- and quaterphenyl for use as scintillation solutes[2] we have observed an unexpected and previously unrecognized specificity of addition in this reaction. We wish to report upon a portion of our activities in this area and in particular upon the reaction of 3-phenylpyridine with phenyllithium, the singular nature of the product isolated and the unequivocal proof of its identity as 2,5-diphenylpyridine. The selectivity of this addition is of additional interest because it makes pyridine analogs of terphenyl available for the first time by a direct route.

The addition of phenyllithium to 3-phenylpyridine was run in sodium-dried ether under oxygen-free nitrogen and allowed to proceed for 24 hours at room temperature. The crude product isolated from the water-washed ether solution was put into benzene, eluted through a column of acidic alumina and found to contain only one component, m.p. 174–175°, λ_{max}^{KBr} 1580, 1470, 1460, 1370, 1072, 1017, 1003, 905, 835, 752, 735, 687 cm.$^{-1}$ *Anal.* Calcd. for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.18; H, 5.79; N, 6.10.

On the basis of the above analytical and spectral data, in particular the C-H out of plane deformation frequencies, the product was tentatively assigned the 2,5-diphenylpyridine structure rather than that of the alternate and slightly less probable 2,3-diphenylpyridine. The validity of this assignment was confirmed by independent synthesis of the diphenylpyridine *via* alkaline permanganate oxidation of 3-phenylbenzo[*f*]quinoline to 2-phenyl-5-(*o*-carboxyphenyl)-6-carboxypyridine, m.p. 196°, reported 198°,[3] λ_{max}^{KBr} 1765, 1670, 1600, 1475, 1450, 1330, 1300, 1258, 930, 852, 848, 775, 758, 725, 705, 687 cm.$^{-1}$ This dicarboxylic derivative of 2,5-diphenylpyridine lost carbon dioxide upon melting to form 2-phenyl-5-(*o*-carboxyphenyl) pyridine, m.p. 195° (mixed m.p. 151°), λ_{max}^{KBr} 1670, 1600, 1575, 1470, 1365, 1270, 1250, 935, 838, 808, 778, 752, 733, 697, 685. *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 78.53, H, 4.76. Found: C, 78.40; H, 4.81. The decarboxylation of this monocarboxylic acid was accomplished by pyrolysis of the compound with electrolytic copper in an atmosphere of oxygen-free nitrogen. The product 2,5-diphenylpyridine, m.p. 174°, was obtained by benzene extraction of the reaction mass. A mixed melting point of this substance with that obtained from the addition of phenyl lithium to 3-phenylpyridine was 174°.

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(1) E. A. Braude, in Progress in Organic Chemistry, Vol. 3, Academic Press, New York, 1955.

(2) This research was performed under contract No. AT-(40-1)-2162 between the Atomic Energy Commission and the University of Louisville. We gratefully acknowledge this support.

(3) R. Cuisa and A. Buogo, *Atti. accad. naz. Lincei, Rend. Classe sci. fis. mat. e nat.*, (5) 23, II, 265.