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Photochemical Reactions of Diketones. The 1,4-Addition of Ethers to 9,10-Phenanthrenequinone

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A new photochemical reaction of phenanthrenequinone (PQ), the reversible 1,4-addition of ethers, is described. In the resulting 1:1 adducts the original ether function is converted to an acetal group. Attempts to apply the photoreaction for cleavage of ethers by hydrolysis of the adducts have met with limited success; 3β-methoxycholestane was converted to a mixture of cholestanone plus cholestanol in 50% yield while 3β-methoxycholestene was not cleaved.

Since the first report of a light-catalyzed reaction of 9,10-phenanthrenequinone (PQ) in 1886,[1] many investigators, notably Schönberg and his collaborators, have described studies of four photochemical addition reactions of PQ and related *o*-quinones.[2a,b] These are the addition of sulfur dioxide to form a cyclic sulfate,[3] of olefins to form dioxenes,[4] of aldehydes to give monoesters of 9,10-dihydroxyphenanthrene,[5] and of substituted methylbenzenes to form 9,10-dihydro-9-keto-10-hydroxy-10(X-benzyl)phenanthrenes.[6] The extent of these investigations may be illustrated by the fact that olefin addition reactions involving at least thirteen *o*-quinones and forty-five olefins have been documented.[4] This report describes the photochemical addition of ethers to PQ,[8] representing the fifth example of what promises to be a very general class of reactions.

Irradiation of a suspension of PQ in dioxane resulted in isolation, after removal of excess dioxane, of a crystalline 1:1 adduct (Ia) in 90% yield. The conversion of the ether to an acetal was confirmed by facile hydrolysis in the present of dilute mineral acid to give PQ in high yield.[9] Further evidence on this point was provided by the results obtained with 3β-methoxycholestane (II) (visible-infrared).

The ultraviolet spectrum of Ia was rich in detail (six maxima) and corresponded closely to that of the adduct (Id) of benzaldehyde and PQ.[10] This spectrum underwent marked change in alkaline solution as expected of a phenol. Further confirmation that 1,4-addition across the dione moiety had occurred was provided by infrared and n.m.r. spectra. The infrared spectrum exhibited a strong hydroxyl band at 3.0 μ and no significant absorption in the 5.5–6.05-μ region. In addition to the expected complex absorption at low field characteristic of phenanthrenes and the phenolic hydroxyl group in the n.m.r., a quartet centered at 4.96 τ (O–CH–O) and a complex group of lines at 5.7–6.3 τ (O–CH–OH–O) were observed. The ratio of the integrated areas of these three groups of lines was 9:1:6 in agreement with the structure assigned.

The photochemical reversibility of the addition was demonstrated by irradiation of Ia in refluxing benzene.[11] Analysis by chromatography on Florisil after irradiation for seventy-two hours indicated 69% Ia, 22% PQ, and 9% phenanthrenequinhydrone.[12] This appears to approximate the photostationary state since a mixture of essentially the same composition was obtained from irradiation of an equimolar solution of PQ and dioxane under similar conditions. The amount of quinhydrone formed increased slowly on more prolonged irradiation.

Adducts similar to Ia were also obtained from tetrahydrofuran (97% yield) and anisole (86% yield) As expected, the tetrahydrofuran adduct (Ib) resulted from attack at the α- rather than the β-position of tetrahydrofuran. This was clearly established by the n.m.r. spec-

(1) H. Klinger, *Ber.*, **19**, 1862 (1886).

(2) (a) An excellent general summary is to be found in "Präparative Organische Photochemie," A. Schönberg, Springer-Verlag, Berlin, 1958; (b) *cf.* also "Ultraviolet Photochemistry," P. de Mayo, in "Advances in Organic Chemistry," Vol. II, Interscience Publishers, New York, N. Y., 1960, pp. 367–425.

(3) G. O. Schenck and G. A. Schmidt-Thomee, *Ann.*, **584**, 199 (1953).

(4) Ref. 2a, p. 89 ff.

(5) Ref. 2a, p. 101.

(6) The earlier assignment[7a,b] of the 9-hydroxy-10(X-benzyloxy)phenanthrene structure to these adducts has been shown to be incorrect; M. B. Rubin and P. Zwitkowits, to be published.

(7) (a) A. Benrath and A. Von Meyer, *J. prakt. Chem.*, **89**, 258 (1914); (b) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 3405 (1953).

(8) Klinger[1] reported the formation of a crystalline product on exposure of a diethyl ether solution of PQ to sunlight. This product was converted to the diacetate of 9,10-dihydroxyphenanthrene by hot acetic acid, but was not otherwise characterized.

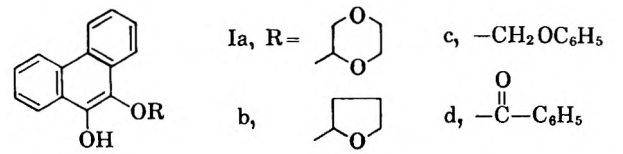
(9) The anticipated hydrolysis product, 9,10-dihydroxyphenanthrene, undergoes rapid air oxidation to PQ.

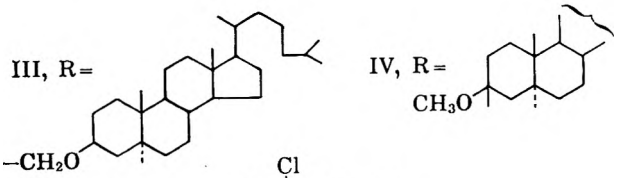
(10) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953).

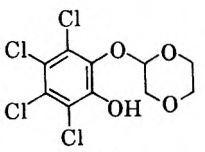
(11) In the absence of light Ia was recovered quantitatively after 72 hr. reflux in benzene solution.

(12) Phenanthrenequinhydrone presumably is formed by dimerization of intermediate semiquinone radicals.[7b]

trum which showed a poorly resolved triplet centered at 4.96 τ (O–CH–O), and multiplets centered at 6.34 τ (C–CH_2–O) and 8.49 τ (C–CH_2–C) with areas in the ratio of 1:2:4 in addition to the expected complex lower field absorption. Both Ib and the anisole adduct (Ic) had ultraviolet spectra essentially identical with that of Ia.







VI

An intriguing aspect of this new addition reaction is the conversion of the normally unreactive ether function to the readily hydrolyzable acetal or ketal group, suggesting the possibility of a convenient, two-step procedure for cleavage of ethers. As a model compound for investigation of this attractive possibility we selected 3β-methoxycholestane (II). A further point of interest in this choice lay in the fact that two adducts, III and IV, are possible, resulting from reaction either at the primary or tertiary carbon atoms adjacent to the ether oxygen. Since acid hydrolysis of III would lead to cholestanol and of IV to cholestanone, this experiment also was expected to provide information on the behavior of unsymmetrical ethers.

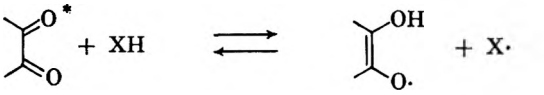
In the event, irradiation of a benzene solution of PQ and II did lead to formation of adduct(s) as shown by spectroscopic examination of fractions separated by chromatography. The best fractions obtained, however, were contaminated with II and contained about 50% of adduct (based on ultraviolet spectra). Since no crystalline material could be obtained, the crude irradiation product was hydrolyzed directly in aqueous acidic dioxane. Chromatographic separation of the resulting mixture afforded recovered PQ, II (24%), cholestanol (15%), and cholestanone (4.2%). It is noteworthy that the 3.6:1 ratio of cholestanol to cholestanone which reflects a corresponding ratio of adducts III and IV is close to the 3:1 ratio would be predicted on purely statistical grounds.

Results previously presented represent the best yield of ether cleavage products obtained by varying time, temperature, and concentration of reactants. In an effort to improve these results we investigated the photochemical reaction of PQ and II in benzene–acetic acid and benzene–acetic acid–water solutions. It was anticipated that the presence of acetic acid would lead to hydrolysis of the adducts to cholestanol and cholestanone (*cf.* reference 9) with concomitant shifting of the photochemical equilibrium and thus provide in higher yield a one-step ether cleavage. This expectation was realized to a limited extent. Irradiation of PQ and II for seventy-one hours in benzene containing 15% of acetic acid afforded recovered II (30%), cholestanol (15%), and cholestanone (35%), representing a two and one-half fold improvement in total cleavage product. Similar results were obtained in benzene–acetic acid–water solution. The change in cholestanol cholestanone ratio from 3.6:1 to 0.43:1 probably does not reflect a change in the ratio of adducts III and IV, since it was demonstrated that cholestanol undergoes oxidation under the conditions of the photochemical reaction.

A further limitation on any practical value of the ether cleavage reaction was revealed by irradiation of PQ and 3β-methoxy-5-cholestene (V) in benzene or benzene–acetic acid solution. In addition to considerable recovered ether there could be isolated by chromatography noncrystalline fractions with complex ultraviolet spectra. These apparently contained adducts formed by addition of the olefinic bond of V to PQ since they exhibited characteristic methoxyl absorption at 9.1 μ and afforded unchanged spectra after attempted acid-catalyzed hydrolysis.

The photochemical behavior of a number of other quinones was also investigated in dioxane solution (or suspension). Tetrachloro-*o*-benzoquinone gave a 1:1 adduct (VI) in 20% yield.[13] Benzil and acenaphthenequinone underwent photochemical change as shown by infrared analysis of crude reaction product but no pure substances have been isolated from these reactions. *p*-Benzoquinone, 1,4-naphthoquinone, and 9,10-anthraquinone were recovered substantially unchanged after prolonged irradiation.

The mechanism of photochemical addition and dehydrogenation reactions of PQ is generally accepted[3,7b,10,14a,b] as being of a free radical nature. Moore and Waters have proposed that the benzaldehyde and *p*-xylene addition reactions involve abstraction of a hydrogen atom by an excited PQ molecule to give a semiquinone radical and a benzoyl or *p*-methylbenzyl radical. For the reactions described in this work, a se-



quence involving initial abstraction of hydrogen atom from the carbon adjacent to oxygen seems eminently reasonable. Both radical recombination and radical chain mechanisms have been suggested for the subsequent steps in the earlier additions although no experimental evidence is available. We currently are investigating this question particularly with regard to providing an explanation for the occurrence of 1,2-addition with substituted toluenes and of 1,4-addition with aldehydes and ethers.

Experimental[15]

Photoirradiations.—Except where noted otherwise, the photoirradiations were performed in an atmosphere of nitrogen using a

(13) The low yield is presumably due to competing photoreactions of tetrachloro-*o*-quinone itself since irradiation of the quinone alone in benzene solution resulted in pronounced alteration of its ultraviolet spectrum.

(14) (a) H. L. J. Bäckström, *Z. Physik. Chem.*, **25**, 99 (1934); *Naturwissenschaften*, **22**, 170 (1934). (b) G. O. Schenck, *Z. Elektrochemie*, **64**, 997 (1960).

General Electric 1000-w., water-cooled, high pressure mercury lamp (AH-6) with Corning 7-51 glass filter to eliminate radiation below 3000 Å.

Photoadduct of Phenanthrenequinone and Dioxane (Ia).—A suspension of 1.00 g. of quinone in 20 ml. of dioxane[16] was irradiated for 20 hr. The solid had completely dissolved and the characteristic orange color of the quinone faded to a pale yellow. The solution fluoresced strongly. Removal of excess dioxane under reduced pressure left 1.37 g. of tan solid which was washed through a column of 50 g. of Florisil with 500 ml. of benzene to give 1.21 g. (90%) of nearly colorless crystals of Ia, m.p. 105–106°. The analytical sample was obtained by recrystallization from isopropyl ether, m.p. 105–105.5°; λ_{max} (CH_3OH) 249 mμ (sh) (44,000), 255 (51,000), 273 (14,000), 295 (9000), 307 (9000), 327 (sh) (800), 343 (1200), 360 (1300); (0.1 *M* NaOH, 40% dioxane) 256 mμ (37,000), 335 (6000), 385 (sh) (2000); (KBr) 3.0 μ.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 72.96; H, 5.44. Found: C 72.93; H, 5.59.

Ia gave a negative ferric chloride test in alcohol solution.

Refluxing 331 mg. of Ia in benzene under nitrogen for 72 hr. in the absence of light gave 327 mg. of recovered starting material, m.p. 104.5–106°.

Extraction of a chloroform solution of Ia with five portions of 5% aqueous sodium hydroxide afforded after acidification, etc., 30% of Ia. The remaining 70% was recovered by evaporation of the neutral fraction.

Hydrolysis of Ia.—A solution of 29 mg. of Ia in 2 ml. of methanol containing 1 drop of concentrated hydrochloric acid was kept at 50° for 10 min. Sodium bicarbonate and water were added and the mixture concentrated under reduced pressure to remove methanol. The aqueous residue was extracted with ethyl acetate and these extracts, after drying and concentration under reduced pressure, yielded 26 mg. of orange solid. Recrystallization from ethyl acetate–petroleum ether gave 16 mg. (80%) of orange needles, m.p. 208–210°, identical with PQ.

Photoadduct of PQ and Benzaldehyde (Id).—This compound, m.p. 186–187°, was prepared by the procedure of Moore and Waters[10,17] in order to determine the ultraviolet spectrum for comparison purposes; λ_{max} (dioxane) 249 mμ (sh) (51,000), 254 (56,000), 274 (18,000), 295 (10,000), 306 (9000), 325 (1500), 341 (1800), 359 (1900). The spectrum underwent rapid change in alkaline solution.

Photochemical Reversibility of PQ–Dioxane Addition.[18]—Two experiments were performed in Pyrex flasks fitted with reflux condensers. One flask (forward reaction) contained 0.50 ml. (0.0117 mole) of dioxane and 1.207 g. (0.0117 mole) of PQ in 75 ml. of benzene and the second (reverse reaction) contained 1.732 g. (0.0117 mole) of Ia in 75 ml. of benzene, both in nitrogen atmospheres. Each flask was irradiated with a General Electric S-4 mercury vapor lamp placed about 2 in. below the bottom of the flask so that reflux was maintained by the heat of the lamp. Aliquots of each were withdrawn after 24 and 72 hr. and analyzed by chromatography on Florisil. Elution with 50% benzene–petroleum ether, 90% benzene–petroleum ether, and pure benzene gave the adduct Ia; ethyl acetate eluted PQ; and methanol eluted phenanthrenequinhydrone (characterized by color reactions and by oxidation to PQ). The composition of the mixtures was as follows: after 24 hr., forward reaction, 63% Ia, 27% PQ, 7% quinhydrone; reverse reaction, 76% Ia, 15% PQ, 8% quinhydrone; after 72 hr., forward reaction, 72% Ia, 21% PQ, 6% quinhydrone; reverse reaction, 69% Ia, 22% PQ, 9% quinhydrone.

Photoadduct of PQ and Tetrahydrofuran (Ib).—The experiment was performed as described for the dioxane reaction. From 1.00 g. of quinone and 20 ml. of tetrahydrofuran (distilled over lithium aluminum hydride) there was obtained after chromatography on Florisil 1.10 g. (82%, 97% based on recovered starting material) of nearly colorless adduct (Ib), m.p. 94–96°, and 0.16 g. of PQ (eluted with ethyl acetate). The analytical sample of Ib was obtained by crystallization from isopropyl ether, m.p. 96.5–97.5°; λ_{max} (CH_3OH) 249 mμ (sh) (48,000), 256 (54,000), 272 (15,000), 295 (9000), 308 (9000), 326 (sh) (900), 345 (1300), 362 (1400); (KBr) 3.0 μ.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.21; H, 5.98.

Photoadduct of PQ and Anisole (Ic).—Irradiation of a suspension of 1.00 g. of quinone in 20 ml. of distilled anisole was continued for 130 hr., when all the quinone had dissolved. Removal of excess anisole under reduced pressure left 1.50 g. of red-orange solid which was washed through a column of 50 g. of Florisil with 500 ml. of benzene to give 1.30 g. (86%) of nearly colorless crystals, m.p. 93.5–96.5°. The analytical sample was obtained by recrystallization from isopropyl ether, m.p. 115–115.5°; λ_{max} (CH_3OH) 249 mμ (sh) (45,000), 254 (51,000), 270 (sh) (14,000), 295 (9000), 307 (9000), 328 (sh) (800), 343 (1200), 361 (1200); (KBr) 3.0 μ. N.m.r., singlet at 4.25 τ (O–CH_2–O) in addition to aromatic and phenolic protons.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.72; H, 5.09. Found: C, 79.43; H, 5.40.

Photoaddition of PQ and 3β-Methoxycholestane (II) in Benzene.—A solution of 0.50 g. of quinone and 1.00 g. of II[19] in 50 ml. of dry benzene was irradiated for 92 hr. A 5-ml. aliquot was chromatographed on 10 g. of Florisil. Elution with 350 ml. of benzene and 100 ml. of 1% ethyl acetate–benzene afforded 113 mg. of nearly colorless oil which could not be induced to crystallize; λ_{max} (dioxane) 251 mμ (sh) (22,800), 257 (25,500), 271 (sh) (9000), 298 (4600), 310 (4600), 334 (1100), 364 (700); (CH_2Cl_2) 3.0 μ, 6.1, 6.2. Elution with 100 ml. of ethyl acetate gave 33 mg. of PQ and with 100 ml. of methanol gave 22 mg. of quinhydrone.

Hydrolysis of Adduct(s) of PQ and 3β-Methoxycholestane (II).—The crude reaction mixture from irradiation of 0.50 g. of PQ and 0.50 g. of II in 50 ml. of benzene for 72 hr. was dissolved (after removal of benzene) in 25 ml. of dioxane, and 5 ml. of water containing 0.5 ml. of concentrated sulfuric acid was added. Clear solution was heated on the steam bath for 1.5 hr., cooled, and excess solid sodium carbonate added. The mixture was concentrated to *ca.* 5 ml. under reduced pressure and the residue taken up in ethyl acetate. The layers were separated, the organic layer washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and concentrated to dryness on the steam bath under reduced pressure. The benzene-soluble portion (545 mg.) of the yellow residue was chromatographed on 20 g. of Florisil collecting 200-ml. fractions. Elution with 20% benzene in petroleum ether gave 120 mg. (24%) of crystalline II.

Further elution with 90% benzene in petroleum ether and pure benzene gave 135 mg. of light orange solid. This was rechromatographed on 4 g. of alumina collecting 40-ml. fractions. With 20% benzene in petroleum ether there was obtained 20 mg. (4.2%) of cholestanone, white crystals, m.p. 114–121°, identical by infrared spectral comparison with an authentic sample.[20] One recrystallization from methanol gave 11 mg., m.p. 127–129° (reported[20] m.p. 129–129.5°).

Elution with 50% benzene in petroleum ether and pure benzene gave 72 mg. (15%) of cholestanol, m.p. 139–142° (reported[21] m.p. 140–141°), identical by infrared spectra with an authentic sample.

Irradiation of PQ and II in Benzene–Acetic Acid.—A suspension of 1.00 g. of PQ and 0.91 g. of II in 50 ml. of 15% acetic acid in benzene (v./v.) was irradiated for 71 hr. The quinone dissolved slowly and the solution became dark, wine red in color. The solvents were removed under reduced pressure on the steam bath and the dark residue was treated with three 5-ml. portions of hot benzene.

Chromatographic separation of the benzene-soluble portion on Florisil and alumina as described earlier afforded 274 mg. (30%) of II, 303 mg. (35%) of cholestanone, and 130 mg. (15%) of cholestanol.

Photooxidation of Cholestanol with PQ.—A suspension of 1.0 g. of PQ and 1.0 g. of cholestanol in 50 ml. of 15% acetic acid in benzene was irradiated for 24 hr. The clear, wine red solution was concentrated under reduced pressure and the residue treated

(15) Melting points are corrected. N.m.r. spectra were determined in deuteriochloroform at 60 Mc. using tetramethylsilane as internal standard. Microanalyses were performed by Weiler and Strauss and by Galbraith Laboratories. Petroleum ether was a fraction of b.p. 66–75°.

(16) Purified over alumina; W. Dosler and C. D. Bauer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 52 (1946).

(17) The authors revised the earlier proposal of a cyclic pseudo-ester structure on the basis of a strong band at 5.82 μ in Nujol. We observed this band in potassium bromide and in methylene chloride solution.

(18) Experiments performed by J. Yevich.

(19) L. Dunn, I. M. Heilbron, R. J. Pnipers, K. M. Samant, and F. S. Spring, *J. Chem. Soc.*, 1576 (1934); *cf.* also J. C. Babcock and L. F. Fieser, *J. Am. Chem. Soc.*, **74**, 5472 (1952). In order to eliminate the possibility of contamination by cholestanol the recrystallized ether was washed through alumina with petroleum ether.

(20) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 139.

(21) W. F. Bruce and J. O. Ralls, *ibid.*, p. 191.

with three portions of benzene. The benzene-soluble material was washed through 50 g. of Florisil with 1.5 l. of benzene to give 0.98 g. of faintly yellow, oily solid. This was chromatographed on 30 g. of alumina collecting 300-ml. fractions. Elution with petroleum ether and two fractions of 20% benzene in petroleum ether gave 0.275 g. (28%) of cholestanone, m.p. 125.5–128°, identical with an authentic sample.[20] Elution with 50% benzene in petroleum ether and pure benzene gave 0.497 g. (50%) of recovered cholestanol, m.p. 141.5–142.5°.

Photoirradiation of PQ and 3β-Methoxy-5-cholestene (V).—A suspension of 2 g. of PQ and 0.91 g. of V[19] in 70 ml. of benzene was irradiated for 94 hr. The dark, wine red solution was concentrated on the steam bath to 10 ml., the 0.44-g. sample of unchanged PQ was filtered, and the filtrate washed through 50 g. of Florisil to give 1.19 g. of faintly yellow oil. This was dissolved in petroleum ether and chromatographed on 50 g. of Florisil, collecting 250-ml. fractions. Elution with four fractions of 10% benzene–petroleum ether, two of 20%, and one of 30% afforded 0.29 g. of nearly colorless oil, identical by infrared spectra with V.

Further elution with one fraction each of 30%, 50%, and 90% benzene–petroleum ether and one of pure benzene yielded 0.66 g. of faintly yellow oil; λ_{max} (dioxane) 251 mμ (sh) (39,000), 256 (47,500), 272 (sh) (18,800), 305 (7500), 318 (9100), 335 (6000), 373 (1500), 395 (770) (extinctions based on molecular weight of a 1:1 adduct); (CH_2Cl_2) 6.1 μ, 6.2, 9.1, no absorption at 2.5–3.1. Treatment of 287 mg. of the oil with aqueous acidic dioxane as described for the adducts of PQ and II afforded 262 mg. of crude product with essentially unchanged ultraviolet and infrared spectra. Repeated chromatography on Florisil failed to give any crystalline products.

Photoadduct (VI) of Tetrachloro-o-quinone and Dioxane.—A solution of 3 g. of quinone in 90 ml. of dioxane was irradiated for 14 hr. when the deep red color had faded to light orange. The excess dioxane was removed under reduced pressure without heating to give a tan solid which after one recrystallization from ethyl acetate gave 946 mg. (20%) of V as white needles, m.p. 159–161°. The analytical sample was obtained by crystallization from ethyl acetate, m.p. 167–168°; λ_{max} (dioxane) 291 mμ (sh) (2000), 298 (2400); (KBr) 3.05 μ, no strong maxima at 5.5–6.05.

Anal. Calcd. for $C_{10}H_8O_4Cl_4$: C, 35.96; H, 2.41; Cl, 42.46. Found: C, 35.78; H, 2.23; Cl, 42.28.

Attempted isolation of additional product yielded only solids with broad melting ranges.

Acknowledgment.—The author wishes to acknowledge the generous cooperation of Professor G. J. Mains and Dr. R. Doepker in the photoirradiation experiments and of Professor R. J. Kurland in the determination and interpretation of n.m.r. spectra.

Allene Chemistry. I. Free Radical Addition of Thiols to Allene

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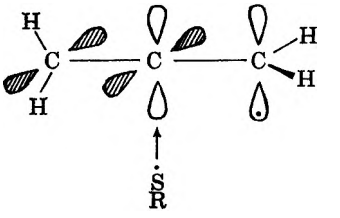
Methanethiol, benzenethiol, and thiolacetic acid added readily to allene under homolytic conditions. The initial attack of the corresponding thiyl radicals occurred quite selectively at the terminal positions of allene, to yield 1:1 and 2:1 adducts. The methanethiol–allene reaction has been studied in greater detail with the help of capillary gas chromatography, n.m.r., and infrared analysis. Allyl methyl sulfide, 1,3-bis(methylthio)propane, and 1,2-bis(methylthio)propane were the reaction products. The yield of the 1:1 adduct (allyl methyl sulfide) varied between 40 and 75 mole % when the reaction temperature was changed from −75 to +17°. 1,3-Bis(methylthio)propane was derived from allyl methyl sulfide, whereas 1,2-bis(methylthio)propane was mainly (>93%) derived from 2-methylthiopropene, the product of a center attack to allene. The selectivity of the initial attack of the thiyl radicals at the terminal positions of allene increased with decreasing reaction temperature. It was found to be 88% at 17° and 95% at −75°. In the addition of thiolacetic acid to allene terminal attack by the thiyl radical occurs with about 91% selectivity, whereas the benzenethiol–allene reaction is less selective. At 17° only about 80% terminal attack was observed.

Free radical reactions of diolefins containing isolated[3] and conjugated[4–6] double bonds have been examined previously in this laboratory. This paper reports about the consequent extension of these studies to the cumulative double bond system of allene.

The over-all course of free radical addition reactions to allene is obviously dependent on the point of initial attack of the radical species which starts the chain. In the case of unsymmetrically substituted mono-[7a] and diolefins,[5] it has been generally demonstrated that the reaction path involving the more stable of the possible radical intermediates is preferred. On this basis it might at first glance seem that initial attack at the center carbon of allene should be favored, since one can write a resonance-stabilized allylic radical intermediate (I), whereas terminal attack leads to a vinylic radical (II). However, in view of the special geometry of the allene molecule, such a representation of the initial attack is certainly oversimplified. The incipient radical from a center attack resembles a primary radical rather than an allylic one, since the orbital of the odd electron does not overlap with the π-orbitals of the remaining double bond.



This complication, though it might cause an increase of the activation energy for the center attack and possibly favor terminal addition, has never been discussed in previous publications on this subject.

The question of terminal and center attack in free radical additions to allene has been answered differently by previous workers. Szwarc and co-workers[8] have

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(2) Analytical Research Division, Esso Research and Engineering Co., P. O. Box 121, Linden, N. J.

(3) A. A. Oswald and F. Noel, *J. Org. Chem.*, **26**, 3948 (1961).

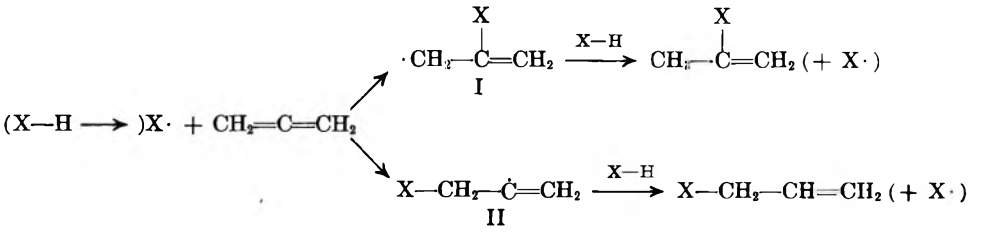
(4) A. A. Oswald, B. E. Hudson, Jr., G. Rodgers, and F. Noel, *ibid.*, **27**, 2439 (1962).

(5) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, Jr., *J. Am. Chem. Soc.*, **84**, 3897 (1962).

(6) A. A. Oswald, K. Griesbaum, and B. E. Hudson, Jr., *J. Org. Chem.*, **28**, 1262 (1963).

(7) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957: (a) p. 314; (b) pp. 321–323.

(8) A. P. Stefani, L. Herk, and M. Szwarc, *J. Am. Chem. Soc.*, **83**, 4732 (1961).



studied the rate constants for the addition of CF_3 and CH_3 radicals to allene and substituted allenes. They concluded from their work that the point of initial attack to the unsubstituted allene is dependent upon the polarity of the starting radical. Thus, the slightly nucleophilic[9] methyl radicals were reported to attack at the center carbon atom, whereas the highly electrophilic trifluoromethyl radical was assumed to attack at the terminal positions.

On the other hand, Pullman[10] suggested that free radicals generally attack at the terminal positions of allene. His prediction was based on a calculation of the radical polarization energies of the carbon atoms in allene.

Aside from these theoretical considerations and some thermally[11,12] and photochemically[13] induced reactions which yielded polymers of unidentified structures, there was only one known definitely free radical addition to allene when this work was started. Haszeldine and co-workers[14] found that the photochemical addition of trifluoroiodomethane yields 4,4,4-trifluoroiodobut-1-ene by an exclusively terminal attack of the starting CF_3 radical on allene.

$$(F_3CI \longrightarrow)F_3C\cdot + CH_2{=}C{=}CH_2 \longrightarrow$$

$$F_3C{-}CH_2{-}\dot{C}{=}CH_2 \xrightarrow{F_3CI} F_3C{-}CH_2{-}CI{=}CH_2 (+ F_3C\cdot)$$

Kovachic and Leitch[15] claim to have added hydrogen bromide and deuterium bromide to allene and deuterated allenes by a free radical mechanism. The main reaction products were the corresponding 2-bromopropenes. Their formation was assumed to be the consequence of a preferential center attack by the bromine atom in the first propagation step.

$$(HBr \longrightarrow)Br\cdot + CH_2{=}C{=}CH_2 \longrightarrow$$

$$CH_2{=}CBr{-}CH_2\cdot \xrightarrow{HBr} CH_2{=}CBr{-}CH_3 (+ Br\cdot)$$

However, the 2-bromopropenes also could have been formed by an ionic mechanism, analogous to the one reported for the addition of hydrogen chloride to allene.[16]

$$CH_2{=}C{=}CH_2 \xrightarrow{H^+} CH_2{=}\overset{+}{C}{-}CH_3 \xrightarrow{X^-}$$

$$CH_2{=}CX{-}CH_3 (X = Cl, Br)$$

Having this somewhat conflicting literature information, we selected thiols[17] as adding agents, since their reactions with diolefins in general can be carried out readily by an exclusively free radical mechanism to yield stable compounds.

Results

Mixtures containing 0.1 mole of a thiol, 0.3 mole of allene, and 0.001 mole of *t*-butyl hydroperoxide were irradiated in quartz tubes for different lengths of times and at different temperatures (Table I). The crude reaction mixtures were analyzed by gas–liquid chromatography as well as n.m.r. and infrared spectroscopy.

TABLE I

EXPERIMENTAL AND ANALYTICAL DATA OF THIOL–ALLENE ADDITIONS

R	Thiols used	Peroxide added	Temp., °C.	Time, hr.	Conversion of thiols, %	Yield[a] of adduct mixture	Amount of components in mixture, mole % RS—CH_2—CH=CH_3	RS—$(CH_2)_3$—SR	RS—CH(CH_3)—CH_2—SR	Center attack[b] on allene, %
CH_3	Methanethiol	Yes	15–17	56	100	88	66[c]	19[d]	15[e]	14
CH_3	Methanethiol	Yes	17	4.66	100	87	76	12	12	11
CH_3	Methanethiol	Yes	17	1.5	100	86	76	13	11	10
CH_3	Methanethiol	Yes	17	15 min.	58	54	74	13	13	12
CH_3	Methanethiol	No	−45	25	...	..	39	53	8	8
CH_3	Methanethiol	Yes	−75	12	100	71	57	37	6	6
CH_3—CO	Thiolacetic acid	Yes	17	15 min.	...	92	73	18	9	9
C_6H_5	Benzenethiol	Yes	17-18	52	100	..	70	11	19	19
C_6H_5	Benzenethiol	No	Ambient	35	100	75	73	10	17	17
C_6H_5	Benzenethiol	Yes	17	3.5	100	83	72	7	21	21

[a] Based on thiol conversion and product distribution. [b] Based on the amount of VI in the product mixture less the amount of VI formed from III. [c] Retention time, 6.8 min. [d] Retention time, 24.4 min. [e] Retention time, 22.7 min.

The peaks in the gas chromatograms have been individually identified by authentic compounds. The g.l.c. results have been supported by semiquantitative n.m.r. analyses. These were based on the relative areas of peaks which were characteristic of the individual components and which did not interfere with each other in the spectra of the reaction mixtures (Fig. 1).

The free radical character of these peroxide- and

(9) A. Rajbenbach and M. Szwarc, *Proc. Roy. Soc.* (London), **251A**, 349 (1959).

(10) B. Pullman, *J. chim. phys.*, **55**, 790 (1958).

(11) S. Lebedew, *Chem. Zentr.*, **I**, 1410 (1914).

(12) J. B. Harkners, G. B. Kistiakowski, and W. H. Mears, *J. Chem. Phys.*, **5**, 684 (1937).

(13) S. C. Lind and R. Livingston, *J. Am. Chem. Soc.*, **55**, 1038 (1933).

(14) R. N. Haszeldine, K. Leedham, and B. R. Steele, *J. Chem. Soc.*, 2040 (1954).

(15) D. Kovachic and L. C. Leitch, *Can. J. Chem.*, **39**, 363 (1961).

(16) T. L. Jacobs and R. N. Johnson, *J. Am. Chem. Soc.*, **82**, 6397 (1960).

(17) When the experimental studies of this work were finished, we learned of a similar investigation by T. L. Jacobs and G. E. Illingworth at the University of California.

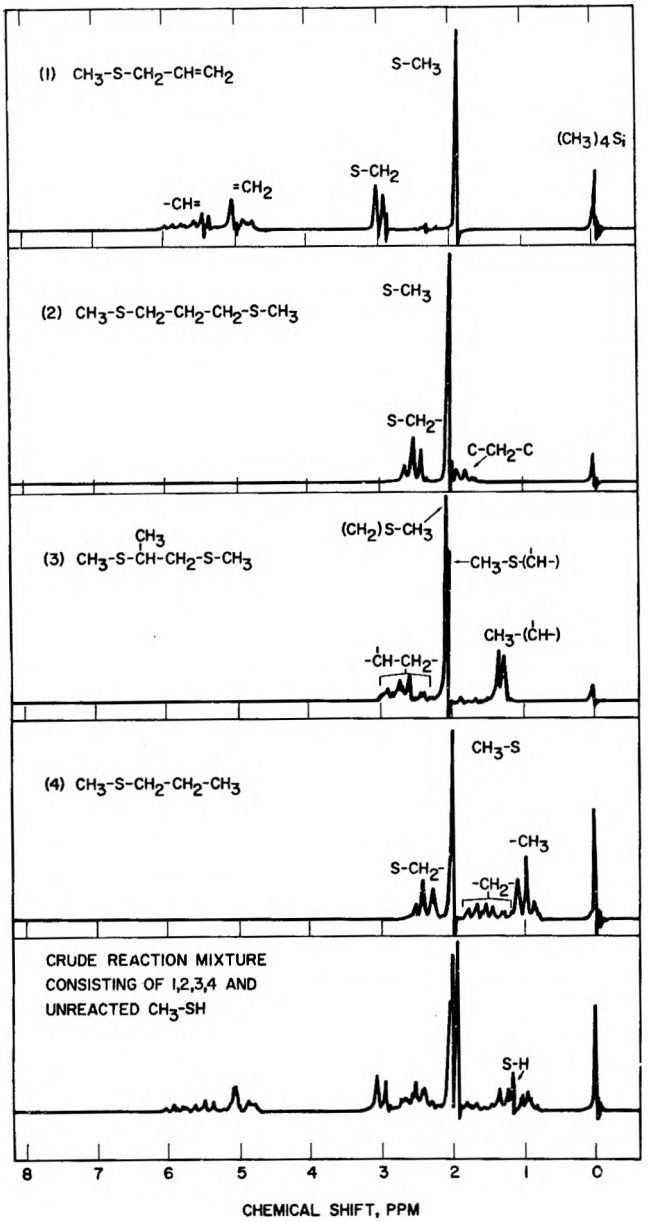


Fig. 1.—Nuclear magnetic resonance spectra of methanethiol–allene adducts.

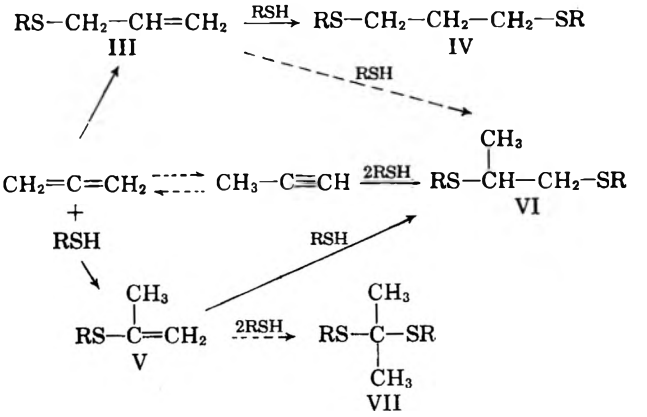
ultraviolet-catalyzed reactions has been demonstrated in the case of the benzenethiol–allene additions. Mixtures of allene and benzenethiol have been treated without any initiation, with ultraviolet initiation, and with a combined peroxide and ultraviolet initiation. The relative rates, based on the thiol decrease, were 1:5.5:7.5, respectively.

Methanethiol.—The main part of the work has been carried out using methanethiol as the adding agent. This resulted in reaction mixtures consisting of relatively low boiling components which could be easily analyzed by capillary gas chromatography. Furthermore, in the semiquantitative n.m.r. analysis of these mixtures the interference of the signals arising from the alkyl group of the starting thiol was reduced to a minimum (Fig. 1).

At 17° the reaction was half completed in fifteen minutes. After ninety minutes no unchanged mercaptan could be detected. The colorless liquid reaction mixture consisted of allyl methyl sulfide (IIIa), 1,3-bis(methylthio)propane (IVa), and 1,2-bis(methylthio)propane (VIa) in the average molar ratio of 6.5:1:1. Methyl propyl sulfide also was formed from a propylene impurity in the starting allene. Only trace amounts of unidentified impurities showed up in the gas chromatograms, and none of the other possible reaction products Va or VIIa were present.

If the reaction was carried out at lower temperatures, much longer reaction times were required. The mixtures again consisted of the same components; however, their ratio was considerably changed. Thus, at −75° the yield of the monoadduct IIIa had dropped in favor of the 1,3-diadduct IVa and the actual ratio (IIIa:IVa:VIa) was 10:6.4:1.

These results can be generally explained by the following reaction sequences.



R = CH_3 (a); CH_3—CO (b); C_6H_5 (c)

It is obvious that the allyl methyl sulfide (IIIa) and the 1,3-bis(methylthio)propane (IVa) originally are derived from a terminal attack of the thiyl radical on the allene molecule. The third reaction product, 1,2-bis(methylthio)propane (VIa), however, can arise by three different routes.

Center attack of the thiyl radical on allene would lead to methyl 2-propenyl sulfide (Va), which could react subsequently with methanethiol to form the diadduct VIa. If this were the exclusive reaction path, the per cent of VIa in the reaction mixture could be related directly to the amount of center attack. The fact that no monoadduct Va was ever found is not surprising, since it has been shown recently by Shostakowskii and co-workers[18] that the corresponding ethyl 2-propenyl sulfide is very reactive towards ethanethiol and readily forms the corresponding 1,2-bis(diethylthio)propane.

An alternate route to form VIa starts out with a possible isomerization of allene to methylacetylene under the influence of ultraviolet irradiation or thiyl radicals. We showed in an independent experiment that methylacetylene reacts readily with methanethiol to form the diadduct VIa. Therefore, the critical step would be the isomerization reaction. It was known that allene does not isomerize below 320–400° in the absence of a catalyst.[12] However, the combined effect of ultraviolet light and thiyl radicals on allene isomerizations was not known. Therefore, the excess of allene from the addition reaction was analyzed by g.l.c. It could be shown that no methylacetylene was present. Of course, this evidence is conclusive only if the thiol

(18) M. F. Shostakovskii, E. P. Gracheva, and N. N. Kul'bovskaya, *Zh. Obsch. Khim.*, **30**, 383 (1960).

is added with about equal rates to allene and methylacetylene.

This could be confirmed by treating a mixture of the two with less than the required amount of thiol and analyzing the unchanged gaseous allene–methylacetylene mixture as well as the liquid products formed. We can, therefore, rule out this route to VIa under the prevailing reaction conditions.

The third route to VIa, namely thiol addition to IIIa, is highly improbable in view of the general direction of free radical additions of thiols to olefins.[7a] In independent experiments we could indeed show that this "reverse" addition occurs to less than 7%.

On the basis of these results it can be concluded that at least 93% of the 1,2-bis(methylthio)propane formation occurs through the vinyl sulfide Va and, therefore, reflects the amount of center attack to allene. At 17° center attack occurs with 12%, at −45° it occurs with only 8%, and at −75° the ratio drops to 6%. The situation is, however, just the reverse for the ratio of mono- (IIIa) to diadduct (IVa). At 17° this ratio was about 5:1 as compared to 1.5:1 at −75°.

Thiolacetic Acid.—Addition of thiolacetic acid to allene also occurred readily under the conditions described before. A mixture of the monoadduct IIIb and two diadducts IVb and VIb was formed (Table I). With the assumption that the previous conclusion concerning the mode of formation of the diadduct VIb can be generalized, terminal attack was found to occur with 91%. The molar ratio of the mono- (IIIb) to the diadduct VIb is 4:1.

Benzenethiol.—The peroxide- and ultraviolet-catalyzed addition of benzenethiol to allene was completed in three and a half hours.

The crude reaction mixtures consisted of the monoadduct IIIc, the two diadducts IVc and VIc, very little phenyl propyl sulfide, and between 5–10% unidentified impurities. The main impurity showed a single peak in the n.m.r. at the same position (1.45 p.p.m.) as the diadduct VIIc. V.p.c. analysis of a blend, containing synthetic VIIc and the crude benzenethiol–allene adduct, demonstrated, however, that VIIc was not a product of the addition reaction. Fractional distillation of the reaction mixture largely confirmed the results of the g.l.c. and n.m.r. analyses. The per cent of the diadduct VIc in the reaction mixture was higher than in the two previous cases (Table I). It was shown that less than 2% of VIc arises from the allyl phenyl sulfide IIIc. Assuming that benzenethiyl radicals do not isomerize allene, the amount of terminal attack is thus only 80%.

Discussion

The present work has shown that thiyl radicals add selectively to the terminal positions of allene. In the second propagation step, the vinylic type radical intermediate then abstracts hydrogen from the thiol to yield alkyl (or aryl) allyl sulfides. The over-all reaction is, therefore, a 1,2-addition of a thiol to allene.[19a] This reaction course is largely in line with Pullman's theory. Since thiyl radicals are electrophilic species,[19b] one would expect, however, the same results on the basis of Szwarc's prediction. Therefore, the information which was obtained in the present investigation does not allow a decision between the two conflicting theories. Nevertheless, the thiol addition reaction might be a potential means of solving this question, using various *para*-substituted benzenethiols as adding reagents. A correlation between the nature of the substituent and its effect on the selectivity of the reaction should give an indication as to the validity of Szwarc's prediction.

The observed difference in selectivity between the thiyl radicals derived from methanethiol and thiolacetic acid on one side and benzenethiol on the other side is somewhat puzzling. Since the latter thiyl radicals are resonance stabilized and less reactive[7b] than the former ones, one might have anticipated an increased selectivity for the benzenethiol–allene addition. Even though the reverse has been observed, the effect is too small to suggest any definite conclusion.

The yield of the diadduct IVa is increasing at the expense of the monoadduct IIIa with falling reaction temperatures. It is believed that this effect reflects the higher reactivity of the monoadduct over that of allene. The first propagation step in this diadduct formation might involve a fast equilibrium of the following type.

$$RS{-}CH_2{-}CH{=}CH_2 + \cdot SR \overset{\text{fast}}{\rightleftharpoons}$$

$$RS{-}CH_2{-}\dot{C}H{-}CH_2{-}SR \xrightarrow[\text{slow}]{RSH} RS{-}CH_2{-}CH_2{-}CH_2{-}SR$$

The lower ratio of the diadduct IVc relative to the monoadduct IIIc in the benzenethiol–allene addition reaction seems to support this assumption. The enhanced stability of the resonance-stabilized thiyl radical, derived from benzenethiol, would favor the reversibility of the first propagation step and thus decrease the over-all yield of the diadduct IVc.

Experimental

Materials.—The allene and methylacetylene used were Matheson products. Allene contained 0.038% of propane and between 0.5 and 7.3% (depending on the batch) of propylene; however, no methylacetylene was present. The thiols used were C.P. chemicals. All reference samples have been prepared by known methods, starting from the corresponding bromides or chlorides and sodium mercaptides. Characteristic n.m.r. parameters of them are listed in Table II.

Method of Analyses.—The adduct mixtures of methanethiol, thiolacetic acid, and allene have been analyzed by capillary gas chromatography. A Perkin-Elmer Model 226 linear programmed temperature gas chromatograph with a 200-ft., 0.02-in. i.d. Golay column coated with a mixture of 50% phenylsilicone and 50% nitrilesilicone was used. Temperatures of the injection block and detector were 270° and 190°, respectively. The temperature of the column was first held for 10 min. at 50°; afterwards, it was programmed at a rate of 10° per min. up to 160° and then maintained at that temperature isothermally until the end of the analyses. A CRS-1 digital chromatogram integrator (supplied by Infotronics Co., Houston, Tex.) was used for recording the peak areas. Data from the integrator were automatically transferred to a printer which in turn printed out peak retention times and peak areas on a printer tape.

The higher boiling benzenethiol–allene adducts were separated on a F & M Model 500 linear programmed temperature gas chromatograph with a 2-ft., 0.25-in. o.d. column. The column

(19) (a) NOTE ADDED IN PROOF.—After this work was submitted for publication we learned that workers at Shell [H. J. Van der Ploeg, J. Knoterus, and A. F. Bickel, *Rec. trav. chim.*, **81**, 775 (1962)] concluded that thiol additions to allene are rather indiscriminate. We feel that their conclusion is valid only when a large excess of allene is used. (b) W. A. Pryor, "Mechanism of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 85.

TABLE II

PARAMETERS OF NUCLEAR MAGNETIC RESONANCE SPECTRA OF THIOL–ALLENE ADDUCTS

(Chemical shifts of structural units, p.p.m. downfield from tetramethylsilane internal reference; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet)

	RS—CH_2—CH=CH_2				RS—CH_2—CH_2—CH_2—SR				RS—CH_2—CH(—CH_3)—S—R				
R	RS—	—CH_2—	—CH=	=CH_2	RS—	—S—CH_2	—CH_2—	RS—	—CH_2—	—CH—	(—CH_3)	—SR	
CH_3	s 1.94	d 3.05[a]	m 5.77[b]	m 5.02, m 5.04[c]	s 2.07	t 2.57[a]	m 1.82[a]	s 2.08	q 2.53, q 2.80[h]	m 2.86[e]	d 1.32[d]	s 2.07	
CH_3CO—	s 2.23	d 3.49[a]	m 5.82[b]	m 5.03, m 5.16[c]	s 2.29	t 2.90[a]	m 1.79[a]	s 2.32	d 3.10, d 3.12[f]	m 3.67[g]	d 1.27[a]	s 2.27[a]	
C_6H_5	m 7.0–7.5	d 3.38[a]	m 5.82[b]	m 4.93, m 5.00[c]	m 6.8–7.4	t 2.84[a]	m 1.77[a]	m 7.0–7.4	q 2.68, m ca. 3.0[i]	m ~3.0[j]	d 1.33[d]	m 7.0–7.4	

[a] J = 7 c.p.s. [b] X part of an $ABXY_2$ spin system, J = 9 c.p.s., 17 c.p.s., and 7 c.p.s. [c] AB part of an $ABXY_2$ spin system, J_{AB} = 3 c.p.s., remote coupling constant 1 c.p.s. [d] J = 6 c.p.s. [e] X part of an $ABXY_3$ spin system, J_{AX} = 9 c.p.s., J_{BX} = 12 c.p.s., J_{XY} = 7 c.p.s. [f] AB part of an $ABXY_3$ spin system. [g] X part of an $ABXY_3$ spin system, J_{AX} = 9 c.p.s., J_{BX} = 7 c.p.s. [h] AB part of an $ABXY_3$ spin system. [i] AB part of an $ABXY_3$ spin system not sufficiently resolved for detailed assignments. [j] X part of an $ABXY_3$ spin system not sufficiently resolved for detailed assignments.

packing consisted of 3% Dowfax 9N40 (obtainable from Dow Chemical Co., Midland, Mich.) on 60–80-mesh Gas Chrom P.

Operating conditions were as follows: detector cell temperature, 370°; detector cell current, 150 ma.; injector part temperature, 295°; helium flow at exit, 60 cc./min.; column heating rate, 5.6°/min.; starting column temperature, 100°; finished column temperature, 225°; sample size, 0.5 μl.

The crude reaction mixtures were analyzed as such or after removal of the excess thiol. The components were identified by comparison of their retention times with those of the pure compounds. In addition to that, blends, containing the reaction mixture and the authentic compound, were individually run for each component. The added components showed up in the area of the respective peaks and did not cause any change (broadening or splitting) in the shape of the peaks.

The response factors for the adducts of methanethiol and allene have been determined with synthetic blends of the individual components. It was found that the relative areas can be directly related to the weight per cent.[20]

Allene and the allene–methylacetylene mixtures were analyzed on the F & M Model 500 gas chromatograph, using a 10-ft. column, packed with 20% dimethyl sulfolane on Chromosorb P. The column temperature was maintained at 30°.

N.m.r. spectra were recorded and integrated on a Varian Model A-60 proton resonance spectrometer. The infrared spectra were obtained using a Baird recording spectrophotometer, Model B.

Addition of Thiols to Allene.—In a 100-ml. quartz tube 12 g. (0.3 mole) of allene was condensed at −80°; 0.1 mole of a mercaptan and 0.001 mole of *t*-butyl hydroperoxide were added. The sealed tube was placed into a temperature-controlled water (17 ± 1°) or "Freon 11" bath. A 100-w. Hanovia ultraviolet immersion lamp was placed about 5 cm. from the reaction tube. If the reaction was carried out below room temperature, the lamp was surrounded by a quartz mantle to avoid excessive cooling of the lamp.

After an arbitrary period of reaction time the tubes were opened at −80°. If methanethiol was the adding agent, the excess gases subsequently were passed through a saturated methanol solution of lead acetate and a wet test meter to determine the unreacted thiol and allene selectively. The lead–bismethyl sulfide was determined gravimetrically. In the benzenethiol–allene reaction mixtures the excess thiol was titrated potentiometrically with silver nitrate and was removed by washing with a 5% aqueous sodium hydroxide solution. The remaining crude reaction mixtures were in all cases colorless or slightly yellow liquids, depending on the reaction times.

In one experiment, 9.1 g. of a crude benzenethiol–allene adduct mixture was distilled to yield 4.7 g. (51.7 wt. % as compared to 56% by g.l.c. analysis) of allyl phenyl sulfide, b.p. 68–69° (1 mm.). The remaining mixture of higher boiling diadducts was subsequently analyzed by g.l.c. and n.m.r.

Addition of Methanethiol to Methylacetylene.—A mixture of 4 g. (0.1 mole) of methylacetylene, 9.6 g. (0.2 mole) of methanethiol, and 90 mg. of *t*-butyl hydroperoxide was irradiated in a sealed quartz tube for 4.5 hr. at 15°. The crude reaction product (11.8 g., 86%) was a colorless liquid. G.l.c. analysis showed that it consisted with 93% of the diadduct, VIa, b.p. 84° (20 mm.).

Anal. Calcd. for $C_5H_{12}S_2$: C, 44.07; H, 8.87; S, 47.06. Found: C, 44.31; H, 8.86; S, 47.06.

Addition of Methanethiol of a Mixture of Allene and Methylacetylene.—A mixture, containing 0.05 mole of allene and methylacetylene each, 90 mg. of *t*-butyl hydroperoxide, and 0.05 mole of methanethiol was irradiated in a sealed quartz tube for 1 hr. at 15°. The unchanged gaseous allene–methylacetylene mixture and the liquid reaction product were analyzed by g.l.c.

	Allene	Methylacetylene
Mole % at start	48	52
Mole % after reaction	53	47
Mole % product derived from	52	48

The discrepancy in the analyses of the unchanged gases and of the liquid reaction mixture might be due to the fact that two different chromatographic instruments were used.

Addition of Methanethiol to Allyl Methyl Sulfide.—Mixtures containing 2 g. (0.023 mole) of allyl methyl sulfide, 1.2 g. (0.025 mole) of methanethiol, and 10 mg. of *t*-butyl hydroperoxide were irradiated in sealed quartz tubes for the indicated lengths of time at 17°. The reaction products were analyzed by g.l.c. and n.m.r.

Reaction time, hr.	Yield of crude adduct, %	Ratio of the diadducts in mixture IVa	VIa
2	94	93	7
18	100	94	6

Relative Rates of Benzenethiol–Allene Additions Dependent on the Initiation.—Mixtures of 0.3 mole of allene and 0.1 mole of benzenethiol reacted for 20 min. at 17° under the indicated different conditions. At the end the amount of unchanged benzenethiol in the liquid reaction mixture was potentiometrically titrated with a silver nitrate solution.

Reaction vessel	Ultraviolet irradiation	*t*-Butyl hydroperoxide	Thiol reacted, %	Relative rates
Glass tube	No	No	11.7	1
Quartz tube	Yes	No	65	5.5
Quartz tube	Yes	0.001%	87.5	7.5

Addition of Benzenethiol to Allyl Phenyl Sulfide.—Allyl pheny sulfide (7.5 g., 0.05 mole) and benzenethiol (5.5 g., 0.05 mole) were irradiated in the presence of 10 mg. of *t*-butyl hydroperoxide at 17°. After 2 hr. only 53% of the thiol had disappeared. The crude reaction product was washed with a 5% aqueous solution of sodium hydroxide and water. The dried (over sodium sulfate) product was analyzed by g.l.c. It consisted of 98% of 1,3-bis(phenylthio)propane and 2% of 1,2-bis(phenylthio)propane.

Independent Syntheses of the G.c. Reference Samples.—

(20) See also N. D. Nogare and R. S. Juvet, Jr., "Gas Liquid Chromatography," Interscience, New York, N. Y. 1962, p. 197.

The **monoadducts** have been prepared by the method of Price and Gillis.[21] Allyl methyl sulfide[21]: b.p. 93.5–95°; infrared,[22] 3.27 (=CH),[23a] 5.45 (overtone to $=CH_2$),[23b] 6.14 (C=C),[23c] 10.95 μ ($=CH_2$ deform.).[23d] Allyl acetyl sulfide: b.p. 48–49° (27 mm.) (*Anal.* Calcd. for C_5H_8OS: C, 51.69; H, 6.94. Found: C, 51.98; H, 6.97); infrared, 3.26 (=CH),[23a] 5.45 (overtone to $=CH_2$),[23b] 6.13 (C=C),[23c] 10.90 μ ($=CH_2$ deform.).[23d] Allyl phenyl sulfide[24]: b.p. 51–52° (0.4 mm.); infrared, 6.12 (C=C olefinic),[23c] 10.90 μ ($=CH_2$ deform.).[23d]

The **diadducts** have been prepared by the general method of Mann and Purdie.[25] 1,3-Bis(methylthio)propane[26]: b.p. 99–100° (27 mm.); infrared, 3.45, 7.0, 7.95, 8.04, 10.50 μ. 1,3-Bis-(acetylthio)propane: b.p. 105–106° (2 mm.) (*Anal.* Calcd. for $C_7H_{12}O_2S_2$: C, 43.73; H, 6.29. Found: C, 43.53; H, 6.25); infrared, 3.40, 5.90, 6.97, 7.39, 8.07, 8.80 μ. 1,3-Bis(phenylthio)propane[25]: b.p. 170–171° (0.3 mm.). 1,2-Bis(methylthio)-propane: b.p. 90.5–91° (27 mm.) (*Anal.* Calcd. for $C_5H_{12}S_2$: C, 44.06; H, 8.87; S, 47.06. Found: C, 44.45; H, 9.01; S, 47.1); infrared, 3.36 and 3.43, 6.99, 7.29, 7.60, 7.94, 8.17, 8.43, 9.05, 9.38, 9.83, 10.47, 14.82 μ. 1,2-Bis(acetylthio)propane: b.p. 70–72° (0.2 mm.) (*Anal.* Calcd. for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29. Found: C, 43.59; H, 6.15). 1,2-Bis(phenylthio)-propane: b.p., 158–160° (0.3 mm.) (*Anal.* Calcd. for $C_{15}H_{16}S_2$: C, 69.18; H, 6.19; S, 24.63. Found: C, 69.50; H, 6.36; S, 24.75); infrared, 3.29, 3.40, 3.45, 6.34, 6.77, 6.97, 7.32, 8.50, 9.20, 9.77, 13.50, 14.50 μ.

(21) C. C. Price and R. G. Gillis, *J. Am. Chem. Soc.*, **75**, 4750 (1953).

(22) For the monoadducts the bands characteristic of the double bond are reported. For the diadducts the strongest bands of the spectrum are reported without correlating them to particular structural elements.

(23) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959: (a) p. 43; (b) p. 50; (c) pp. 35–38; (d) pp. 49–51.

(24) C. D. Hurd and H. Greengard, *J. Am. Chem. Soc.*, **52**, 3356 (1930).

Acknowledgment.—The authors wish to thank A. M. Palmer and G. F. Shea for technical help and Miss M. J. Doolan for the g.c. analyses.

(25) F. G. Mann and D. Purdie, *J. Chem. Soc.*, 1557 (1935).

(26) See also S. Mathias, *Bol. Fac. Filosof., cienc. letras, Univ. São Paulo; Quim. No. 1*, **14**, 75 (1942).

Transannular Sulfoxide–Ketone Salt Formation across a Seven-Membered Ring[1]

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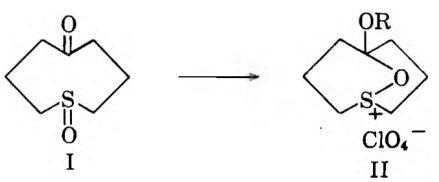
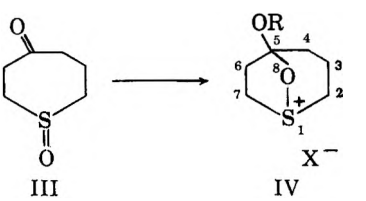
This investigation has established for the first time the occurrence of a transannular reaction between sulfoxide and ketone groups, with protonation, across a seven-membered ring: 1-thiacycloheptan-4-one 1-oxide (III) with perchloric or fluoboric acid gave the corresponding 5-hydroxy-8-oxa-1-thioniabicyclo[3.2.1]octane salt (IVa,b), with an oxygen bridge between the sulfur and the carbonyl carbon. The bicyclic fluoborate was methylated with 2,2-dimethoxypropane to give 5-methoxy-8-oxa-1-thioniabicyclo[3.2.1]octane fluoborate (IVc). Hydrolysis of both the bridgehead hydroxy and methoxy salts occurred so readily that all operations had to be conducted in a dry box. We found it hazardous to work with the perchlorate salts in this bicyclic series.

In an investigation of the occurrence of transannular interactions and reactions of diametric sulfoxide and ketone groups in medium rings (eight–eleven members), monocyclic 1-thiacyclooctan-5-one 1-oxide (I) was converted to a bicyclic perchlorate salt by transannular reaction involving protonation of the carbonyl oxygen.[2] The protonic salt and its methoxy and acetoxy derivatives were shown to have 1-thioniabicyclo[3.3.1]nonane structures (II), with an oxygen bridge between the sulfur and the carbonyl carbon. This type of bridging generates two six-membered rings from an eight-membered ring rather than two five-membered rings, as would have been the case had sulfur acted as the donor. The action of oxygen of the sulfoxide as the donor suggested that in the seven-membered ring system, 1-thiacycloheptan-4-one 1-oxide (III), similar bridging could lead to a probable structure of the 1-thioniabicyclo[3.2.1]octane type (IV) consisting of a five- and a six-membered ring, whereas the result of direct sulfur–carbon bridging would be a structure consisting of four- and five-membered rings, thermodynamically unstable under the reversible conditions of salt formation.



I II

IIa, R = H
b, R = CH_3
c, R = $COCH_3$



III IV

IVa, R = H, X = ClO_4
b, R = H, X = BF_4
c, R = CH_3, X = BF_4

A test of the ability of III, and possibly of a six-membered-ring compound of the 1-thiacyclohexan-4-one 1-oxide type, to undergo transannular reaction is also of theoretical interest because it should provide information concerning the lower limits of ring size for this phenomenon to occur. The lower limit for transannular bond formation, accompanying protonation, between diametric tertiaryamine and ketone[3] or sulfide and ketone functions[4,5] is presently at the eight-membered ring. However, when an additional atom is introduced between amino nitrogen and the 4-carbon of a six-membered ring in configuration and conformation favorable for reaction, a bridge may be formed creating two five-membered rings in an azoniabicyclo[2.2.1]heptane system. Thus, Bell and Archer[6] have shown that the salt of 3α-phenyl-3β-tropanyl phenyl ketone exists mainly in a transannular bridged structure (>N⁺—C(OH)—C<) and Polonovski and Polonovski[7] reported that scopin-

(1) Support of this work by research grants (NSF-G6040 and NSF-G14121) from the National Science Foundation is gratefully acknowledged.

(2) N. J. Leonard and C. R. Johnson, *J. Am. Chem. Soc.*, **84**, 3701 (1962).

(3) N. J. Leonard, R. C. Fox, and M. Ōki, *ibid.*, **76**, 5708 (1954).

(4) N. J. Leonard, T. L. Brown, and T. W. Milligan, *ibid.*, **81**, 504 (1959); **82**, 4075 (1960).

(5) C. G. Overberger and A. Lusi, *ibid.*, **81**, 506 (1959).

(6) M. R. Bell and S. Archer, *ibid.*, **82**, 151 (1960).

ium tropate (containing $>\overset{+}{N}—O—C<$) is formed when *l*-scopolamine is treated with hydrogen peroxide. In carbocyclic systems, Cope, Liss, and Wood[3] have provided an example of a proximity effect operating across a seven-membered ring, by detection of 2.4% of transannular products in the solvolysis of cycloheptene oxide with dilute hydrochloric acid; further, by careful product isolation procedures evidence was found for transannular participation to the extent of 0.3% in a six-membered ring analog.

The synthesis of the required 1-thiacycloheptan-4-one 1-oxide (III), m.p. 75.5–76°, was accomplished by oxidation of 1-thiacycloheptan-4-one[9] with aqueous sodium metaperiodate.[10] The infrared spectrum of III, as in the case of the analogous eight-membered ring compound, showed no anomaly. The ultraviolet spectrum in cyclohexane solution exhibited a maximum corresponding to the low energy carbonyl transition at 287 mμ and a second maximum at 217 mμ, which is in the region of absorption of some model sulfoxides. The absorption curve did not show an intermediate maximum such as that observed for 1-thiacyclooctan-5-one 1-oxide (I), *i.e.*, at 235 mμ, responsive to solvent change.[2] The electron donor and basic characteristics of sulfoxides have been demonstrated by the obtainment of salts with perchloric acid.[11] Addition of 70% perchloric, 48% and 70% fluoboric, and 70% nitric acid to ether solutions of 1-thiacycloheptan-4-one 1-oxide uniformly failed to produce any separation of salt. We ascribe the failure to the presence of water, which has been shown to hydrolyze 5-hydroxy-9-oxa-1-thioniabicyclo[3.3.1]nonane perchlorate (IIa) very rapidly.[2] In order to reduce the water content of the acids a distribution of the strong acid between its concentrated aqueous solution and ether was utilized. Upon admixture of a saturated ethereal solution of the sulfoxide–ketone and the appropriate ethereal-distributed acid, only perchloric acid among the three cited before produced an ether-insoluble salt. The mixture resulting from the addition of ethereal-distributed perchloric acid to the sulfoxide ketone in ether was allowed to stand six hours in a nitrogen-filled dry box, or until the salt had separated completely and the supernatant was clear. The microcrystalline perchlorate was triturated with fresh anhydrous ether. The salt–ether suspension was filtered through a coarse glass fritted filter. It was advisable because of the electrostatic and explosive nature of the perchlorate to perform all transfers of the salt as an ether slush and to perform microanalytical and spectral analyses immediately when the salt reached constant weight. The salt underwent rapid decomposition when dry. An attempt to obtain a 180-mg. sample failed when the sample exploded *in vacuo*. A better acid—nonaqueous, nonoxidizing, strong,[12,13] and having an anion of low nucleophilicity—to employ in salt formation was anhydrous hydrogen tetrafluoborate.[14] A stoichiometric quantity of distilled boron trifluoride ethereate was brought into contact with freshly condensed dry hydrogen fluoride. To the fuming oil anhydrous ether was added in a drybox. After shaking and allowing the solution, in which some of the oil was suspended, to settle, dropwise addition of the ethereal hydrogen tetrafluoborate to 1-thiacycloheptan-4-one 1-oxide (III) dissolved in anhydrous ether produced a white milky mixture. The supernatant became clear after standing overnight and was decanted and replaced by fresh anhydrous ether. The microcrystalline residue was shaved from the sides of the flask with a spatula and triturated with ether. The hygroscopic ethereal slush was transferred and analyzed satisfactorily as described for the perchlorate salt.

Both the perchlorate and the fluoborate of III exhibited strong infrared absorption (in acetonitrile solution) at 3320 cm.$^{-1}$ indicative of O—H. Neither salt was transparent in the region of S=O stretch because of absorption by the anions, but neither salt showed a strong absorption band in the 1245 cm.$^{-1}$ region corresponding to S^{+}=O stretch as in trimethyloxosulfonium perchlorate (in acetonitrile).[2] The spectral observations require modification of both ketone and sulfoxide function in III on salt formation. The presence of strong O—H absorption and apparent absence of an $>S^{+}$=O function in the cationic species limit the structure to IV (a or b), 5-hydroxy-8-oxa-1-thioniabicyclo[3.2.1]octane perchlorate or fluoborate. The very weak absorption of these salts observed just above 1700 cm.$^{-1}$ is considered to arise from the formation of the original sulfoxide ketone ($\nu_{max}^{CH_3CN}$ 1704 cm.$^{-1}$) as a result of very rapid hydrolysis of the salt. In support, when a Nujol mull of the hydroxy salt was exposed to a moist atmosphere the hydroxyl band disappeared and the carbonyl band became intense. The alternative possibility that the salts contain a mixture of $>\overset{+}{S}—O—\underset{|}{\overset{|}{C}}—OH$ and $>\overset{+}{S}—OH$ $>C$=O cations is less likely on the basis of n.m.r. spectra and the behavior of model compounds, such as methyl 4-ketopentyl sulfoxide and 1-thiacyclohexan-4-one 1-oxide,[2,10] on attempted salt formation.

Recovery of the original sulfoxide ketone (III) from the salt was possible by titration with base followed by continuous extraction with methylene chloride, thereby establishing the point that compound III had not undergone rearrangement during acid treatment and completing the assignment of the salt structure as IV (a or b). Chemical evidence for the transannular salt structure was obtained, as in the case of the eight-membered ring analog,[2] by the preparation of an O-methyl derivative. This was accomplished by addition of 2,2-dimethoxypropane to an acetone solution of 5-hydroxy-8-oxa-1-thioniabicyclo[3.2.1]octane fluoborate (IVb). A compound was obtained which had the correct analysis for IVb plus CH_2, consistent with the structure IVc. Any alternative alkylated structure appears less likely in view of the failure of C=O models to add CH_2 and of S=O models to form derivatives under the the reaction conditions specified. The crystals of 5-methoxy-8-oxa-1-thioniabicyclo[3.2.1]octane fluoborate (IVc) were electrostatic and hygroscopic, reverting

(7) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **43**, 79 (1928); *Compt. rend.*, **185**, 277 (1927).

(8) A. C. Cope, T. A. Liss, and G. W. Wood, *Chem. Ind.* (London), 823 (1956); *J. Am. Chem. Soc.*, **79**, 6287 (1957).

(9) C. G. Overberger and A. Katchman, *ibid.*, **78**, 1965 (1956).

(10) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(11) J. de Pascual Teresa, *Anales soc. espan. fis. y quim.*, **45B**, 235 (1949); *Chem. Abstr.*, **44**, 3935 (1950).

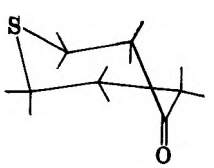
(12) E. L. Mackor, A. Hofstra, and J. H. van der Waals, *Trans. Faraday Soc.*, **54**, 66 (1958).

(13) E. Wilke-Dörfurt, *Z. angew. Chem.*, **37**, 712 (1924).

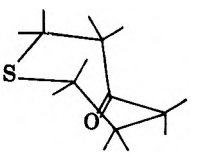
(14) E. Müller and H. Huber-Emden, *Ann.*, **649**, 70 (1961).

rapidly by hydrolysis to the sulfoxide ketone (III), as evidenced by the appearance of carbonyl absorption in the infrared spectrum. In comparison with the corresponding transannular hydroxy and methoxy salts of the eight-membered ring sulfoxide ketone (IIa and b),[2] compounds IVa, b, and c are much less stable and are more susceptible to hydrolysis.

The n.m.r. spectrum of 1-thiacycloheptan-4-one 1-oxide (III) in deuteriochloroform was complicated and consisted of overlapping sets of signals corresponding to the ten different C—H protons in the unsymmetrical molecule. Reading from high to low field, one encounters two proton signals with different chemical shifts and different splitting patterns corresponding to the C-6 hydrogens, signals corresponding to the four protons adjacent to C=O and signals for the four protons adjacent to S=O. There was no proton resonance at lower field than τ value 6.2.[15] Both the perchlorate and fluoborate salt, which were determined in trifluoroacetic acid solution, showed a shift of the low field group, due to the protons on the carbons adjacent to sulfur, terminating downfield at τ value 5.5, consistent with the introduction of a positive charge on the sulfur. The conformation of the O_{CO}-protonated bicyclic salt structure IVa,b is relatively fixed, with a near-planar or envelope-conformed five-membered ring on one side and a six-membered ring, with probable preferred chair structure, on the other. Two postulated conformations of 1-thiacycloheptan-4-one may be constructed, V and VI, in which 1,2-interactions are at a minimum and the opposing H:H interactions have been balanced as much as possible.[16] The sulfoxide oxygen may then be introduced into V or VI on either side of the C—S—C plane to indicate the possible preferred conformations of 1-thiacycloheptan-4-one 1-oxide (III). The dynamic process of protonation and bridging has not been investigated.



V



VI

Experimental[17]

1-Thiacycloheptan-4-one 1-Oxide (III).—1-Thiacycloheptan-4-one[9] (6.78 g., 0.052 mole) was added to an ice-cold magnetically stirred solution of sodium metaperiodate (12.24 g., 0.057 mole) in 212 ml. of water. The mixture was stirred for 21 hr. in the ice bath. The precipitated sodium iodate was removed by filtration and the solution was extracted continuously with methylene chloride. The contents of the flask containing the methylene chloride was changed frequently to avoid pyrolysis of the accumulating sulfoxide.[18] The solvent was evaporated at reduced pressure. The crude product was twice sublimed at 50° (0.1 mm.) to give analytically pure 1-thiacycloheptan-4-one 1-oxide, m.p. 75.5–76°; $\nu_{max}^{CH_3CN(5\%)}$ 1704 cm.$^{-1}$ (C=O) and $\nu_{max}^{CHCl_3}$ 1705 (C=O) and 1017 cm.$^{-1}$ (S=O); $\lambda_{max}^{CH_3CN}$ 287 and 217 mμ, with the magnitude of the extinction coefficients in some doubt due to the hygroscopic nature of the compound.

Anal. Calcd. for $C_6H_{10}O_2S$: C, 49.30; H, 6.89. Found: C, 49.64; H, 6.68.

5-Hydroxy-8-oxa-1-thioniabicyclo[3.2.1]octane Perchlorate (IVa).—A mixture of 10 g. of 70% aqueous perchloric acid and 300 g. of anhydrous ether was shaken and allowed to stand in order to separate completely. A freshly prepared solution may be utilized if the upper layer is first centrifuged to separate suspended water. In a drybox under nitrogen the ethereal perchloric acid was added dropwise to an ether solution containing *ca.* 300 mg. of 1-thiacycloheptan-4-one 1-oxide until precipitation was complete and the presence of excess perchloric acid was indicated. The crystals which separated from the mixture after 6 hr. were scraped from the flask, washed onto a coarse fritted glass filter, and thoroughly washed with ether. The electrostatically charged crystals were easily transferred when wet with ether to the platinum combustion boat which was placed in an aluminum pig. The sample was dried under high vacuum and weighed at 3-min. intervals until a constant weight was obtained. It was then quickly transferred to the combustion train for analysis. It *explodes* at 77°. The infrared spectrum (15% in acetonitrile) had only slight absorption in the carbonyl region but exhibited a strong band at 3320 cm.$^{-1}$ (O–H). Special precautions were taken during combustion for microanalysis.

Anal. Calcd. for $C_6H_{11}ClO_6S$: C, 29.21; H, 4.50; neut. equiv., 246.6. Found: C, 29.17; H, 4.49; neut. equiv. (titration in cold ethanol), 247.6.

Upon attempted vacuum desiccation (complete ether removal), a 180-mg. sample exploded.

5-Hydroxy-8-oxa-1-thioniabicyclo[3.2.1]octane Fluoborate (IVb).—Anhydrous hydrogen tetrafluoborate in ether[14] was prepared in the following manner. Redistilled boron trifluoride etherate (14.379 g., 0.1014 mole) was contained in a tightly closed 30-ml. polyethylene bottle. The requisite amount (2.025 g., 0.1014 mole) of anhydrous hydrogen fluoride was condensed in a dry, nitrogen-filled 250-ml. side-siphon polyethylene wash bottle. The gas was passed from a cylinder of anhydrous hydrogen fluoride through polyethylene tubing and safety bottle to a 5-ft. coiled piece of 304 stainless steel tubing which had been immersed in a ice–salt bath. The first few milliliters of the liquefied gas were discarded. A slight excess of the liquid hydrogen fluoride was passed into the polyethylene bottle. The cap was secured, and the excess hydrogen fluoride was allowed to evaporate. Slight pressure was applied to the bottle while the exit tube was below the surface of the boron trifluoride etherate. Upon releasing the pressure, the liquid was drawn into the wash bottle containing hydrogen fluoride. In a drybox, anhydrous ether was added to the small polyethylene bottle containing the remaining boron trifluoride etherate and then drawn into the wash bottle. Additional anhydrous ether was added with shaking to the anhydrous hydrogen tetrafluoborate, bringing the volume to about 200 ml. After standing for 1 hr. a small amount of straw-colored liquid remained undissolved. The depth of the dispensing tube was adjusted to deliver only the colorless solution. To 200 ml. of anhydrous ether containing *ca.* 200 mg. of 1-thiacycloheptan-4-one 1-oxide which had been filtered in the dry box, ethereal acid was added until no further cloudiness appeared and the mixture was allowed to stand 6 hr. The ether was decanted from the deposited solid and replaced by fresh anhydrous ether. After the crystals were scraped from the flask onto a coarse fritted glass filter, a few milligrams were transferred to a preweighed analytical boat in an aluminum pig. These electrostatic crystals were dried to a constant weight and then analyzed immediately. The compound decomposes at 92°. The infrared spectrum (10% in acetonitrile) had only slight absorption in the carbonyl region but exhibited a strong band at 3320 cm.$^{-1}$ (O–H).

Anal. Calcd. for $C_6H_{11}BF_4O_2S$: C, 30.79; H, 4.74. Found: C, 31.02; H, 4.85.

5-Methoxy-8-oxa-1-thioniabicyclo[3.2.1]octane Fluoborate (IVc).—To 100 mg. of 5-hydroxy-8-oxa-1-thioniabicyclo[3.2.1]-octane fluoborate in 2 ml. of acetone was added 2 ml. of 2,2-dimethoxypropane. The sample immediately became orange-yellow. Anhydrous ether (10 ml.) was added and the sample

(15) G. V. D. Tiers, "Table of τ Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(16) Data from heats of combustion have shown that replacement of a methylene group in a cycloalkane by a sulfur atom relieves strain due to H:H nonbonded interactions (Sj. Kaarsemaker and J. Coops, *Rec. trav. chim.*, **71**, 261 (1952)).

(17) The authors are indebted to Josef Nemeth for the microanalyses and to Oliver Norton and Dick Johnson for the n.m.r. and the infrared spectra. All transfers of analytical samples to preweighed analytical platinum boats enclosed in aluminum pigs for n.m.r. and infrared spectra were performed in a drybox through which dry nitrogen was recirculated after passing through a drying tower.

(18) C. A. Kingsbury and D. J. Cram, *J. Am. Chem. Soc.*, **82**, 1810 (1960).

was transferred to a refrigerator at 5° for 4 hr. to complete the crystallization. The supernatant liquid was decanted and the crystals were triturated with ether. These hygroscopic, electrostatic crystals were transferred to an analytical boat and dried to a constant weight prior to analysis. The infrared spectrum (Nujol) was not free of O–H absorption.

Anal. Calcd. for $C_7H_{13}BF_4O_2S$: C, 33.89; H, 5.28. Found: C, 34.07; H, 5.50.

Co-Reductions with Alkali Metals. I. Styrene and Acetone with Sodium

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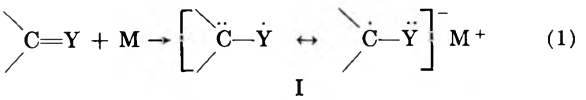
Received February 8, 1963

The reductive condensation of styrene and acetone by sodium metal to form phenylmethylbutanols, dimethylphenylhexanediol, dimethyldiphenyloctanediols, and related co-reduction products has been examined. The formation and distribution of these condensation products are highly solvent dependent. It is postulated that the styrene radical-anion, $PhCH{=}CH_2$, is the intermediate directly responsible for the products of co-reduction. The mechanism of the reactions is discussed with respect to the nucleophilic properties of the styrene radical-anion and the effect of solvent on the dimerization equilibrium to form styrene dimer dianion, $[\cdot\ddot{C}HPh{-}CH_2{-}CH_2{-}\ddot{C}HPh]Na_2$. Initiation by electron transfer from sodium to styrene *via* the ketyl of acetone is discussed.

The addition of alkali metals to multiple bonds of organic compounds to form ion-radical intermediates I is a relatively common process.



(1)

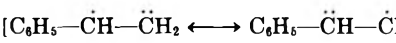
I

Y = C, O, N, etc.
M = alkali metal.

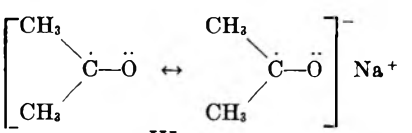
With compounds which contain carbon–carbon unsaturation, such species as I (Y = carbon) have been postulated in the sodium or lithium ammonia[2a] and amine[2b] reduction of aromatic compounds, in displacement reactions[3a] and the polymerization of conjugated olefins such as butadiene[3b,c] and styrene.[4a,b] Such intermediates as I from aromatic compounds also have been detected and studied spectroscopically.[5] In a similar manner heteropolar multiple bonds, especially between carbon and oxygen (Y = oxygen), have been subjected to reaction by alkali metals as in the pinacolic reduction of ketones,[6] acyloin condensation of esters,[7] and reduction of esters to alcohols.[8] Metal ketyls (I, Y = oxygen) have been postulated as intermediates in the reduction of these carbonyl-containing compounds, and also as "carriers" for electron transfer reactions from sodium to peroxides[9] and unsaturated compounds.[10]

In many of these cases where ion-radicals from unsaturated compounds or metal ketyls from carbonyl compounds are formed as intermediates, condensations to yield dimers or polymers as well as simple reduction products result. Although crossed products from unlike unsaturated compounds (for example in the anionic copolymerization of monomers)[3c] or from unlike metal ketyls in mixed acyloin condensations[11] have been effected, crossed condensation between ion radicals from unsaturated compounds and ketyls appears not to have been studied.

In this series of studies we examined the chemistry of radical ions and ketyls derived *simultaneously* as intermediates from alkali metals and such organic compounds possessing unsaturated centers as aromatic, olefinic, carbonyl, and nitrile-containing compounds. In this report we wish to describe the co-reduction[12] of styrene and acetone with sodium. The possible ion-radical intermediates in this case are the styrene radical-anion (II) and the ketyl (III) from acetone.



II



III

These co-reductions, under conditions in which the unsaturated and carbonyl compounds react together with sodium, differ from those condensations of alkali metal adducts of hydrocarbons with electrophilic reagents such as carbon dioxide[13] and ethylene oxide[14] described recently. In the latter cases the alkali metal is first treated with the unsaturated compound to *preform* the organoalkali metal adduct which is then treated with the electrophilic reagent in a subsequent step. These reactions are, thus, essentially those of "conventional" carbanions such as Grignard,[15] organolithium,[16]

(1) Department of Chemistry, Case Institute of Technology.

(2)(a) A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959); J. J. Eisch and W. C. Kaska, *J. Org. Chem.*, **27**, 3745, 4171 (1962); (b) R. A. Benkeser, *J. Am. Chem. Soc.*, **77**, 3230, 3378, 6042 (1955).

(3)(a) D. R. Weyenberg and L. H. Toporcer, *ibid.*, **84**, 2844 (1962); (b) M. Sittig, "Sodium," Reinhold Publishing Co., New York, N. Y., 1956, pp. 313 ff.; (c) A. V. Tobolsky, *et al.*, *J. Polymer Sci.*, **31**, 115, 123 (1958).

(4)(a) M. Szwarc, M. Levy, and R. Milkovich, *J. Am. Chem. Soc.*, **78**, 2657 (1956); (b) C. Geacintov, J. Smid, and M. Szwarc, *ibid.*, **84**, 2508 (1962).

(5)(a) D. E. Paul, D. Lipkin, and S. I. Weissman, *ibid.*, **80**, 5342 (1958); 116 (1956); *J. Chem. Phys.*, **21**, 2227 (1953); **25**, 188 (1956); (b) T. L. Chu and S. C. Yu, *ibid.*, **76**, 3367 (1954); ref. 27, p. 159 f.

(6)(a) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 793 ff.; (b) J. Wieman, *Bull. soc. chim. France*, 63 (1954); *Compt. rend.*, **232**, 1941, 2029 (1951).

(7) M. Kharasch, E. Sternfeld, and F. Mayo, *J. Org. Chem.*, **5**, 362 (1940).

(8)(a) Ref. 4a, p. 286 ff.; (b) G. Darzens, *Compt. rend.*, **224**, 570 (1947); (c) S. M. McElvain, *Org. Reactions*, **4**, Chap. 4 (1948).

(9) J. F. Garst, D. Walmsley, and W. R. Richards, *J. Org. Chem.*, **27**, 2924 (1962).

(10) A. Zilkha, P. Neta, and M. Frankel, *Proc. Chem. Soc.*, 364 (1960).

(11) J. Kapron, *Compt. rend.*, **223**, 421 (1946); *Ann. chim.*, 12, **3**, 117 (1948).

(12) We wish to apply the term "co-reduction" to those condensations effected by alkali metals or related reducing agents in the presence of both components simultaneously.

(13) T. M. Lyssy, *J. Org. Chem.*, **27**, 5 (1962); C. E. Frank and W. E. Foster, *ibid.*, **26**, 303 (1961); C. E. Frank, *et al.*, *ibid.*, **26**, 307 (1961).

(14) J. F. Nobis and E. A. Allgeier, U. S. Patent 2,850,538 (1958).

(15) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954.

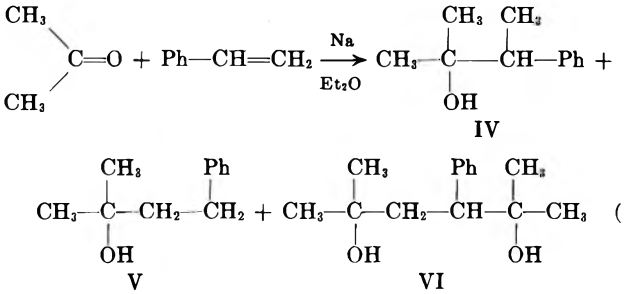
sodium,[17] and aluminum[18] reagents. Although the stoichiometry of both types of reactions is the same, the co-reductions we wish to describe here are more related to the chemistry of radical-anion intermediates.

Results

The reaction of acetone and styrene with sodium is an exothermic one. In most cases the temperature was regulated between $-10°$ and $+10°$, but, if the reaction was allowed to warm up, a reaction ensued which led to polymerization of styrene.

To maintain control, acetone that was diluted in solvent was added dropwise to a stirred mixture of styrene in ethereal solution and freshly pressed sodium wire at the requisite low temperatures. Styrene is polymerized by sodium in ether solvents even at $-10°$. In order to obviate the anionic polymerization of the styrene, it was added to the mixture of sodium and ethereal solvent at $-78°$. Acetone prevented the polymerization of styrene and, if a small amount was added at $-78°$ and the temperature was slowly allowed to rise to $-10°$, the co-reduction could be carried out smoothly with very little polymerization of styrene.

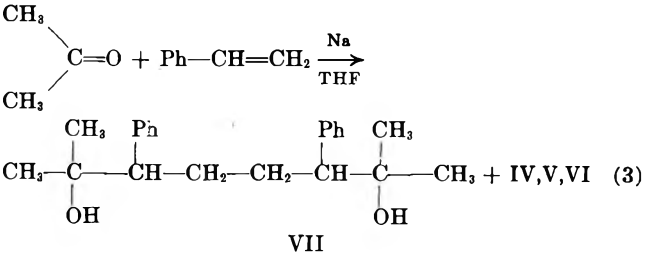
The products obtained from the co-reduction of styrene and acetone are highly dependent on the solvent employed. In diethyl ether the most important products were the 1:1 acetone–styrene adducts, 2-methyl-3-phenylbutanol-2 (IV) (26%) and 2-methyl-4-phenylbutanol-2 (V) (28%), in addition to the 2:1 adduct, 2,5-dimethyl-3-phenylhexanediol-2,5 (VI) (6%).



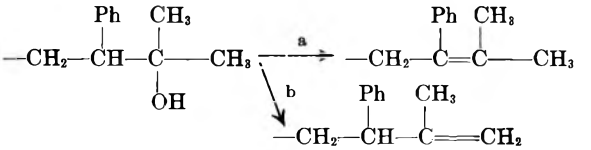
Structures of the isomeric 1:1 adducts IV and V were proved by comparison of their infrared and nuclear magnetic resonance spectra and phenyl carbamate derivatives with authentic samples. The Grignard reaction was used to prepare authentic 2-methyl-3-phenylbutanol-2 from α-phenethylmagnesium bromide and acetone and 2-methyl-4-phenylbutanol-2 from ethyl hydrocinnamate and methylmagnesium iodide.

The structure of the diol VI was assigned primarily on the basis of its elemental and hydroxyl group analysis and molecular weight. The infrared spectrum indicated the presence of a monosubstituted benzene ring and this, together with the nuclear magnetic resonance spectrum indicating two pairs of nonequivalent methyl groups, further strengthened the case for the assignment of structure VI.

In tetrahydrofuran as solvent, the most important product was the 2:2 acetone–styrene adduct, 2,7-dimethyl-3,6-diphenyloctanediol-2,7 (VII) (31%), in addition to 1:1 adducts (13%) IV and V, and the 2:1 adduct (2%) VI.

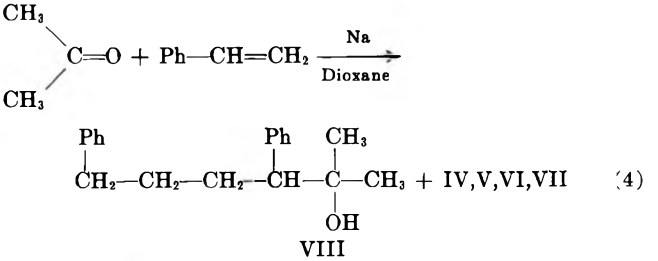


Diol VII was isolated in two diastereomeric forms which melted at 118° and 138°. These two isomers, which exhibited different solubility behavior, both underwent facile iodine-catalyzed dehydration to a mixture of diolefins. In each case the mixture of diolefins was ozonized to yield 1,2-dibenzoylethane in 21% (118° isomer) and 46% (138° isomer) yields, in addition to other ketonic products which were not identified. Although electronic factors controlling the dehydration of a tertiary alcohol such as VII would favor the internal olefin (a), it is possible that steric control[19] may be imposed by the neighboring groups to cause a significant amount of dehydration to the terminal position (b). The less than quantitative yields of dibenzoylethane are attributed to partial dehydration through route b.



Infrared spectra of the ketonic by-products indicated the presence of carbonyl groups at saturated (5.82 μ) center as well as at unsaturated centers (5.95 μ) and are compatible with a mixture consisting of diacetyl and acetyl–benzoyl end groups.

In dioxane–diethyl ether solutions (80% by volume) a mixture of all four compounds, IV (7%), V (8%), VI (16%), and VII (27%), in addition to the 1:2 acetone–styrene adduct, 2-methyl-3,6-diphenylhexanol-2 (VIII) (27%), was formed.



Diphenylhexanol VIII was easily dehydrated with iodine to yield an olefin which, on ozonolysis, yielded, 1,4-diphenylbutanone-1 (IX) in 88% yield. (see p. 1962, col. 1)

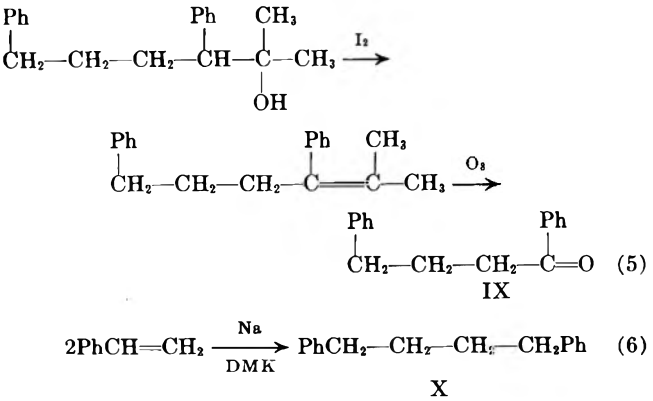
In addition to these alcohols the simple reduction products isopropyl alcohol and ethylbenzene were formed in small yields. The homobimolecular reduction product from styrene, 1,4-diphenylbutane (X), was formed in varying yields depending on the temperature of the reaction. The isomeric 1,3-diphenyl- and 2,3-diphenylbutanes were not formed.

(16) D. L. Esmay, in "Metal-Organic Compounds," Advances in Chemistry Series, American Chemical Society, Washington, D. C., 1959, p. 46 ff.

(17) J. F. Nobis, L. F. Moormeir, and R. E. Robinson, *ibid.*, p. 63 ff.

(18) K. Ziegler, in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold Publishing Corp., New York, N. Y., 1960, p. 194 ff.

(19) H. C. Brown, *et al.*, *J. Am. Chem. Soc.*, **77**, 3607, 3610, 3614, 3619, 3623 (1955).



IX (5)

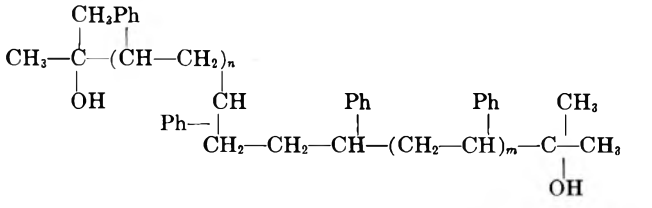
X (6)

Bimolecular reduction product from acetone, pinacol, was not found, although under the alkaline conditions of the experiments the acetone condensation products, mesityl oxide, isophorone, and a crystalline ketone, were present, especially when acetone was added in excessive amounts. In tetrahydrofuran in the absence of olefin, acetone was reduced by sodium solely to isopropyl alcohol.

The effect of a *carbon dioxide atmosphere* on the reaction is a *retarding one*. In the presence of carbon dioxide the reaction of sodium with acetone and styrene was very slow under the usual reaction conditions. However, at elevated temperatures the reaction proceeded quite readily. Thus, if a nitrogen atmosphere is replaced by carbon dioxide, the reaction in diethyl ether could be carried out at 65° and slight excess carbon dioxide pressure in a controllable manner, whereas under the usual operating conditions extensive homopolymerization of styrene would have resulted at these temperatures.

It is interesting to note that the yields of 1,4-diphenylbutane and ethylbenzene at 65° were significantly higher under these conditions than at 0° and the absence of carbon dioxide. The low yields of carboxylic acids formed under a carbon dioxide atmosphere indicated that the concentration of carbon dioxide in solution at the elevated temperatures was small (probably due to the high partial pressure of the solvent).

In addition to solvent and temperature effects the yields of products also were dependent on the concentration of the olefinic component. In fairly concentrated solutions, telomers higher than the 2:2 adduct were formed. Polystyrene (mol. wt., 150,000), containing the dimethylcarbinol end groups, in addition to an amorphous mixture of lower molecular weight (~500) material which contained three and four styrene units associated with two acetone moieties, was observed. The structures of these compounds taken by analogy with lower condensation products are assigned as XI.



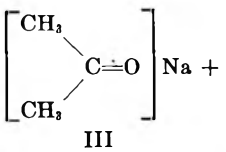
XI

Conditions for the optimum formation of these higher molecular weight products were not explored further.

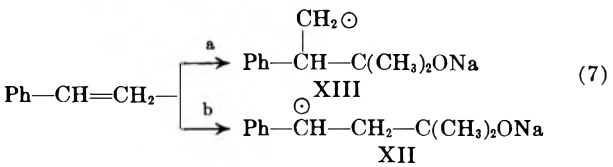
The reaction of diacetone alcohol and styrene with sodium yielded products which are the same as those obtained with acetone. Less contamination from mesityl oxide and isophorone, however, was apparent. The retroaldol reaction of diacetone alcohol is apparently faster than the condensation with styrene under these conditions.

Discussion

The co-reduction of styrene and acetone with sodium is more akin in many ways to the anionic polymerization of styrene than the pinacolic reduction of acetone. Although sodium ketyl may be actually the first intermediate in the reaction (*vide infra*), the actual intermediate which leads directly to products appears to be the styrene radical-anion II. There is no direct evidence that sodium ketyl reacts with styrene in a reaction such as 7 to form the radical-alkoxides XII or XIII, and ultimately to yield the 1:1 reduction products IV and V, respectively, by either an electron

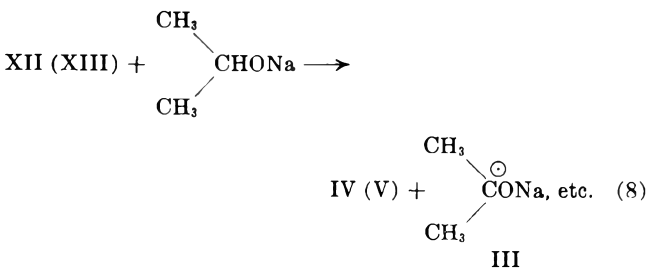


III



XII (7)

transfer to the anion-alkoxide followed by proton transfer or by a free radical chain transfer of hydrogen. With respect to the latter, isopropyl alcohol or its sodium salt, which are reasonably effective radical chain transfer agents for free alkyl radicals such as XII or XIII, did not increase the yield of either IV or V. The possibility of a radical chain addition (7, 8) of sodium isopropoxide to styrene *via* a ketyl intermediate



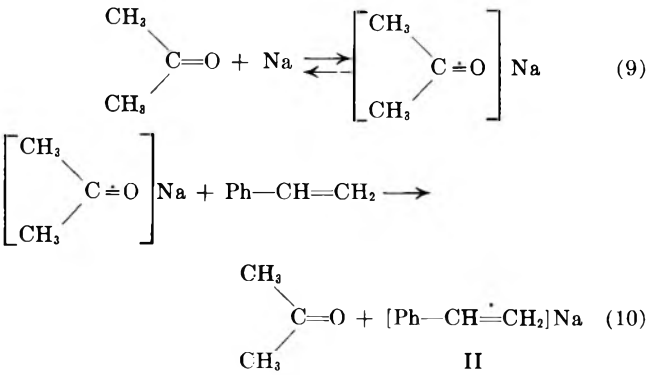
III (8)

was, therefore, not realized. On the contrary, active hydrogen compounds decreased the yields of co-reduction products by reacting directly with sodium metal. Furthermore the addition, if possible, of sodium ketyl to styrene is expected not to differ significantly from the behavior of other free radicals to styrene.[20] The formation of the 1:1 adduct IV in amounts equal to the isomeric V by a ketyl addition to styrene as in reactions 7 is highly unlikely since free radical addition would be expected to occur more readily at the β-position of styrene to produce the more stable benzylic radical XIII. That ketyl is formed is indicated by the formation of small amounts of isopropyl alcohol from acetone even in the presence of styrene. The ketyl itself, how-

(20) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957.

ever, does not appear to be the addendum directly responsible for the co-reduction products.

On the other hand, if the styrene radical-anion II is postulated as the intermediate leading directly to products, a more coherent reaction path can be delineated. This olefin radical-anion could be formed in the primary step from sodium as evidenced by the formation initially of colored intermediates when styrene is added to sodium; the color is readily discharged by carbonylic compounds. We have observed qualitatively that the rate of co-reduction of styrene with carbonyl compounds varies significantly[21] with the structure of the carbonyl component. For this reason we prefer an alternative postulation in which the styrene radical-anion is formed by electron transfer from an initially formed sodium ketyl to styrene.



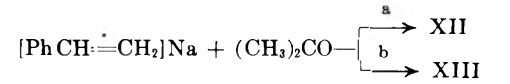
(9)

(10)

It can be argued, mainly on intuitive grounds, that the more electronegative carbonyl group would be reduced to the anion-radical in competition with the olefin moiety. The relative rates of reduction of compounds such as these by sodium are unknown, but *thermodynamic* values of the energy changes involved may be of some guide. Streitwieser[22a] has shown that in a series of related compounds, the polarographic reduction potentials are related to the energies of the lowest unoccupied molecular orbital. The half-wave potentials[22b] of acetone (−2.46 *vs.* S.C.E.) and styrene (−2.35 volts *vs.* S.C.E.) in 75% dioxane are similar. We have made crude Hückel molecular orbital calculations of the energies of the lowest unoccupied molecular orbitals in acetone and styrene, and they indicate that the formation of the ketyl III requires about 2 kcal./mole less energy than the formation of the styrene radical-anion II. Thus, the relative values of the polarographic reduction potentials of acetone and styrene are reasonably consistent with the calculated energies of the lowest unoccupied molecular orbital. If these gross thermodynamic comparisons are valid, it might be expected that they may be interpreted in terms of activation processes[22c] if, in addition, the electronegative oxygen atom in acetone facilitates the rate of electron transfer from the sodium surface.

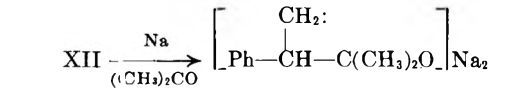
The variation in rates of reaction with the carbonyl component is then attributed to the formation of ketyls in the initial step. The subsequent electron transfer from ketyl to olefin[10] has been demonstrated with benzophenone ketyl[9] and the naphthalene radical-anion[23] as initiators in anionic polymerizations and as reducing agents.

The styrene radical-anion in diethyl ether solvent reacts as a nucleophile[24] with acetone at either the α- or β-position to produce the isomeric 4-phenylbutyl and 3-phenylbutyl radicals XII and XIII, respectively.[25]



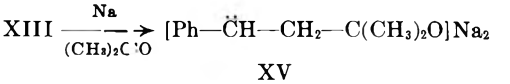
(11)

The radical-alkoxides XII and XIII are easily reduced[7] further by sodium or ketyl to the dianions XIV and XV, respectively, which react with acetone by proton



(12)

XIV



(13)

XV

transfer to yield the isomeric 1:1 adducts, IV and V, or by addition to the carbonyl group to yield the 1:2 styrene–acetone adduct, VI.

Since this bimolecular reaction must compete with the polymerization of styrene, the free energy of activation of the addition of the styrene radical-anion to acetone must be lower than that of the addition to styrene. The anionic polymerization of styrene is exothermic and the activation energy of the propagation step is low (1.0 kcal./mole in tetrahydrofuran).[4,25] It can be concluded on the basis of Hammond's postulate[26] that the transition state of the addition of styrene radical-anion to styrene has a high degree of *carbanionic* character. By the same token, the transition state for the addition of the styrene radical-anion to acetone must have at least as much or more carbanionic character. Therefore, the relative spin densities at various positions in the styrene radical-anion can serve as a suitable model for determining the relative rates of reaction of acetone at these positions of the radical-anion. In Fig. 1 is given the calculated spin densities in the radical-anion, using the simple Hückel molecular orbital method.[27]

This model correctly predicts[28a] that nucleophilic centers of the styrene radical-anion reside at both the

(21) See following paper, J. K. Kochi, *J. Org. Chem.*, **28**, 1969 (1963).

(22)(a) Ref. 27, p. 173 ff. (b) I. M. Kolthoff and J. J. Lingane, "Polarography," Vol. 2, Interscience Publishers, New York, N. Y., 1952, pp. 635, 661. (c) The correlation between electron density and the rate of proton transfer has been applied to the reduction of unsaturated hydrocarbons at the dropping mercury electrode by Hoijtink [*Rec. trav. chim.*, **76**, 885 (1957); **72**, 691 (1953); **71**, 1089 (1952)] and by Streitwieser (ref. 27, p. 425) to the reduction of aromatic compounds by alkali metals in the presence of a proton source. See also discussion presented earlier.

(23)(a) M. Szwarc, *Makromol. Chem.*, **35**, 133 (1960); (b) M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, **82**, 521 (1960); (c) A. V. Tobolsky and D. B. Hartley, *Ibid.* **84**, 1391 (1962).

(24) The rate of addition of styrene radical-anion to acetone is certainly not so fast as the reaction of a conventional organosodium compound since the negative charge is delocalized in the radical-anion. The relative rate of addition of these nucleophiles to acetone compared to styrene should be much faster if taken in analogy with organometallic reagents such as Grignard compounds, etc.[15-18]

(25) Radical alkoxides XII and XIII are the same intermediates as those produced by the addition of acetone ketyl to styrene by another mechanism (*vide supra*).

(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(27) A. Streitwieser, "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961.

(28)(a) This assumes that the additions are irreversible and that the subsequent reduction followed by protonation of the radical-alkoxides, XII and XIII, proceed in comparable fashion. See also J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, New York, N. Y., 1956, p. 207 ff. (b) The relative high electron density at the *para*-position would indicate the formation of another isomer, *p*-ethylphenyldimethyl carbinol, as a possibility. We observed no such product.

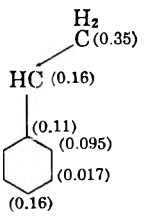


Fig. 1.—Spin densities at various positions in the styrene radical-anion.

α- and β-carbon atoms. The formation of the isomeric (1:1) adducts IV and V are in accord with this.[28b]

The same result, however, is obtainable if a styrene dianion XVI is postulated as an intermediate whose condensation with acetone occurs more or less randomly at either the α- or β-position. It is unlikely that

$$[\mathrm{Ph{-}CH{=}CH_2}]\mathrm{Na} + \mathrm{Na} \rightleftharpoons \underset{\text{XVI}}{[\mathrm{Ph{-}\ddot{C}H{-}\ddot{C}H_2}]\mathrm{Na_2}} \quad (14)$$

$$2[\mathrm{Ph{-}CH{=}CH_2}]\mathrm{Na} \rightleftharpoons \mathrm{PhCH{=}CH_2} + [\mathrm{Ph{-}\ddot{C}H{-}\ddot{C}H_2}]\mathrm{Na_2} \quad (15)[28]$$

the formation of such a dianion from the styrene radical-anion[29] can compete with such processes of low activation energy as condensation or proton transfer with acetone or polymerization. Moreover, there is no *a priori* basis for styrene radical-anion to be reduced more easily to the dianion by electron transfer in ether than in tetrahydrofuran[31] (*vide infra*). The formation of ethylbenzene is not necessarily evidence in favor of the styrene dianion XVI since it is possible for it to arise *via* two successive pairs of electron and proton transfers from styrene.

In tetrahydrofuran as solvent, the 1:1 and 2:1 acetone–styrene adducts are replaced largely by 2:2 (VII) and 1:2 (VIII) adducts and 1,4-diphenylbutane, which arise from the dimer dianion XVII by condensation with either two or one acetone moieties or by proton transfer.

$$\underset{\text{XVII}}{[\mathrm{Ph{-}\ddot{C}H{-}CH_2{-}CH_2{-}\ddot{C}H{-}Ph}]\mathrm{Na_2}} + (\mathrm{CH_3})_2\mathrm{CO} \longrightarrow$$

$$\mathrm{Ph{-}\ddot{C}H{-}CH_2{-}CH_2{-}\underset{\text{XVIII}}{\underset{|}{\overset{\mathrm{Ph}}{\overset{|}{\mathrm{C}}}}H{-}C(CH_3)_2ONa}} \quad (16)$$

$$\underset{\text{XIX}}{\left[\mathrm{{-}CH_2{-}\overset{\mathrm{Ph}}{\overset{|}{\mathrm{C}}}H{-}C(CH_3)_2O{-}}\right]_2\mathrm{Na_2}}$$

$$\mathrm{XVIII} + (\mathrm{CH_3})_2\mathrm{CO} \begin{cases} \xrightarrow{a} \\ \xrightarrow{b} \end{cases} \quad (17)$$

$$\mathrm{Ph{-}CH_2CH_2CH_2\overset{\mathrm{Ph}}{\overset{|}{\mathrm{C}}}H{-}C(CH_3)_2ONa} + \mathrm{CH_3COCH_2Na}$$
$$\text{XX}$$

The dimer dianion (XVII) can arise *via* several paths: the dimerization of styrene radical-anion (18)[4a] or the addition of the styrene radical-anion to styrene (19)

$$2[\mathrm{Ph{-}CH{=}\dot{C}H_2}]\mathrm{Na} \rightleftharpoons \underset{\text{XVII}}{[\mathrm{Ph\dot{C}H{-}CH_2CH_2{-}\dot{C}HPh}]\mathrm{Na_2}} \quad (18)$$

to form the dimer anion-radical XXI followed by reduction (20) by electron transfer to the dimer dianion XVII.

$$[\mathrm{Ph{-}CH{=}\dot{C}H_2}]\mathrm{Na} + \mathrm{Ph{-}CH{=}CH_2} \longrightarrow \underset{\text{XXI}}{[\mathrm{Ph{-}\dot{C}H{-}CH_2CH_2{-}\dot{C}H{-}Ph}]\mathrm{Na}} \quad (19)$$

$$\mathrm{XXI} + \mathrm{Na(S)} \longrightarrow \mathrm{XVII} \quad (20)$$

The formation of the 2:2 diastereomeric adducts VII by the former path through the dimer dianion (equations 16–17) is preferred to alternative paths. Since the activation energies for the dimerization of carbon radicals is generally low, the coupling of the radical alkoxide XIII to the dialkoxide XIX should not be favored particularly over the coupling of the isomeric radical-alkoxide XII or the mixed coupling of XII and XIII. Therefore, the absence of structural isomers of the 2:2 adducts VII precludes the formation of the latter by this route. Alternatively, the dimer anion-radical XXI could condense with acetone to form the dimer radical-alkoxide XXII as an intermediate which subsequently is reduced by electron transfer to the dimer

$$\mathrm{XXI} + (\mathrm{CH_3})_2\mathrm{CO} \longrightarrow$$

$$\mathrm{Ph{-}\dot{C}H{-}CH_2CH_2{-}\underset{\text{XXII}}{\underset{|}{\overset{\mathrm{Ph}}{\overset{|}{\mathrm{C}}}}HC(CH_3)_2ONa}} \quad (21)$$

anion-alkoxide XVIII followed by reaction 17. However, it is not expected that the free radical intermediates are of such reactivity to enable these reactions to compete with their facile destruction by electron transfer.[2,4,23,25,32]

The validity of the latter alternative path (equations 19 and 21) for the formation of 2:2 adducts is difficult to assess, but we question whether the dimer anion-radical XXI or the dimer radical-alkoxide XXII are significant intermediates in these reactions.

Szwarc in his extensive studies of the mechanism of anionic polymerization has indicated that with olefins such as 1,1-diphenylethylene[33] and α-methylstyrene,[34] the rate constants for dimerization of the radical-anion, and the addition of the radical-anion to another olefin unit are within orders of magnitude the same. Our qualitative results, of course, cannot serve to distinguish between these two possibilities for the formation of the dimer dianion XVII.[35] However, we disfavor the dimer radical-anion as an intermediate in our co-reduction reactions. There is a rather striking alteration in the complexion of the reaction from the formation of monomeric styrene products (*i.e.*, 1:1 and 2:1 acetone–styrene adducts) in diethyl ether to largely dimeric styrene products (2:2 and 1:2 acetone–styrene adducts)

(29) The dianion XVI possibly could also be formed by the disproportionation of the styrene radical-anion.[4b]

(30) J. F. Garst and R. S. Cole, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N.J., September, 1962, p. 5Q.

(31) However, Garst and Cole[30] have shown recently that in an equilibrium such as 15 involving tetraphenyl ethylene, good solvating media such as dimethoxyethane favor the radical-anion and diethyl ether favors the dianion. The analogy applicable to tetraphenylethylene cannot be extended easily to styrene because the absence of phenyl groups to stabilize the methylene carbanionic center in the styrene dianion XVI.

(32) Since the electron transfer reaction is partially heterogeneous, the surface area as well as the state of the surface of the sodium and the steady state concentration of ketyls will affect these rates.

(33) G. Spach, H. Monteiro, M. Levy, and M. Szwarc, *Trans. Faraday Soc.*, **58**, 1809 (1962).

(34) M. Szwarc and R. Asami, *J. Am. Chem. Soc.*, **84**, 2269 (1962).

(35) That is, after electron transfer to the dimer anion-radical formed by the addition process.

in tetrahydrofuran. This is difficult to reconcile with the occurrence of a reaction sequence such as 19 and 21 (which involve the dimer radical-anion XXI as an intermediate) as a major route for the production of dimeric styrene adducts XIX and XX.[36] It is known that solvents such as tetrahydrofuran facilitate solvation of alkali ketyls[37] and anion-radicals.[39] The change in the course of the co-reduction with solvent can be reasonably accommodated if the dimerization of styrene radical-anion (equation 18) is considered reversible.[40] The variation in the complexion of the products with solvent can then be attributed to the different equilibrium (or steady state) concentrations of the styrene radical-anion as monomer II or dimer XVII in tetrahydrofuran, dioxane, and diethyl ether solvents. The equilibrium constant for formation of the dimer dianion would be expected to be favored by such solvents as tetrahydrofuran, dioxane and, to a higher degree, dimethoxyethane (a solvent unfortunately not employed in these studies) and less favored by the relatively poorly solvating diethyl ether.[41,42]

The inhibitory effect of carbon dioxide is at present not explained too adequately. Since the reaction is heterogeneous the surface of the sodium is an important factor to be considered. It is possible that the carbon dioxide reacts with either styrene radical-anion or the dimer dianion[13] to form insoluble sodium carboxylates. This is apparent by the dull surface of the sodium when a carbon dioxide atmosphere is maintained. Whether carbon dioxide also prevents electron transfer from sodium by some other mechanism is unclear.

Experimental

Materials.—Sodium: A. R. grade, Mallinckrodt Chemical Works. Ether: A. R. grade, Mallinckrodt Chemical Works. Tetrahydrofuran: Du Pont Co., refluxed with lithium aluminum hydride two days and distilled, under nitrogen, b.p. 68°. Dioxane: Du Pont Co., distilled from potassium hydroxide and then from lithium aluminum hydride. Styrene: Eastman Kodak, distilled, b.p. 49.5–50.5 (25 mm.). Carbon dioxide: Pureco (99.87 +%) passed over manganous oxide (gas reduced, Foote Chemical Co.), at 150° then through a tube packed with lithium aluminum hydride.

Synthesis of 1-Methyl-3-phenylbutanol-2.—The Grignard reagent of α-bromoethylbenzene (50 g.) was prepared from 12 g. of magnesium. It was treated with 20 g. of acetone in 50 ml. of ether. The reaction mixture separated into two liquid layers, but it was worked up in the usual manner using ammonium chloride. The crude ethereal solution on distillation yielded 5 g. of desired alcohol, 2-methyl-3-phenylbutanol-2 (b.p. 62–63° (1 mm.); m.p. 40–42°; $n^{20}D$ 1.5161; lit.[43] b.p. 105–107° (12 mm.); $n^{20}D$ 1.5193) and 33 g. of 2,3-diphenylbutane (recrystallized from methylcyclohexane–petroleum ether, (b.p. 40–50°)) (m.m.p. 125–126°). The phenylurethane of 2-methyl-3-phenylbutanol-2 was made by heating on a steam bath a solution of 1 g. of the alcohol, 0.5 g. of phenyl isocyanate, and 1 drop of pyridine in a sealed tube for 36 hr. It was recrystallized twice from petroleum ether (b.p. 40-50°) (m.p. 101.5–102.0°).

Anal. Calcd. for 2-methyl-3-phenylbutanol-2 ($C_{11}H_{16}O$): C, 80.5; H, 9.82. Found: C, 79.67, 79.82; H, 9.87, 9.86.

Anal. Calcd. for urethane of 2-methyl-3-phenylbutanol-2 ($C_{18}H_{21}NO_2$): C, 76.4; H, 7.48; N, 4.95. Found: C, 76.3 H, 7.77; N, 5.00.

Anal. Calcd. for 2,3-diphenylbutane ($C_{16}H_{18}$): C, 91.4; H, 8.6. Found: C, 91.7; H, 8.6.

Synthesis of 2-Methyl-4-phenylbutanol-2.—This alcohol was prepared by K. Dewhirst from ethyl hydrocinnamate and methylmagnesium iodide. Further rectification through a spinning band column gave material boiling at 86–87° (1 mm.) ($n^{20}D$ 1.5103). The urethane was prepared by heating a mixture of 1 g. of alcohol with 0.5 g. of phenyl isocyanate and 1 drop of pyridine in a sealed tube over a steam bath for 18 hr.; recrystallization from petroleum ether (b.p. 40–50° yielded material melting at 138.5–139.5° (lit.[44] m.p. 138–139°)).

Anal. Calcd. for 2-methyl-4-phenylbutanol-2 ($C_{11}H_{16}O$) C, 80.5; H, 9.86. Found: C, 79.6; H, 9.8.

Anal. Calcd. for urethane of 2-methyl-4-phenylbutanol-2 ($C_{18}H_{21}NO_2$): C, 76.4; H, 7.48; N, 4.95. Found: C, 76.1 H, 7.6; N, 4.92.

Synthesis of 1,4-Diphenylbutane.—Phenethyl Grignard reagent was prepared from α-phenethyl chloride (10 g.) and magnesium (4 g.) in ether. Anhydrous cobaltous chloride (1 g.) and α-phenethyl chloride (5 g.) were added and the reaction refluxed for 1 hr. Water was added and the reaction worked up in the usual manner. 1,4-Diphenylbutane was obtained in 31% yield (b.p. 127–131° (3.5 mm.), m.p. 52–53°).

Anal. Calcd. for 1,4-diphenylbutane ($C_{16}H_{18}$): C, 91.5; H, 8.63; mol. wt. (cryoscopic in dioxane), 210. Found: C, 91.5; H, 8.6; mol. wt., 185 ± 5.

Synthesis of 2,5-Dimethyl-3-phenylhexanediol-2,5.—The subject diol was obtained from the reaction of styrene and acetone with sodium in ether (*vide infra*) and represented the condensation of two acetone units with one of styrene. After repeated rectification it was obtained pure (b.p. 130–132° (2 mm.), $n^{20}D$ 1.5272). On prolonged standing it crystallized into dense crystals, m.p. 73–74°. The crystalline diol, however, after melting, supercooled badly and was difficult to crystallize. A solution of the diol in isopentane on chilling in a Dry Ice bath absorbed enough moisture to deposit fine needles of hemihydrate, m.p. 62–63°.

Anal. Calcd. for 2,5-dimethyl-3-phenylhexanediol-2,5 ($C_{14}H_{22}O_2$): C, 75.6; H, 9.97; hydroxyl value (equiv./100 g.), 0 900; mol. wt., 222. Found: C, 75.4, 75.7; H, 10.0, 10.1; hydroxyl value, 0.894; mol. wt., 228 ± 7.

Anal. Calcd. for 2,5-dimethyl-3-phenylhexanediol-2,5-hemihydrate ($C_{14}H_{22}O_2 \cdot 1/2\ H_2O$): C, 72.8; H, 10.0; mol. wt. (ethanol azeotrope), 231.3; hydroxyl value ($LiAlH_4$), 0.862; water (% weight) (Fischer), 3.9. Found: C, 72.9, 72.7; H, 10.1, 10.0; mol. wt., 242 ± 7; hydroxyl value, 0.85; water, 3.8.

Synthesis of 2-Methyl-3,6-diphenylhexanol-2 ($C_{19}H_{24}O$).—The subject alcohol was a product obtained from the reaction of styrene and acetone with sodium in dioxane (*vide infra*) and represented the incorporation of two styrene moieties with each acetone. Distillation yielded material boiling at 168–175° at 2.5 mm. which was a viscous liquid ($n^{25}D$ 1.5483), but could not be crystallized. A urethane was prepared from a mixture of 2 g. of the alcohol, 1 g. of phenyl isocyanate, and 1 drop of pyridine heated in a sealed tube on a steam bath for 60 hr. It was recrystallized from *n*-hexane to yield phenylurethane melting at 122.5–123.0°.

Anal. Calcd. for 2-methyl-3,6-diphenylhexanol-2 ($C_{19}H_{24}O$):

(36) Unless solvent plays a larger role in the addition of the styrene radical-anion to styrene than it does with addition to acetone. Alternatively the formation of the dimer radical-anion could be reversible and the equilibrium constant highly solvent dependent.

(37) The mechanism of this solvation has not been fully developed.[38-41]

(38) J. F. Garst, *et al.*, *J. Am. Chem. Soc.*, **83**, 5034 (1961); J. F. Garst and R. J. Cole, *ibid.*, **84**, 4352 (1962).

(39) R. L. Ward and S. I. Weissman, *ibid.*, **79**, 2086 (1957).

(40) M. Szwarc and R. Asami[34] have given a value, however, for the activation energy of the dimer dianion from 1,1-diphenylethylene as approximately 10 kcal., and the rate of dissociation (8×10^{-7} sec.$^{-1}$ at 30°) is estimated to be approximately an order of magnitude faster than that of the dimer dianion of α-methylstyrene.

(41)(a) N. D. Scott, J. F. Walker, and V. L. Hansley, *J. Am. Chem. Soc.*, **58**, 2442 (1936); (b) G. E. Coates, "Organo-Metallic Compounds," Methuen and Co., London, 1960, p. 33.

(42) For example the dimerization equilibrium of benzophenone ketyl is highly solvent dependent.[6a]

$$2[Ph_2C{=}O]Na \rightleftharpoons (Ph_2CO)_2Na_2 \qquad (22)$$

However, at present the effect solvents will have on such reversible equilibria as 18 and 22 is difficult to state unequivocably. If solvents such as tetrahydrofuran and dimethoxyethane solvate the metal cations,[41] they also would serve to put more of an effective charge on the anionic centers. If such is the case, these solvents should increase the forces of coulombic repulsions in the dimer dianion and *decrease* the formation constants of these dianions relative to those in poorly solvating media. If these solvents affect the degree or kind of ionic aggregates in solution,[38] they may well stabilize dianions.

(43) A. Lepin, *Chem. Zentr.*, **IIb**, 2080 (1912).

(44) A. Birch, *J. Chem. Soc.*, 809 (1945).

C, 85.0; H, 9.03; mol. wt., 268.4; hydroxyl value (equiv./100 g.), 0.373. Found: C, 84.5, 84.7; H, 9.2, 9.1; mol. wt., 284 ± 5; hydroxyl value, 0.368, 0.405.

Anal. Calcd. for urethane of methyldiphenylhexanol ($C_{25}H_{27}O_2N$): C, 80.3; H, 7.28; N (Kjeldahl), 3.75. Found: C, 80.60, 80.68; H, 7.55, 7.62; N, 3.61, 3.69.

The Proof of Structure of 2-Methyl-3,6-diphenylhexanol-2. Iodine Dehydration.—A mixture of 6 g. of 2-methyl-3,6-diphenylhexanol-2 and 0.1 g. of iodine was intimately ground.[45] It was then heated to 130° for 0.5 hr. under nitrogen. Water and iodine were then distilled *in vacuo*. The residue (containing no hydroxyl bands in the infrared spectrum) was taken up in isopentane, washed twice with sodium bisulfite solution, and then added dropwise to a refluxing mixture of 13 g. of zinc dust and 75 ml. of ethanol over 0.5 hr. The mixture after refluxing for 2 hr. was diluted with water and extracted with *n*-pentane. The solution after drying overnight with calcium chloride was distilled *in vacuo* to yield 4.5 g. of hydrocarbon boiling at 147.5–149.5° at 2 mm. ($n^{25}D$ 1.5542–1.555). The infrared spectra of all the fractions were the same.

Anal. Calcd. for 2-methyl-3,6-diphenylhexene-2 ($C_{19}H_{22}$): C, 91.1; H, 8.85; bromine no. (g./100 g.), 63.8. Found: C, 91.1, 91.3; H, 8.8, 9.0; bromine no., 69.3.

Ozonolysis.—A solution of 2.3 g. of 2-methyl-3,6-diphenylhexene-2 in 15 ml. of methylene chloride was ozonized at −78°.[46] The methylene chloride solution was added dropwise to a refluxing 50% solution of aqueous acetic acid and 3 g. of zinc dust. The mixture was refluxed for 1.5 hr. after the methylene chloride had distilled. It was then taken up in ether, and the ethereal solution washed with aqueous sodium iodide (2%), dilute sodium hydroxide (8%), dilute hydrochloric acid, and twice with water, and dried with calcium chloride. Distillation of the ether yielded a ketonic oil. Sublimation of the oil (50–65° at 3 mm.) yielded a colorless solid (1.8 g., 88%, m.p. 55.0–55.5°) identified as 1,4-diphenylbutanone-1 (lit.[47] m.p. 55–56°).

Anal. Calcd. for 1,4-diphenylbutanone-1 ($C_{16}H_{16}O$): C, 85.7; H, 7.15. Found: C, 85.4; H, 7.2.

A 2,4-dinitrophenylhydrazone derivative recrystallized from ethyl acetate–ethanol solutions yielded orange needles (m.p. 145.0–145.5°; lit.[48] m.p. 144.5–145.0°).

Anal. Calcd. for 1,4-diphenylbutanone-1 2,4-dinitrophenylhydrazone ($C_{22}H_{20}N_4O_4$): C, 65.3; H, 4.98; N, 13.84. Found: C, 65.1; N, 4.8; N, 13.9.

Synthesis of 2,7-Dimethyl-3,6-diphenyloctanediol-2,7.—The diol, 2,7-dimethyl-3,6-diphenyloctanediol-2,7, exists as two diastereoisomers, *dl* and *meso*. Both compounds were isolated from the reaction of styrene and acetone with sodium in dioxane or tetrahydrofuran and represented the condensation of two styrene and two acetone units. They were crystalline compounds recrystallizable from methylcyclohexane and were roughly separable by cooling their concentrated solution in isopentane, whereupon the higher melting isomer crystallized quickly. Filtration and further standing allowed the lower melting isomer to separate. They were further purified by recrystallization from absolute ethanol in which the higher melting isomer was quite soluble and the lower melting isomer crystallized in beautiful hexagonal crystals containing loose molecules of solvation. The ethanol of solvation deliquesced in air to leave a colorless white solid (m.p. 118–119°; b.p. 192–196° (1 mm.)). The higher melting isomer was recrystallized from methylcyclohexane to yield colorless crystals melting at 135.5–136.0°. The diurethane of the 118° isomer melted with decomposition at 188.5°.

Anal. Calcd. for 2,7-dimethyl-3,6-diphenyloctanediol-2,7 ($C_{22}H_{30}O_2$) (118° isomer): C, 81.0; H, 9.27; hydroxyl value (equiv./100 g.; $LiAlH_4$), 0.613. Found: C, 81.44, 81.38; H, 9.32, 9.33; hydroxyl value, 0.605.

Anal. Calcd. for bisphenylurethane of dimethyldiphenyloctanediol-2,7 ($C_{36}H_{40}O_4N_2$) (118° isomer): C, 76.6; H, 7.15; N, 4.96. Found: C, 76.7, 76.9; H, 7.3, 7.4; N, 4.97.

Anal. Calcd. for 2,7-dimethyl-3,6-diphenyloctanediol-2,7 ($C_{22}H_{30}O_2$) (136° isomer): C, 81.0; H, 9.27; hydroxyl value, 0.613. Found: C, 81.0; H, 9.3; hydroxyl value, 0.606.

Proof of Structure of 2,7-Dimethyl-3,6-diphenyloctanediol-2,7 118° Isomer.—A mixture of 1.50 g. of diol and 0.05 g. of iodine was heated under nitrogen for 1 hr. The water and iodine were vacuum distilled and the residue taken up in chloroform. The chloroform solution was added to a refluxing mixture of zinc and ethanol and heated for an additional hour after distilling the chloroform. The mixture was diluted with water and taken up in *n*-hexane. The hexane solution was washed with sodium thiosulfate and water, dried with calcium chloride, and distilled from zinc dust. The first fraction (b.p. 146–148° (2 mm.)) crystallized on standing. Recrystallization from isopentane yielded colorless crystals (m.p. 112–114°). The presence of infrared absorption bands at 10.25 and 10.9 μ indicated that the olefin probably contained the *isopropenyl* structure.

Anal. Calcd. for $C_{22}H_{26}$: C, 91.0; H, 9.0. Found: C, 91.0; H, 9.1.

The major dehydration product (1 g.) boiled at 148–149° at 2 mm. ($n^{25}D$ 1.5588) and could not be crystallized. It was ozonized in methylene chloride solution at −78°. The ozonide was treated with refluxing ethanol and zinc dust to yield 0.8 g. of ketonic oil and 0.25 g. (21%) of dibenzoylethane. Recrystallization of the 1,2-dibenzoylethane from absolute alcohol yielded colorless needles (m.p. 144.5–145.5°).

Anal. Calcd. for 1,2-dibenzoylethane ($C_{16}H_{14}O_2$): C, 80.6; H, 5.92. Found: C, 79.8, 79.9; H, 6.0, 6.2.

The infrared spectrum (potassium bromide) was identical with an authentic sample.[49] The ketonic oil was treated with DNP reagent but yielded a mixture of 2,4-dinitrophenylhydrazones which were not further investigated.

The crystallized olefin was also ozonized but did not yield the easily identifiable dibenzoylethane. The ketonic product was treated with DNP reagent to give a yellow DNP (m.p. 150–154°, recrystallized twice from aqueous ethanol solutions).

136° Isomer.—The diol (10 g.) was dehydrated by heating with iodine (0.1 g.) at 140–150°. The water and iodine were vacuum distilled and the residue treated with zinc and ethanol in the usual manner to yield 8 g. of hydrocarbon boiling at 151–152° ($n^{25}D$ 1.5582–1.5588). The infrared spectrum was quite similar (especially in the fingerprint region) to the liquid olefin obtained from the dehydration of the 118° isomer.

Anal. Calcd. for $C_{22}H_{26}$: C, 91.0; H, 9.04; bromine no., 110. Found: C, 91.06, 90.96; H, 9.07, 9.04; bromine no., 115, 115.

The olefin (1.38 g.) was ozonized in the usual manner to yield 0.46 g. (46%) 1,2-dibenzoylethane.

Reaction of Styrene and Acetone with Sodium.—In a typical experiment a 1-l., three-neck round-bottom flask equipped with a reflux condenser, trubore stirrer, and gas inlet was flushed with dry oxygen-free nitrogen and a head of nitrogen pressure was maintained in all of the subsequent operations. The solvent was added and sodium wire (1.5-mm. diameter) was pressed directly into the kettle. It was then cooled to the appropriate temperature and 5 to 10 ml. of the carbonyl component added with stirring. The latter was necessary particularly if the olefinic component is susceptible to anionic polymerization (*e.g.*, butadiene and styrene). As the olefin was added the surface of the sodium turned yellow to red depending on the olefin; the color probably was due to the formation of a carbanion since it was readily discharged by the addition of the carbonyl compound. The progress of the reaction was readily followed by the disappearance of the sodium. With reactive systems (carbonyl component) the surface of the sodium remained shiny until it was consumed completely.

Reaction of Styrene and Acetone with Sodium in Diethyl Ether.—Sodium (30 g.) was pressed in wire form into 600 ml. of absolute ether. The mixture was continuously flushed with dry nitrogen. It was cooled to −40° and 10 ml. of anhydrous acetone added. This was followed by the simultaneous addition of 150 ml. of styrene and 95 ml. of acetone at such a rate to maintain the temperature at approximately −10° (~1 hr.). As the reaction proceeded the surface of the sodium remained shiny and appeared molten. The reaction was stirred for an additional hour until the sodium was completely consumed; the mixture was homogeneous and appeared faintly gray. Acetic acid (100 ml.) and water were added simultaneously and the temperature maintained at 0°. The mixture was poured into an ice–water slurry and extracted twice with ether. The colorless ethereal extract was washed with sodium bicarbonate twice and dried to yield a colorless ethereal solution. Vacuum distillation yielded unchanged styrene (19 g., b.p. 49–52° (30 mm.)) contaminated with

(45) F. Whitmore, *J. Am. Chem. Soc.*, **51**, 1485 (1929); **56**, 180 (1934).

(46) A. Henne and P. Hill, *ibid.*, **65**, 752 (1943).

(47) von Auwers, *J. prakt. Chem.*, **109**, 124 (1925); J. Brewster, *J. Am. Chem. Soc.*, **74**, 5179 (1952).

(48) C. Rondesvedt, *J. Org. Chem.*, **19**, 548 (1954); D. Cram, *J. Am. Chem. Soc.*, **76**, 726 (1954).

(49) I. Bengelsdorf, *J. Org. Chem.*, **25**, 1468 (1960).

mesityl oxide and ethylbenzene. The latter were identified by gas–liquid chromatography using a 6-ft. DC-710 silicone firebrick column operated at 105–107° and 9 p.s.i. The emergence times are mesityl oxide, 7.5 min., ethylbenzene, 10.3 min., and styrene, 14.5 min. The infrared spectrum of the trapped ethylbenzene g.l.c. peak was the same as that of an authentic sample. Mesityl oxide was identified by its 2,4-dinitrophenylhydrazone (m.p. 202°). In addition, there was obtained 58.1 g. of a mixture of the isomeric 3-phenyl- and 4-phenyl-2-methylbutanol-2's (b.p., 62–71° (3 mm.)). Rectification of this mixture resolved it into its component alcohols consisting of 53.5% 3-phenyl-2-methylbutanol-2 (b.p. 62 (2 mm.)) and 46.5% 4-phenyl-2-methylbutanol-2 (b.p. 86° (2 mm.)). The material (17.7 g.) boiling at 110–121° at 3 mm. was predominantly 2,5-dimethyl-3-phenylhexanediol-2,5. The high boiling residue (3.6 g.) was predominantly 2-methyl-3,6-diphenylhexanol-2.

To a mixture of 30 g. of sodium wire and 350 ml. of absolute ether at −75° were added 5 ml. of acetone and 200 ml. of styrene in approximately 5 min. Acetone was then added dropwise to maintain the temperature at −15° to −10° (1 hr.). The reaction was stirred for an additional hour at −10° until most of the sodium was consumed. The homogeneous solution was then cooled to −20° and 130 ml. of acetic acid and occasional portions of water were added to maintain the temperature of 0°. The reaction was then poured into an ice–water slurry and extracted twice with ether. The combined ethereal extracts were washed with water, potassium carbonate solution and water again, and dried over sodium sulfate. The volatile components consisting of ether and styrene were then removed by vacuum distillation to yield 109 g. of styrene and 11 g. of ethylbenzene. The latter was obtained by comparing the relative areas of styrene and ethylbenzene in a g.l.c. chromatogram with known mixtures. There also was obtained 51.5 g. of phenylmethylbutanols (b.p. 76–86° (2.5 mm.)), 17.8 g. of phenyldimethylhexanediol, and 3.1 g of high boiling residues.

The previous reaction was repeated at 0° and yielded 119 g. of recovered styrene, 10 g. of ethylbenzene, 52.4 g. of isomeric phenylmethylbutanols (b.p., 77–90° (4 mm.)), 21.4 g. of dimethylphenylhexanediol (b.p. 125–134° (3 mm.)), 2.0 g. of 1,4-diphenylbutane, and 6.7 g. of high boiling residues.

Reaction of Styrene and Acetone with Sodium and Carbon Dioxide in Ether.—A mixture of 30 g. of sodium wire in 500 ml. of ether was chilled to −78° and 10 ml. of acetone and 150 ml. of styrene were added. The system was then pressured with two atmospheres of carbon dioxide and acetone was added dropwise at a rate such that the temperature was maintained at 0°. The surface of the sodium remained dull. After 60 ml. of acetone had been added the temperature was allowed to rise to 32° (1 hr.). The surface of the sodium appeared dull and a small amount of flocculent solid was found suspended in the ether. The carbon dioxide pressure was replaced with argon and after a short induction period (approximately 5 min.) the temperature rose rapidly (40°, 0.5 hr.). The carbon dioxide pressure was reinstituted but the temperature continued to rise (65°). At this temperature the partial pressure of carbon dioxide in solution was low. With a 0.5-atm. carbon dioxide applied pressure, the addition of acetone was continued and the temperature remained at 60–65°. The reaction mixture became orange and solidified. To the mixture water was added slowly and the whole poured into ice–water. The ether extracts were washed twice with saturated sodium bicarbonate and then water. The sodium bicarbonate extracts were decolorized with Norit and filtered to yield a clear cream-colored solution. It was acidified with dilute sulfuric acid at 0° and reextracted twice with ether. The ether solutions after drying yielded 3.5 g. of a viscous carboxylic acid(s) which was not identified further.

Distillation of the original ethereal solution yielded 60.9 g. of isomeric methylphenylbutanols, 12.1 g. of 1,4-diphenylbutane, 18.5 g. of dimethylphenylhexanediol, 5.5 g. of an unidentified crystalline ketone, 6.3 g. of dimethyldiphenyloctanediol, and 8.5 g. of nondistillable residues. The unidentified ketone was recrystallized from methylcyclohexane and sublimed *in vacuo* to yield colorless crystals (m.p. 127.0–127.5°). The infrared spectrum showed absorption bands at 5.87 (very strong), 6.82 (strong), 6.90 (strong), 7.08 (strong), 7.20 (medium), 7.33 (strong), 7.49 (strong), 7.85 (very strong), and 8.15 (very strong) μ. The characteristic aromatic bands were absent.

Anal. Calcd. for unidentified ketone ($C_{15}H_{24}O_2$): C, 76.2; H, 10.25. Found: C, 76.3, 76.4; H, 10.3, 10.4.

The ketone was treated with DNP reagent to form a yellow DNP which was recrystallized from ethyl acetate (m.p. 240–241°, with decomposition in vacuum capillary). No lower melting derivative was formed.

Anal. Calcd. for $C_{15}H_{24}O_2 \cdot 2$ DNP ($C_{27}H_{32}N_8O_8$): C, 54.5; H, 5.41; N, 18.8. Found: C, 54.4, 54.4; H, 5.4, 5.5; N, 18.8, 18.6.

The material is, therefore, a diketone. This diketone was derived from acetone exclusively since it was also obtained when styrene was not present (*vide infra*).

Since the dimethylphenylhexanediol, 1,4-diphenylbutane, and the ketone codistill it was necessary to separate them by crystallization from isopentane in which the ketone and diphenylbutane were insoluble in the cold. The ketone was separated from the hydrocarbon by recrystallization from isopentane. The dimethylphenylhexanediol was obtained most conveniently as the hemihydrate by chilling an isopentane solution in a Dry Ice bath and allowing atmospheric moisture to condense. It could be purified by sublimation as a supercooled liquid or by distilling off the water of hydration.

If the reaction was repeated continuously maintaining the applied total pressure of carbon dioxide at two atmospheres, the reaction was sluggish. It was moderately exothermic, however, and after half an hour the temperature rose to 37° (90 ml. of acetone added). After an hour the reaction temperature reached 40° and the reaction became more vigorous and maintained itself despite applied carbon dioxide pressure at 56°. At the end of 2.5 hr. the reaction was complete. Under these conditions it appeared that the applied carbon dioxide pressure moderated the reaction and enabled it to be carried out at higher temperatures. Under these conditions 45.0 g. of phenylmethylbutanols, 19.5 g. of dimethylphenylhexanediol, and 5.7 g. of nondistillable residues were obtained.

Reaction of Acetone with Sodium in Tetrahydrofuran.—To 15 g. of sodium wire in 200 ml. of tetrahydrofuran at −20° was added 60 ml. of acetone dropwise. The addition was carried out at a rate such that the temperature was kept at 0–5° (1 hr.). After the reaction was stirred an additional hour, acetic acid (80 ml.) was added and the reaction mixture poured into water. The colorless solution was vacuum distilled directly to yield 15.3 g. (0.255 mole, 78%) of isopropyl alcohol determined by nitrite ester. The residues were extracted with benzene continuously but yielded no pinacol.

Reaction of Styrene and Acetone with Sodium in Tetrahydrofuran.—To 30 g. of sodium wire in 350 ml. of tetrahydrofuran at −60° was added 10 ml. of acetone. Acetone (150 ml.) and 230 ml. of styrene were then added dropwise simultaneously to maintain the temperature at −25° (1 hr.). The reaction was then stirred for 2 hr. at 0°. Acetic acid (100 ml.) and water were added at 0° and the reaction mixture poured into an ice–water slurry. When the mixture was extracted with ether a colorless solid (6 g.) separated. It was identified as polystyrene (with hydroxyl end groups). The intrinsic viscosity was determined in toluene at 25° to be 0.61 dl./g. Applying the equation, mol. wt. = $3.09 \times 10^5 \eta^{1.41}$, the viscosity average molecular weight was 150,000.

Anal. Calcd. for polystyrene $(C_8H_8)_n$: C, 92.3; H, 7.74. Found: C, 92.1, 92.1; H, 7.8, 7.8.

The viscous ethereal solution was treated with 1.5 l. of methanol whereupon more colorless solid (11 g.) precipitated. The analysis was consistent with a compound consisting of three styrene units for each two acetone units. The structure was probably 2,9-dimethyl-3,5-triphenyldecanediol-2.9.

Anal. Calcd. for $(C_8H_8)_3 \cdot (C_3H_7O)_2{=}C_{30}H_{38}O_2$: C, 83.7; H, 8.9; mol. wt., 431. Found: C, 82.8; H, 9.1; mol. wt., 412 ± 16.

Vacuum distillation of the ether–methanol solution yielded a very viscous oil and a crystalline solid. When it was treated with petroleum ether it deposited more heavy crystalline precipitate. The crystalline precipitate (66.6 g.) was a mixture of the diastereomeric dimethyldiphenyloctanediols with the higher melting isomer predominating (~90%). The viscous oil was fractionated into 14.1 g. of methylphenylbutanols, 5 g. of isophorone (2,4-dinitrophenylhydrazone, m.p. 129°), 3 g. of dimethylphenylhexanediol, and 94.7 g. of nondistillable residues (b.p. >140° at 2 mm.).

Anal. Calcd. for isophorone 2,4-dinitrophenylhydrazone ($C_{15}H_{20}N_4O_4$): C, 56.3; H, 6.29; N (Dumas), 17.5. Found: C, 57.5, 56.5; H, 6.1, 5.9; N, 17.7, 17.7.

Anal. Calcd. for residues $(C_8H_8)_4 \cdot (C_3H_7O)_2{=}C_{38}H_{46}O_2$: C,

85.4; H, 8.5; mol. wt., 535; hydroxyl value, 0.372. Found: C, 86.2, 85.9; H, 8.6, 8.6; mol. wt., 551 ± 12; hydroxyl value, 0.348, 0.398.

A mixture of 30 g. of sodium wire and 350 ml. of tetrahydrofuran was chilled to −75°. Initially 5 ml. of acetone was added and then 150 ml. of acetone and 130 ml. styrene were added simultaneously at −40° to −35° (10 min.). The reaction was stirred at 0° and after 20 min. the reaction was viscous and opaque. An additional 120 ml. of acetone was added at 0° (1 hr.) and the reaction stirred for an additional hour. Acetic acid (130 ml.) and water were added to the mixture and the whole poured into an ice–water slurry. The reaction was extracted with ether; the ethereal extract was washed with saturated sodium bicarbonate and water. No polystyrene was formed. Vacuum distillation of the ether and styrene yielded a heterogeneous mixture of a viscous liquid and a crystalline solid. The ethereal distillate was a mixture containing styrene (10.1 g.), ethylbenzene (4.8 g.), and mesityl oxide (3.9 g.). Petroleum ether was added to the semisolid mixture to separate the crystalline insoluble material which was dimethyldiphenyloctanediol (78 g.). The petroleum ether solution on vacuum distillation yielded 17.9 g. of a mixture of methylphenylbutanols, 3.2 g. of isophorone, and 60.5 g. of a light yellow amorphous solid (b.p. >140° (3 ml.)).

The nondistillable amorphous residues showed an hydroxyl absorption at 2.8 μ and characteristic aromatic bands in the infrared spectrum. Its analysis was compatible with a structure consisting of three sytrene and two acetone units.

Anal. Calcd. for $(C_8H_8)_3{\cdot}(C_3H_7O)_2{=}(C_{30}H_{38}O_2)$: C, 83.7; H, 8.9; hydroxyl value (equiv./100 g.), 0.464; mol. wt. (ebull. ethanol, ebull. methylene chloride), 431. Found: C, 83.8; H, 9.0; hydroxyl value, 0.464; mol. wt., ethanol, 315 ± 20, methylene chloride, 350 ± 17.

Reaction of Styrene and Acetone with Sodium and Carbon Dioxide in Tetrahydrofuran.—To 30 g. of sodium wire in 500 ml. of tetrahydrofuran at −45° were added 15 ml. of acetone and then 150 ml. of styrene. The nitrogen was replaced with carbon dioxide and the total applied pressure maintained at 2 atm. Acetone (120 ml.) was added over 1 hr. at 0° but the reaction did not appear to be going. The temperature was allowed to rise to 35° by removing the cold bath (0.5 hr.) and the reaction allowed to proceed at 35–40° for an additional hour. The gray but homogeneous mixture was quenched by pouring it into an ice–dilute sulfuric acid solution. Approximately 10 g. of unchanged sodium remained in the kettle. The light brown mixture was extracted with ether and the ether solutions washed with saturated sodium bicarbonate threee times. The dark brown bicarbonate extracts were treated with Norit and carefully reacidified to yield 3 g. of carboxylic acid(s). Its infrared spectrum was similar to that obtained in ether. The original ether extract yielded styrene (103 g.), methylphenylbutanol (14.1 g.), 1,4-diphenylbutane (3 g.), dimethyldiphenylhexanediol (5.1 g.), and 17 g. of nondistillable residues (b.p. >160°(1 mm.)).

Anal. Calcd. for residues $(C_8H_8)_4{\cdot}(C_3H_7O)_2{=}C_{38}H_{46}O_2$: C, 85.4; H, 8.5; mol. wt., 535; hydroxyl value, 0.372 (equiv./100 g.). Found: C, 86.5; H, 8.5; hydroxyl value, 0.385, 0.356.

Reaction of Styrene and Acetone with Sodium in Dioxane.—To 30 g. of sodium wire in 400 ml. of dioxane and 100 ml. of ether at 3° were added dropwise simultaneously 150 ml. of styrene and 100 ml. of acetone at a rate (0.5 hr.) to maintain the temperature at 3° with external cooling. This was followed by an additional 100 ml. of acetone (1 hr.). Most of the sodium was consumed. The clear colorless fairly viscous solution was treated with 150 ml. of acetic acid and water, and then poured onto 500 ml. of ice–water slurry and extracted with ether. After drying with sodium sulfate the ethereal solution was vacuum distilled to remove styrene (2 g.) and ethylbenzene (3 g.). The residue was a viscous oil (197 g.). Isopentane (100 ml.) was added and the solution on setting overnight deposited crystals of dimethyldiphenyloctanediol (m.p. 135–138°), 30.5 g. More isopentane (50 ml.) was added and the solution cooled to 0° whereupon 6.5 g. of the diasteriomeric dimethyldiphenyloctanediol (m.p. 113–117°) was obtained. The higher melting isomer was purified by crystallization from methylcyclohexane, vacuum sublimation, and recrystallization (m.p. 135.0–135.7°). The lower melting isomer was purified by crystallization from absolute ethanol from which it crystallized as transparent platelets containing ethanol of solvation which was removed by vacuum drying (m.p. 118–119°).

The remaining isopentane mother liquor was vacuum distilled to yield 17.5 g. of isomeric methylphenylbutanols (b.p. 71–94° (3 mm.); $n^{25}D$ 1.4878–1.5202), 22.1 g. of dimethylphenylhexanediol (b.p. 130–147° (3 mm.); $n^{25}D$ 1.5382–1.5453), 46.4 g. of diphenylhexanol (b.p. 168–176° (3 mm.); $n^{25}D$ 1.5483–1.5495), 19.6 g. of additional dimethyldiphenyloctanediol (b.p. 176–192° (1 mm.); $n^{25}D$ 1.5498–1.5490), 7 g. of 1,4-diphenylbutane, and 25.8 g. of nondistillable residues (b.p. >200° (2 mm.)). The latter analyzed approximately for a compound consisting of three styrene and two acetone units.

Anal. Calcd. for residue $(C_8H_8)_3{\cdot}(C_3H_7O)_2{=}C_{30}H_{38}O_2$: C, 83.7; H, 8.9; mol. wt., 431; hydroxyl value, 0.464. Found: C, 83.8; H, 9.2; mol. wt., 392 ± 14; hydroxyl value, 0.497.

Reaction of Styrene and Diacetone Alcohol with Sodium in Ether.—To a mixture of 30 g. of sodium wire in 450 ml. of ether at −54° were added 10 ml. of diacetone alcohol and then 150 ml. of styrene. Diacetone alcohol (100 ml.) was then added dropwise at such a rate as to maintain the temperature at 0–5° (2 hr.). The clear homogeneous solution was chilled to −5° and 100 ml. of acetic acid and 100 ml. of water added. The mixture was then poured into an ice–water slurry and extracted with ether. The ethereal solution yielded 66.4 g. of methyl phenylbutanols (b.p. 68–87° (2.5 mm.); $n^{25}D$ 1.4951–1.5090), 23.6 g. of dimethylphenylhexanediol (b.p. 124–137° (2.5 mm.); $n^{25}D$ 1.5292–1.5211), 14.5 g. of diphenylhexanol (b.p. 163–184° (2.5 mm.); $n^{25}D$ 1.5427–1.5437), and only 4.1 g. of nondistillable residue (b.p. > 185° (2.5 mm.)).

Acknowledgment.—The author wishes to thank Mr. Fred Rust and Drs. Edward Kosower, Charles Reilly, and Donald Whitman for helpful discussions. The author also thanks Mr. Fred Rodgers for technical assistance.

Co-Reduction with Alkali Metals. II. Conjugated Dienes and Carbonyl Compounds

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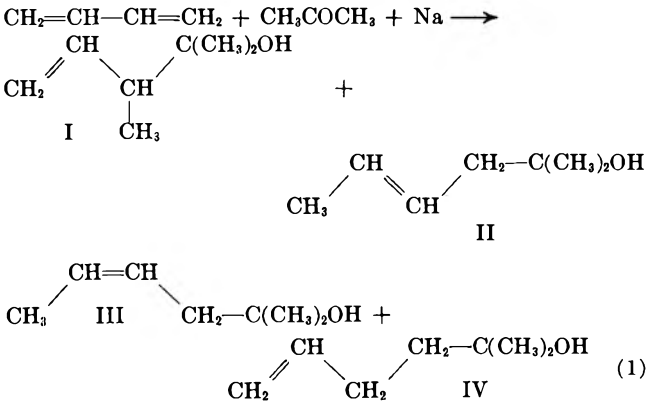
1,3-Butadiene and isoprene react with ketones, esters, and aldehydes in the presence of sodium in ethereal solvents. Butadiene and acetone yield a mixture of 1:1 adducts which are identified as 2,3-dimethylpenten-4-ol-2 (I), *cis*- and *trans*-2-methylhexen-4-ol-2 (II and III), and 2-methylhexen-5-ol-2 (IV). In addition, small amounts of 2:1 adducts incorporating two acetone and one butadiene units and 1:2 adducts are formed. The anionic polymerization is not a significant side reaction. The same mixture of adducts is obtained in diethyl ether and tetrahydrofuran. The absence of dimeric butadiene adducts in tetrahydrofuran contrasts with the condensations using styrene. The difference is examined in terms of the effect of solvent on the formation of dimer dianion from the radical-anion of butadiene and styrene. The nucleophilic properties of the radical-anion of butadiene is discussed by employing a simple theoretical model. The condensation of isoprene with acetone produces in good yield a mixture of octenols by 1,2-, 1,4-, and 4,1-addition to isoprene. A mixture of heptenones and octenones are obtained from the co-reduction of methyl propionate with butadiene and isoprene, respectively. Acetaldehyde and acrolein react sluggishly with butadiene and sodium. Simple alkenes are not co-reduced with acetone by sodium.

In the previous paper[1] the co-reduction of styrene and acetone with sodium to form hydroxylic 1:1, 2:1, 1:2, and 2:2 adducts of acetone and styrene was discussed. These adducts were characterized as phenyl methylbutanols, dimethylphenylhexanediol, diphenylheptanol, and diphenyldecanediols. The reductive condensation to form monomeric or dimeric styrene products was markedly influenced by solvent. The reaction was interpreted to proceed *via* styrene radical-anion and dimer dianion intermediates. In this report we have extended the study of co-reductions with sodium to other conjugated dienes such as butadiene and isoprene with aldehydes or esters as the carbonyl components.

Results

Butadiene and acetone react readily with sodium in tetrahydrofuran at −5° to 0° to produce a mixture of 1:1 acetone–butadiene adducts in 64% yield, in addition to a 2:1 adduct of two acetone and one butadiene units in 16% yield and a 1:2 adduct in 3% yield. Less than 3% undistillable polymeric material was formed. The mixture of 1:1 adducts was examined by distillation, gas–liquid chromatography and ozonolysis. Four component heptenols were identified and characterized: 2,3-dimethylpenten-4-ol-2 (I) (45%), *trans*-2-methylhexen-4-ol-2 (II) (24%), *cis*-2-methylhexen-4-ol-2

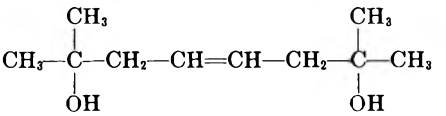


(1)

(III) (18%), and 2-methylhexen-5-ol-2 (IV) (13%). These heptenols were compared with authentic samples.

2,3-Dimethylpenten-4-ol-2 (I) was obtained by the procedure of Roberts and Young[3] which employs "crotyl" magnesium bromide and acetone. In addition to ozonolysis to formaldehyde,[3] we also identified the keto alcohol as the 2,4-dinitrophenylhydrazone of 2,3-dimethylcrotonaldehyde, a product of acid-catalyzed dehydration. The mixture of *cis*- and *trans*-2-methylhexen-4-ol-2 (II and III) was synthesized from 1-lithiopropene-1 and isobutylene oxide. It was hydrogenated to 2-methylhexanol-2 and ozonized to a mixture of acetaldehyde and a keto alcohol which was identified as the 2,4-dinitrophenylhydrazone of senecialdehyde, a product of facile dehydration catalyzed by acid. 2-Methylhexen-5-ol-2 (IV) was synthesized from allylacetone and methylmagnesium bromide. It was hydrogenated to 2-methylhexanol-2 and ozonized to yield formaldehyde.

The 2:1 adduct comprised of two acetone and one butadiene units was obtained as a crystalline solid. On the basis of its infrared spectrum (10.25 and 112 μ), its structure was assigned as the 1,4-adduct, 2,7-dimethyloctene-4-diol-2,7 (V).



V

The same mixture of 1:1 and 2:1 acetone–butadiene adducts was formed in the *same* relative yields in diethyl ether solvent, but less polymeric material was found. This contrasts strongly with the co-reduction of styrene and acetone with sodium, in which the product composition was markedly influenced by solvent. In either solvent the amounts of butadiene polymers formed were much smaller than the polystyrene residues obtained in tetrahydrofuran.

Reaction of Isoprene and Acetone with Sodium.—Isoprene underwent a reaction with acetone in the presence of sodium in a manner analogous to butadiene: There was formed in 81% yield a mixture of 1:1 adducts which were distillable into two fractions (b.p. 70–73° (40 mm.) and b.p. 78–81° (40 mm.)). Each fraction and intermediate fractions all had the same elemental, hydroxyl, and bromine number analyses. In addition they all formed phenyl carbamate derivatives which

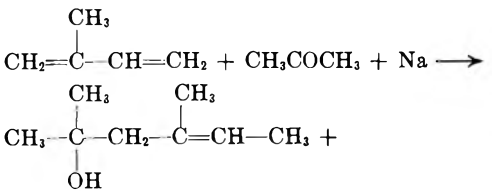
(1) Part I, J. K. Kochi, *J. Org. Chem.*, **28**, 1960 (1963).

(2) Department of Chemistry, Case Institute of Technology, Cleveland 6, Ohio.

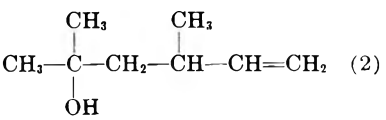
(3) J. D. Roberts and W. G. Young, *J. Am. Chem. Soc.*, **67**, 148 (1944).

were not obtained pure (by melting point), but whose analyses corresponded to the isomeric octenols. The lower boiling fraction (70–73°) appeared homogeneous on g.l.c. while the higher boiling fraction (78–81°) showed two distinct components. Neither was pure since ozonolysis of the various distillation cuts produced acetone, acetaldehyde, and formaldehyde, in varying proportions.

These results indicated that in addition to 1,4 (VI) and 1,2 (VII) addition, 4,1 (VIII) addition was a significant route.



VI



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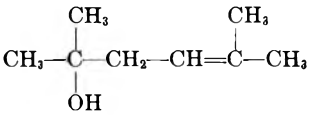
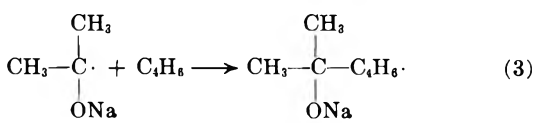
VII



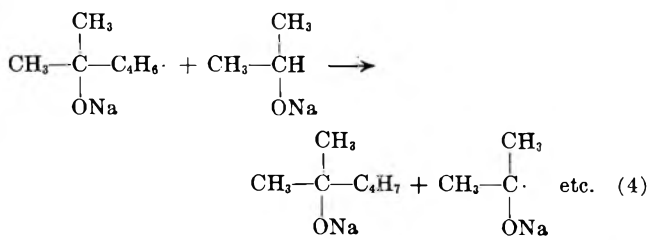
VIII

In addition to the 1:1 adducts of acetone and isoprene there was formed a mixture of 2:1 adducts (10%), 1:2 adducts (3%), and polyisoprene telomers, none of which were resolved. The formation of polymeric residues was a more important process with isoprene than it was with butadiene.

The addition of isopropyl alcohol served to lower the yield of reduction adducts presumably by reacting directly with sodium. Sodium isopropoxide did not enhance the yields of adducts and thus obviated the possibility of a radical chain reaction.

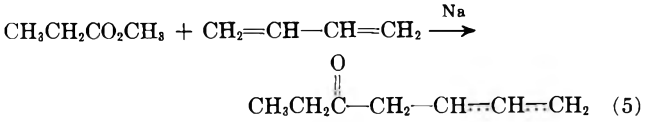


(3)



(4)

Reactions of Esters and Dienes with Sodium.—Methyl propionate reacted readily with sodium in tetrahydrofuran solvent to produce propionoin in 40% yield. Both methyl propionate and ethyl acetate reacted with sodium in the presence of butadiene and isoprene at a reduced rate compared to acetone. Methyl propionate and butadiene reacted with sodium in tetrahydrofuran to produce a mixture of heptenones (27%), which was not separated, in addition to higher boiling unidentified products.



(5)

Methyl propionate and isoprene reacted with sodium in tetrahydrofuran to form a mixture of unsaturated ketones similar to those formed from butadiene in approximately 20% yield. The reaction of methyl propionate and styrene with sodium in diethyl ether was slow compared to the reaction with acetone. Neither condensation products nor polymeric styrene were obtained, and reduction of the reactants to simple monomeric products was the only reaction observed. Although these reactions of esters and dienes with sodium in tetrahydrofuran were carried out at 15–25°, the polymerizations of butadiene or isoprene were not significant side reactions.

Benzalacetone and butadiene reacted with sodium in tetrahydrofuran very slowly to form a viscous amorphous products(s) which was not characterized. After approximately 10% of the reaction was completed, acrolein underwent an undesirable base-catalyzed polymerization to a product similar to disacryl. Mesityl oxide reacted readily with sodium in the presence of butadiene in tetrahydrofuran to form in reasonable yield a product of dimeric reduction of mesityl oxide. Acetaldehyde reacted easily with sodium in the presence of butadiene but after the reaction was approximately 10% complete, the surface of the sodium appeared deactivated. If the reaction was run in the presence of acetic acid, the sodium was consumed readily, largely by its reaction with acetic acid. There was formed in low yields mixtures of alcoholic products which were 1:1 and 1:2 adducts of acetaldehyde and butadiene. If acetic anhydride was used to replace the acetic acid, the yields of adducts were slightly better. There was formed in low yields a mixture of acetates which were not identified.

Reaction of Acetone and Alkenes with Sodium.—When the reduction of acetone with sodium was carried out in the presence of either hexene-1 or 2-methylpentene-1 in tetrahydrofuran, the primary reduction product was isopropyl alcohol. In addition there was formed a variety of base-catalyzed condensation products of acetone which included mesityl oxide, isophorone, and an unidentified crystalline ketone (the same as that obtained from acetone and styrene). There was no indication that either hexene-1 or 2-methylpentene-1 reacted with acetone.

Discussion

The reactions of conjugated dienes such as butadiene and isoprene with acetone and sodium are distinguished from the related condensations which involve styrene in that the ether solvents have a leveling effect with the former olefins. Thus, reactions in diethyl ether and tetrahydrofuran solvents are indistinguishable in coreductions involving butadiene, whereas diethyl ether favors monomeric styrene condensation products and tetrahydrofuran is conducive to the formation of dimeric styrene products.[1] We attribute this difference to the dimer dianion equilibrium involving the radical-anion from each olefin. With styrene radical-anion IX, the equilibrium equation 7 is presumed to be more facile

and sensitive to solvent (*vide infra*) than it is with butadiene radical-anion XI (equation 7).

$$2NaPhCH\dot{-}CH_2 \rightleftharpoons [Ph\dot{C}H-CH_2CH_2-\dot{C}HPh]Na_2 \quad (6)$$
IX X

$$2NaCH_2-CH-CH\dot{-}CH_2 \rightleftharpoons$$
XI

$$[\dot{C}H_2-CH=CH-CH_2CH_2CH=CH-\dot{C}H_2]Na_2 \quad (7)$$
XII

It is difficult to assess quantitatively the magnitude of free energy changes involved in each of the dimerization equilibria 6 and 7. If these changes are reflected mainly in the energy of the anions (*i.e.*, neglecting the sodium counterions, solvation effects, coulombic repulsions, entropy changes, etc.), it is possible to make some attempts to calculate by the use of the simple Hückel molecular orbital method[4] the differences involved in the dimerization reactions 6 and 7. The lowest unoccupied molecular orbital in butadiene is 1.24 β higher in energy than that of the highest filled orbital, and it is 1.32 β higher in styrene. This indicates that the "electron affinity" of butadiene is 0.08 β greater than styrene. Benzyl and allyl carbanions can be used as models for the dimer dianions of styrene X and butadiene XII. The calculated difference in energy between benzyl carbanion and toluene is $2\alpha + 0.72\beta$, while that between allyl carbanion and propylene is $2\alpha + 0.83\beta$. The difference, 0.09 β, measures the amount by which allyl carbanion is more stable than its conjugate acid *relative* to benzyl carbanion and its conjugate acid.[5] The amount that butadiene radical-anion is more stable than styrene radical-anion is vitiated by almost the same amount as the allyl carbanion is stable relative to benzyl carbanion. Therefore, the driving force for dimer dianion formation from the radical-anion on the basis of these crude calculations appears to be the same for butadiene and styrene. If the differences in driving force are real, then it must be attributed to factors other than simple energy considerations, such as solvation, coulombic repulsion, etc.[7]

The alternate route for the formation of dimeric styrene products is *via* the dimer anion-radical intermediate XIII formed from the addition of styrene radical-anion to styrene.[1]

$$NaPhCH\dot{-}CH_2 + PhCH=CH_2 \longrightarrow$$

$$[Ph\dot{C}H-CH_2CH_2-\dot{C}HPh]Na \quad (8)$$
XIII

This was followed by electron transfer.

$$XIII + Na \longrightarrow [Ph\dot{C}H-CH_2CH_2-\dot{C}H-Ph]Na_2 \quad (9)$$
X

If such were the case there is no *a priori* reason for a similar process not to be obtained with butadiene radical-anion, since the latter also readily undergoes anionic polymerization[8] (10 and 11).

$$NaCH_2-CH-CH\dot{-}CH_2 + C_4H_6 \longrightarrow$$

$$[\dot{C}H_2-CH=CH-CH_2CH_2-CH=CH-\dot{C}H_2]Na \quad (10)$$
XIV

$$XIV + Na \longrightarrow$$

$$[\dot{C}H_2-CH=CH-CH_2CH_2-CH=CH-\dot{C}H_2]Na_2 \quad (11)$$
XII

The ineffectiveness of a change in solvent from diethyl ether to tetrahydrofuran to effect the formation of significant quantities of dimeric butadiene adducts of acetone militates against such a mechanism.

Frank and Foster[9a] have shown that such dimeric butadiene products can be formed under special conditions in a manner not dissimilar to the formation of dimeric styrene adducts. There are certain indications that the dimer dianions X or XII are not readily dissociated.[9,10] And it is not necessary to postulate reactions 6 and 7 as reversible (*vide supra*), *provided* solvents affect the *rates* of the dimerizations.[11] The critical role played by solvent in the formation of octadiene dianion XII from butadiene and diphenyl butane dianion X from styrene has been demonstrated.[9]

The composition of the mixture of 1:1 adducts of acetone and butadiene which are the only significant products from sodium, shows interesting distribution of isomers. The intermediate which directly leads to reaction with acetone is the butadiene radical-anion. The calculated spin densities at positions 1 and 2 of this species are shown in Fig. 1. These densities correspond

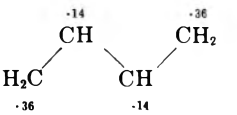


Fig. 1.—Spin densities in the butadiene radical-anion.

to the nucleophilic center being mainly on the terminal positions which react with acetone by addition to form the alkoxide-radical XV in preference to the alkoxide-radical XVI, formed by reaction at the internal positions.

$$\cdot CH_2-CH=CH-CH_2-C(CH_3)_2ONa$$
XV

$$NaCH_2-CH-CH\dot{-}CH_2 + CH_3COCH_3 \quad (12)$$
(a / b)

$$CH_2\cdot$$
$$CH_2=CH-CH-C(CH_3)_2ONa$$
XVI

(4) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961.

(5) If a value of 50 kcal./mole is used for β, this difference amounts to 4.5 kcal. Experimentally, these values should be reflected in pK_a values, but these are not readily available. However, since both benzyl and allyl radicals are odd alternant hydrocarbons, the addition or subtraction of an electron to the 0th molecular orbital involves no change in the relative differences in energy. Therefore, the difference in energies of the benzyl and allyl moieties as carbanions, free radicals, or carbonium ions are the same. The readily accessible bond dissociation energies[6] are in agreement with these calculated values. For example, the bond dissociation energies of $PhCH_2-CH_3$ and $CH_2=CHCH_2-CH_3$ are 63 ± 1.5 and 61.5 kcal./mole, respectively (difference = ~2 kcal./mole), and $PhCH_2-I$ and $CH_2=CHCH_2-I$ are ~39 and 36 ± 1 kcal./mole, respectively (difference = ~3 kcal./mole).

(6) T. L. Cottrell, "The Strengths of Chemical Bonds," Butterworths Scientific Publications, London, 1954, pp. 201, 213.

(7)(a) N. D. Scott, J. F. Walker, and V. L. Hansley, *J. Am. Chem. Soc.*, **58**, 2442 (1936); (b) D. E. Paul, D. Lipkin, and S. I. Weissman, *ibid.*, **78**, 116 (1956); (c) J. L. Down, *et al.*, *Proc. Chem. Soc.*, 209 (1957); (d) M. Szwarc, *Makromol. Chem.*, **35**, 133 (1960).

(8)(a) K. Ziegler, *Angew. Chem.*, **49**, 499 (1936); *Ann.*, **567**, 72 (1950). (b) F. W. Stavely, *et al.*, *Ind. Eng. Chem.*, **48**, 778 (1956); (c) M. Sittig, "Sodium," Reinhold Publishing Corp., New York, N. Y., 1956, p. 313 ff.

(9)(a) C. E. Frank and W. E. Foster, *J. Org. Chem.*, **26**, 303 (1961); (b) C. E. Frank, J. R. Lecbrick, L. F. Moormeir, J. A. Scheben, and O. Homberg, *ibid.*, **26**, 307 (1961).

(10) M. Szwarc and R. Asami, *J. Am. Chem. Soc.*, **84**, 2269 (1962).

(11) This statement is also applicable to our earlier discussion[1] of the formation of styrene dimer dianion.

Formation of terminal adducts II, III, and IV in larger yield (55%) than the sole secondary product I is consistent with this formulation. On the other hand, if acetone ketyl were the intermediate which added to butadiene, only terminally substituted products from the alkoxide-radical intermediate XV are expected.

The reduction by electron transfer of alkoxide-radical XV yields an alkoxide-anion XVII which can suffer protonation at three positions to yield the isomeric heptenols II, III, and IV, or addition to acetone to form decenediol V.

$$CH_2\dot{-}CH{=}CH{-}CH_2{-}C(CH_3)_2ONa + Na \longrightarrow [:CH_2{-}CH{=}CH{-}CH_2{-}C(CH_3)_2O:]Na_2 \quad (13)$$

XVII

$$XVII + CH_3COCH_3 \xrightarrow{a} II \quad \xrightarrow{b} III + CH_3COCH_2Na \quad (14)$$
$$\xrightarrow{c} IV$$

$$XVII + CH_3COCH_3 \longrightarrow V \quad (15)$$

The position of protonation of the allylic carbanion XVII is not easy to predict. The simple butenyl Grignard reagent reacts with acetone and other carbonyl electrophiles[3] and ethylene oxide[12] exclusively at the secondary position. The position it is neutralized to yield butene is dependent on the acid, and is not specific to the 3-position, although butene-1 is usually the predominant product.[13] However, the cinnamyl carbanionic moiety reacts with electrophiles at either the primary or secondary position depending on the electrophile and the metal gegenion.[14,15]

The alkoxide-anion XVII exists in two geometric forms. The formation of approximately equal amounts of *cis*- and *trans*-2-methylhexen-4-ol-2 reflects their relative populations. Statistically, it is expected that protonation at the internal position of XVII to form 2-methylhexen-5-ol-2 (IV) would be favored by a factor of two over either *cis*- or *trans*-2-methylhexen-4-ol-2 (II or III). However, the negative charge on the alkoxide oxygen may repel the negative charge to the terminal position of the allylic system and favor the formation of II or III. The low yield of IV relative to II and III is in accord with such a formulation.

An alternative path involving protonation first of the butadiene radical-anion followed by reduction and condensation with acetone is a possibility which cannot be discounted. The formation of a butadiene dianion, which results from two electron transfers, as an intermediate is disfavored on energetic grounds. The dianion of such a simple structure[7b] would not be expected to produce the heptenols observed in such yields.

The chemistry of isoprene is related to that of butadiene and its reaction with acetone and sodium resembles that of the latter. Whereas free radical additions to isoprene occur predominantly at the 1-position,[16] such adducts are not the sole products of co-reduction. Significant amounts of additions at the 4-position occur, and it is further evidence that the co-reduction reactions are not proceeding *via* an addition of the acetone ketyl intermediate. Although anionic polymerization is quite a facile process with isoprene, little dimeric isoprene condensation products were observed in the reaction with acetone and sodium.

The reaction of esters with conjugated dienes to produce unsaturated ketones is analogous to reactions with acetone. It probably involves the addition of the radical-ion to the ester to form a hemiketal intermediate XVIII which suffers electron transfer, protonation, and

$$CH_2{=}CH{-}CH{=}CH_2 + CH_3CH_2CO_2CH_3 \longrightarrow CH_3CH_2{-}\underset{\underset{OCH_3}{|}}{\overset{\overset{O:}{|}}{C}}{-}CH_2{-}CH{=}CH{-}CH_2 \quad (16)$$

XVIII

hydrolysis. The unreactivity of styrene radical-anion in this reaction is probably due to the slowness of the addition step such as 12. In this respect the anion-radicals of styrene and butadiene show lower nucleophilic reactivity than conventional organo-sodium derivatives.

The possibility of carrying out co-reductive cyclizations with α,β-conjugated carbonyl compounds and butadiene was investigated.

$$CH_2{=}CH{-}CHO + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{Na} \left[CH_2{=}CH{-}\underset{\underset{H}{|}}{\overset{\overset{ONa}{|}}{C}}{-}CH_2{-}CH{=}CH{-}CH_2\right]$$

XIX

$$XIX \longrightarrow \text{(ONa-cycloheptene)} \quad \text{etc.}$$

However, we found no indications that such reactions were successful.

Experimental

Materials.—1,3-Butadiene: Matheson Co., C.P. grade, bulb distilled *in vacuo* after drying over calcium chloride. Isoprene: Phillips Petroleum Co., polymerization grade, redistilled. 2-Methylbutene-1 and hexene-1: Phillips Petroleum Co., pure grade. Methyl propionate, benzalacetone: Eastman Kodak, White Label. Mesityl oxide, acrolein: Shell Chemical Co. 1-Bromopropene-1: Matheson Coleman and Bell. Material was carefully redistilled through a 40-plate Oldershaw column. Other materials were the same as those used in the previous report.[1]

Synthesis of 2,3-Dimethylpenten-4-ol-2 (I).—Butadiene (427 g.) was added to 500 ml. of benzene and chilled to 0°. Anhydrous hydrogen bromide was bubbled through the solution at 0° for 2 hr. The solution was washed with aqueous sodium bicarbonate and dried over calcium chloride. Distillation yielded 350 g. of butenyl bromide boiling at 97–104°. The butenyl bromide (300 g.) in 3 l. of diethyl ether was added slowly over 11 hr. to 160 g. of magnesium in a liter of ether. Acetone (130 g.) in 300 ml. of ether was added over an hour and the reaction worked up under near neutral conditions (ammonium sulfate). It yielded 240 g. of 2,3-dimethylpentene-4-ol-2 boiling at 133–135°; $n^{25}D$ 1.4323–1.4332. It was contaminated with a ketonic impurity which was

(12) L. S. Wu, R. A. Finnegon, and K. W. Greenlee, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 7Q.

(13)(a) W. G. Young, S. Winstein, and A. N. Prater, *J. Am. Chem. Soc.*, **58**, 289 (1936); (b) W. G. Young and M. Eisner, *ibid.*, **63**, 2113 (1941); (c) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Co., New York, N. Y., 1954, pp. 1145 ff.

(14) J. E. Leffler, "The Reactive Intermediates in Organic Chemistry," Interscience Publishers, Inc., New York, 1956, pp. 215–216.

(15) We are examining the effect of structure on the reactions of allylic carbanions.

(16)(a) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 3946 (1962); (b) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, *ibid.*, **84**, 3897 (1962).

readily removed by treatment with Girard P reagent ($n^{25}D$ 1.4331).

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.4; bromine no., 130. Found: C, 73.67; H, 12.36; bromine no., 145.

Hydrogenation over Adam's catalyst in ethyl acetate yielded 2,3-dimethylpentanol-2.[17] Examination by g.l.c. showed the presence of only one component (emergence time: 10-ft. Ucon Polar/firebrick at 114°, 25.7 min.; 10-ft. DEGS/firebrick at 90°, 33 min.).

Synthesis of 2-Methylhexen-4-ol-2 (*cis* and *trans* Mixture) (II and III).—1-Bromopropene-1 (186 g.) was added to a solution of 15.6 g. of lithium in 1 l. of diethyl ether over a period of 4 hr. 1-Lithiopropene-1 then reacted with a solution of 108 g. of isobutylene oxide in 100 ml. of ether. The reaction was worked up under near neutral conditions and yielded 47 g. of 2-methylhexen-4-ol-2 boiling at 142–143°; $n^{25}D$ 1.4365–1.4369.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.4; bromine no., 140. Found: C, 73.2; H, 12.3; bromine no., 142.

It was hydrogenated over platinum to 2-methylhexanol-2.[17] The methylhexenol was examined by g.l.c. and found to consist of two components of approximately equal amounts (emergence times: 29 and 35 min. on 10-ft. Ucon Polar at 114° and 39 and 46 min. on 10-ft. DEGS/firebrick at 90°). The early emerging component was assigned the *trans* structure and the later component the *cis* structure. The infrared spectrum was also consistent with these structures, since strong bands appeared at 965 cm.$^{-1}$ (*trans*) and 980 cm.$^{-1}$ (*cis*).

2-Methylhexen-5-ol-2 (IV) was prepared from allylacetone and methylmagnesium bromide.[17] It was separated by g.l.c. from the isomeric alcohols using a 10-ft. Ucon Polar/firebrick column at 114° (emergence time, 37.3 min.) and less efficiently with a 10-ft. DEGS/firebrick column at 90° (emergence time, 48.7 min.).

Reaction of Butadiene and Acetone with Sodium in Tetrahydrofuran.—Sodium wire (30 g.) and 350 ml. of tetrahydrofuran were cooled to −80° and 5 ml. of acetone and 300 ml. of butadiene were added. Acetone (135 ml.) was added dropwise at 10° to −5° over 1 hr. The reaction was stirred for an additional 10 min. at 0° and then poured onto a mixture of ice and water containing 80 g. of sulfuric acid. It was extracted with ether and the ethereal solution washed with saturated sodium bicarbonate and water. It yielded 55.5 g. of 1:1 adducts (b.p. 122–131°; $n^{25}D$ 1.4313–1.4347), 18 g. of 2:1 adducts, 3.1 g. of 1:2 adducts, and 1.4 g. of nondistillable residue (b.p. >120° (2 mm.); $n^{25}D$ 1.5014).

The same reaction conducted in diethyl ether at −5° to 0° gave essentially the same results. The reaction yielded 47 g. of 1:1 adducts, 10 g. of 2:1 adducts, 1.5 g. of 1:2 adducts, and 1 g. of nondistillable residue.

A similar reaction containing 25 ml. of isopropyl alcohol conducted at 0° in tetrahydrofuran yielded 36.5 g. of 1:1 adducts, 7.1 g. of 2:1 adducts, and 2.3 g. of nondistillable residues (b.p., >150° (2 mm.), $n^{25}D$ 1.4976). These reactions also yielded mesityl oxide and isophorone.

Butadiene–Acetone Adducts. 1:1 Adducts.—The mixture of adducts containing one acetone and one butadiene unit (b.p. 122–131°) was carefully refractionated at 90 mm. with a 3-ft. spinning band column. The distillation pattern is as follows. Fraction, boiling range (°C.), $n^{25}D$, wt. (g.): 16, 77.0–77.5, 1.4398, 5.8; 17, 77.5, 1.4389, 10.8; 18, 76.8–78.0, 1.4389, 15.0; 19, 78.0–77.8, 1.4368, 15.6; 20, 77.8–80.0, 1.4348, 13.0; 21, 80.0–84.0, 1.4343, 12.0; 22, 84.0–85.0, 1.4349, 17.5; 23, 85.0–85.6, 1.4352, 9.2; 24, 85.8–86.5, 1.4352, 15.7.

The analyses for each fraction are as follows. Fraction, C, H, hydroxyl value (equiv./100 g.), bromine no. (g./100 g.): 17, 73.9, 11.5, —, —; 18, 73.1, 11.7, —, —; 19, 72.9, 11.9 (0.809, 0.827), —; 20, 73.6, 12.2 (0.853, 0.907), —; 21, 73.4, 12.4, —, —; 22, 73.5, 12.3 (0.868, 0.898), 135; 23, 13.3, 12.3, —, —; 24, 73.2, 12.3, —, —; theoretical (calcd. for heptenol, $C_7H_{14}O$), 73.6, 12.37, 0.876, 138.

The phenyl carbamate derivatives were obtained crystalline by the same procedure employed for the octenols obtained from isoprene. Fraction 24 yielded a urethane derivative melting at 60–62° and fraction 19 yielded a derivative melting at 48.5–49.5°.

Anal. Calcd. for phenylurethane of fractions 19, 22, 24 ($C_{14}H_{19}NO_2$): C, 72.0; H, 8.22; N, 6.0. Found (fraction 19): C, 72.2; H, 8.2; N, 5.8. (Fraction 22): C, 72.0; H, 8.1; N, 6.1. (Fraction 24): C, 72.1; H, 8.1; N, 5.8.

(17) J. K. Kochi, *J. Am. Chem. Soc.*, **85**, 1958 (1963).

The mixtures of 1:1 adducts of acetone and butadiene were examined by g.l.c. Mesityl oxide was poorly separated from 2,3-dimethylpenten-4-ol-2 on a 10-ft. DEGS/firebrick column at 90° but was cleanly separated on a 10-ft. UCON Polar/firebrick column at 114°. The former column poorly separated *cis*-2-methylhexen-4-ol-2 from 2-methylhexen-5-ol-2 while the latter column separated them cleanly. The two columns used in conjunction enabled determination of four isomeric heptenols. The total yields of heptenols also were determined by hydrogenating an aliquot of the reaction mixture with Adam's catalyst. The heptenols, 2,3-dimethylpentanol-2 and 2-methylhexanol-2, were not separated from each other by g.l.c., but were cleanly separated from 4-methylpentanone-2 and they were analyzed by the marker technique.

The relative yields of heptenols were as follows: 2,3-dimethylpenten-4-ol-2, 44.7%; *trans*-2-methylhexen-4-ol-2, 24.4%; *cis*-2-methylhexen-4-ol-2, 17.6%; 2-methylhexen-5-ol-2, 13.4%. Virtually the same ratios of isomeric heptenols were obtained in diethyl ether and tetrahydrofuran solvents.

Thus, fractions 18 and 19 consisted mainly of 2,3-dimethylpenten-4-ol-2. Fractions 23 and 24 were mixtures of *cis*-2-methylhexen-4-ol-2 and 2-methylhexen-5-ol-2. The intermediate fractions consisted of mixtures of all four components. Further evidence was obtained from ozonolysis studies. As expected, no acetone was formed. The two lower carbonyl compounds were acetaldehyde estimated by g.l.c. and formaldehyde estimated by methone formation. The yields of these two components were as follows: fraction, formaldehyde, acetaldehyde: 19, 18%, —; 20, 4.5%, 12.5%; 23, 8.5%, 38%.

The aqueous mother liquor from the ozonation of fraction 19 was clear and homogeneous. It was treated directly with 2,4-dinitrophenylhydrazine reagent which on standing gave a heavy red precipitate. It was recrystallized twice from ethyl acetate–ethanol mixture to yield dense scarlet crystals, m.p. 195–196°. The same DNP was obtained from the urethane of fraction 19. The reported melting point of the DNP from 2,3-dimethylcrotonaldehyde was 198°[18a] and 200–201°.[18b]

The mixture melting point with an authentic sample[18a] made from the selenium dioxide oxidation of 2,3-dimethylbutene-2 was undepressed (m.p. 194–196°).

Anal. Calcd. for 2,3-dimethylcrotonaldehyde DNP ($C_{12}H_{14}N_4O_4$): C, 51.8; H, 5.08; N, 20.1. Found: C, 51.3, 51.0, 51.2[18a]; H, 5.0, 5.0, 5.0[18a]; N, 20.3, 20.1, 20.2.[18a]

The aqueous mother liquor was treated directly with semicarbazide in ethanol. Within 1 hr. a heavy precipitate of semicarbazone was formed. Recrystallization from methanol yielded platelets (m.p. 239–240°, sealed capillary). Literature value for 2,3-dimethylcrotonaldehyde semicarbazone is 234°[18a] and 239–240°.[18b] The mother liquor was acidified with sulfuric acid and stirred with ether for 36 hr. The ether solution on washing with sodium bicarbonate and water and drying with sodium sulfate, yielded a mixture of carbonylic oils (infrared bands at 5.75 μ (shoulder), 5.82, 6.00, and 6.1 μ). It reacted rapidly with semicarbazide to form the same derivative (m.p. 239–240°) obtained from the mother liquor directly.

Anal. Calcd. for 2,3-dimethylcrotonaldehyde semicarbazone ($C_7H_{13}N_3O$): C, 54.1; H, 8.45; N, 27.1. Found: C, 53.9, 54.2; H, 8.4, 8.5; N, 27.6.

Fraction 24 on ozonolysis yielded primarily acetaldehyde, and the homogeneous aqueous mother liquor on treatment with 2,4-DNP reagent yielded red crystals which on recrystallization from ethyl acetate–ethanol yielded a scarlet DNP, melting at 180.0–180.5°. The DNP of senecialdehyde (β-methylcrotonaldehyde) melted at 181.5°,[19] 181–182°, 179°.

Anal. Calcd. for senecialdehyde DNP ($C_{11}H_{12}N_4O_4$): C, 49.9; H, 4.58; N (Dumas), 21.2. Found: C, 49.3, 49.2; H, 4.5, 4.6; N, 21.2, 21.3.

2:1 Adducts.—The 2:1 adduct consisting of two acetone and one butadiene unit distilled at 82–84° (1 mm.) ($n^{25}D$ 1.4634) and melted at 68–69°. Its infrared absorption spectrum showed prominent bands at 10.25 and 11.10. It was probably the 1,4-adduct, 2,7-dimethyloctene-4-diol-2,7.

Anal. Calcd. for dimethyloctenediol ($C_{10}H_{20}O_2$): C, 69.8; H, 11.69; hydroxyl value, 1.16; bromine no., 93. Found: C,

(18)(a) W. Hickinbottom, *J. Chem. Soc.*, 4400 (1954); (b) E. Braude, *ibid.*, 3334 (1955).

(19) W. Hickinbottom, *ibid.*, 1380 (1955); R. Heilman and Glenat, *Bull. soc. chim. France*, 1586 (1955); M. Julia and J. Surzur, *Comp. rend.*, **238**, 2426 (1954).

69.9, 69.8; H, 11.7, 11.7; hydroxyl value, 1.11, 1.11; bromine no., 93.

Reaction of Isoprene and Acetone with Sodium in Tetrahydrofuran.—To a mixture of sodium wire (33 g.) in 400 ml. of tetrahydrofuran at −40° was added 125 ml. of isoprene. Acetone (150 ml.) was then added dropwise at such a rate to maintain the temperature at 3–5° (30 min.). The light yellow homogeneous reaction was allowed to stir at 25° for 30 min. to react all of the sodium. Sulfuric acid (30%) was added dropwise to the mixture with cooling. The mixture was then added to an ice–water slurry and extracted three times with ether. The ethereal solution was washed with saturated sodium bicarbonate and water and dried with sodium sulfate. The ethereal solution on distillation yielded 67 g. of a mixture of dimethylhexenols (b.p. 143–151°; n^{25}D 1.4746–1.4754), 4 g. of trimethyldecadienols (b.p. 95–125° (2 mm.); n^{25}D 1.4829) and 10.3 g. of nondistillable residue (n^{25}D 1.5018–1.5035; b.p. >190° (2 mm.)). In addition, mesityl oxide (10.5 g.) and isophorone (6.7 g.) were formed from the base-catalyzed condensation of acetone.

If the reaction was carried out at 20–25° the amount of 1:1 adduct (55.9 g.) remained approximately constant. There was formed, however, 33.4 g. of a mixture of 2:1 and 1:2 adducts and 22.2 g. of polyisoprene residues.

The addition of sodium isopropoxide did not enhance the formation of addition products. For example, a reaction consisting of 26 g. of sodium in 375 ml. of tetrahydrofuran and 50 ml. of isopropyl alcohol was refluxed for 3 hr. to convert the alcohol to sodium isopropoxide. The reaction mixture was cooled to −30° and 100 ml. of isoprene added, and followed by the dropwise addition of 75 ml. of acetone. The temperature was maintained at −10° (20 min.). The mixture was stirred for an additional 15 min. at 0°. The homogeneous solution was poured into an ice–water slurry containing 60 g. of sulfuric acid and extracted with ether. The mixture yielded 15.4 g. of 1:1 adducts, 1.5 g. of a mixture of 1:2 and 2:1 adducts, and 3.8 g. of polyisoprene residues.

The addition of isopropyl alcohol decreased the amount of 1:2 and 2:1 adducts. A reaction consisting of 30 g. of sodium wire in 350 ml. of tetrahydrofuran was chilled to −40° and 25 ml. of isopropyl alcohol and 200 ml. of isoprene were added. Acetone (130 ml.) was then added dropwise (30 min.) keeping the temperature at −5° to 0°, and the reaction stirred for 30 min. at 0°. The mixture was poured onto an ice–water slurry containing 70 g. of sulfuric acid and extracted with ether. It yielded 36.1 g. of 1:1 adducts, 6.0 g. of a mixture of 2:1 and 1:2 adducts, and 4.7 g. of nondistillable residues.

Isoprene–Acetone Adducts. 1:1 Adducts.—The 1:1 adducts of isoprene and acetone consisted of a mixture containing, at most, four possible structural isomers: 2,4-dimethylhexen-4-ol-2, 2,4-dimethylhexen-5-ol-2, 2,5-dimethylhexen-4-ol-2, and 2,5-dimethylhexen-5-ol-2. The distillation pattern is as follows. Fraction, boiling range, n^{25}D, weight: 3, 67.5–69.5°, 1.443, 2.4 g.; 4, 69.5–71.0°, 1.4438, 7.3 g.; 5, 71.0–73.5°, 1.4438, 6.8 g.; 6, 73.5–75.2°, 1.4438, 7.8 g.; 7, 75.2–76.7°, 1.4444, 4.4 g.; 8, 76.7–76.8°, 1.4443, 4.6 g.; 9, 76.8–78.8, 1.4452, 7.8 g.; 10, 78.8–80.2°, 1.4442, 9.8 g.; 11, 80.2–80.5°, 1.4440, 52 g.; 12, 80.5–98.0°, 1.4440, 2.7 g.

Analyses of various fractions were also obtained. Fraction, C, H, bromine no. (g./100 g.), hydroxyl value (equiv./100 g.): 3, 77.1%, 12.2%, —, —; 4, 77.3%; 12.5%, —, —; 5, 76.4%, 12.5%, —, —; 6, 76.0%; 12.5%, —, —; 7, (75.18, 75.14), (12.53, 12.52), —, .732; 8, 75.0%, 12.5%, 149, —; 9, 74.7%, 12.5%, —, —; 10, 74.9%, 12.5%, 111, .763; 11, 74.9%, 12.5%, —, —; 12, 73.6%, 12.3%, —, —; theoretical (calculated for $C_8H_{16}O$, octenol): 75.0%, 12.6%, 125, 0.771. Fraction 6 was treated with phenyl isocyanate and 1 drop of pyridine on a steam bath for 48 hr. The mixture was diluted with isopentane and filtered to remove the diphenylureas. The filtrate was vacuum distilled to remove solvent and unchanged alcohol. The viscous residue was chromatographed over neutral alumina and the eluate yielded colorless crystals. Recrystallization three times from isopentane yielded phenyl carbamate derivatives melting at 67–72°.

Anal. Calcd. for phenylurethane of fraction 6 ($C_{18}H_{21}NO_2$): C, 72.9; H, 8.65, N (Kjeldahl), 5.67. Found: C, 73.0; H, 8.6; N (Kjeldahl), 5.7.

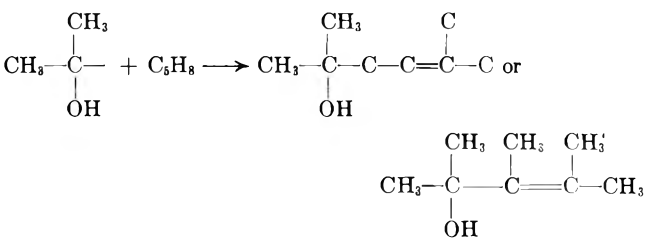
A similar treatment of fraction 10 gave a urethane which was much more difficult to purify (melting point criterion). Recrystallization six times from isopentane yielded material melting at 52–59°.

Anal. Calcd. for phenylurethane of fraction 10 ($C_{15}H_{21}O_2N$): C, 72.9; H, 8.65; N, 5.67. Found: C, 72.6; H, 8.5; N, 5.7.

The alcohol fractions were examined by g.l.c. on a 5-ft. UCON Polar/acid-washed Chromosorb at 113°. There were three important constituents with emergence times: A (10.7 min.), B (14.8 min.), and C (18.1 min.). Fraction 5 contained all three constituents in the approximate ratio A:B:C as 1:5:1. In fraction 7 the ratio was 1:5:7; in fraction 9, 1:1:5; and fraction 10, 2:30:1.

Ozonolysis studies indicated further that the fractions contained more than one component. The compounds were ozonized in methylene chloride at −78°. The methylene chloride solution was then added to a mixture of zinc in 50% aqueous acetic acid and the methylene chloride distillate condensed in an ice bath. Acetaldehyde and acetone were analyzed by g.l.c. on a 10-ft. oxydipropionitrile column at 42°. The emergence times were: methylene chloride, 5.6 min.; acetaldehyde, 3.3 min.; and acetone, 9.5 min. Formaldehyde was determined by weighing the methone derivative formed from the aqueous mother liquors. The estimates of the yields of these three carbonyl components are as follows: fraction, formaldehyde, acetaldehyde, acetone: 5, 13%, 20%, 7%; 6, —, 7%, —; 8, 23%, 20%, 6%; 10, 25%, 1%, 13%; 11, 15%, 4.2%, 9%.

The positive identification of acetone in these ozonolyses indicate the presence of an isopropylidene end group, which can arise only if the addition of the hydroxy isopropyl moiety is added to isoprene at the 3- or 4-position.



Since mechanistically it is difficult to rationalize addition at the 3-position, structure 3,5-dimethylhexen-4-ol-2 was preferred for the isomer yielding acetone on ozonolysis.

2:1 Adducts.—The mixture of adducts consisting of two acetone and one isoprene units boiled at 84–95° (2 mm.) and was not resolved into its components. Its structure was presumably predominantly that of the 1,4-adduct, 2,4,7-trimethyloctene-4-diol-2,7.

Anal. Calcd. for trimethyloctenediol ($C_{11}H_{22}O_2$): C, 70.9; H, 11.9; hydroxyl value (equiv./100 g.), 1.076; bromine no. (g./100 g.), 86. Found: C, 71.9, 71.4; H, 11.7, 11.7; hydroxyl value, 0.963; bromine no., 93.

1:2 Adducts.—The mixture of adducts consisting of one acetone and two isoprene units boiled at 95–125° (2 mm.) and was a mixture of several isomers. A possible structure is related to 2,4,8-trimethyldecadien-4,8-ol-2.

Anal. Calcd. for trimethyldecadienol ($C_{13}H_{24}O$): C, 79.4; H, 12.3; hydroxyl value, 0.51; bromine no., 172. Found: C, 79.8, 77.6; H, 11.0, 11.7; hydroxyl value, 0.452; bromine no., 150.

Analysis for Nondistillable Residues (Polyisoprene) $(C_5H_8)_n$.—The infrared spectra of these residues showed the presence in varying degrees of intensity hydroxyl absorptions (2.95 μ).

Anal. Calcd. for C_5H_8: C, 88.2; H, 11.8. Found: C, 87.0, 86.5; H, 11.8, 11.9.

Reaction of Mesityl Oxide and Butadiene with Sodium in Tetrahydrofuran.—Sodium wire (30 g.) and 350 ml. of tetrahydrofuran were cooled to −80° and 300 ml. of butadiene and 80 ml. of mesityl oxide added. The reaction was allowed to warm to 0° and an additional 70 ml. of mesityl oxide was added dropwise (20 min.). The reaction was stirred for 40 min. at 0° and 80 min. at 6°. To the light yellow fairly mobile solution was added 200 ml. of isopropyl alcohol and the whole poured onto a mixture of 80 g. of sulfuric acid and an ice–water slurry. The ether extracts after washing with sodium bicarbonate were dried with sodium sulfate and distilled. Fraction, pressure (mm.), boiling range, n^{25}D, weight, C, H: 5, 30, 36–50°, 1.4266, 11.9 (mesityl oxide); 6, 30, 55–55°, 1.4406, 17.6 (mesityl oxide); 7, 3, 55–66°, 1.4581, 11.1, 76.5, 11.6; 8, 3, 66–67°, 1.4652, 23.6, 75.7, 11.4; 9, 2, 67–69°, 1.4688, 11.4, 74.3, 11.1; 10, 2, 70–94°, 1.4758, 5.5, 75.4, 11.2; 11, 2, 94–119°, 1.4806, 7.9, 76.2, 11.2; 12, 2, 119–

122°, 1.4817, 3.4, 76.1, 11.4; 13, 2, 122–150°, 1.4848, 2.8, 76.7, 11.5; residue, —, —, 1.4981, 5.6, 82.3, 11.3.

Fractions 8, 9, 10, and 11 were quite similar and showed the presence of hydroxyl (2.95 μ) and carbonyl (5.95, 6.05 μ) bands in the infrared spectra.

Fractions 9 and 10 crystallized partially. After filtering, the solid recrystallized from petroleum ether to yield colorless solid (m.p. 73–74°). The infrared spectrum in carbon tetrachloride showed important absorption bands at 2.90, 5.95, 8.60, 9.43, 9.75, 10.62, 11.00, and 12.00 μ.

Anal. Calcd. for hydroxy ketone ($C_{12}H_{20}O_2$): C, 73.5; H, 10.3; hydroxyl value ($LiAlH_4$) (equiv./100 g.), 0.510; carbonyl value (equiv./100 g.), 0.510. Found: C, 73.5, 73.6; H, 10.3, 10.3; hydroxyl value, 0.557; carbonyl value, 0.393.

Reaction of Methyl Propionate with Sodium in Tetrahydrofuran.—Sodium wire (23 g.) in 500 ml. of tetrahydrofuran was cooled to 20° and a solution of 100 g. of methyl propionate in 100 ml. of tetrahydrofuran added dropwise. The temperature was maintained at 20–25° (1.5 hr.). Acetic acid (80 g.) and water were added to the clear homogeneous solution and the reaction mixture then poured into a large excess of water. It was extracted several times with ether, washed with sodium bicarbonate, and dried over sodium sulfate. Distillation yielded 12.1 g. of material boiling at 64–66° at 15.5 mm. ($n^{25}D$ 1.4252).

Anal. Calcd. for propionoin ($C_6H_{12}O_2$): C, 62.1; H, 10.42. Found: C, 62.2, 61.9; H, 10.3, 10.3.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–water mixtures (m.p. 124.0–125.5°; lit.[3] m.p. 154°).

Anal. Calcd. for propionoin DNP ($C_{12}H_{16}N_4O_5$): C, 48.7; H, 5.45; N, 18.9. Found: C, 48.9, 48.5; H, 5.4, 5.2; N, 18.7, 19.0.

Reaction of Methyl Propionate and Butadiene with Sodium in Tetrahydrofuran.—Butadiene (300 ml.) was added to a mixture of 30 g. of sodium wire and 350 ml. of tetrahydrofuran at −10°. Methyl propionate (130 g.) was added dropwise at a temperature of approximately 15° (1.5 hr.). The reaction was allowed to stir at 15° for 4 hr. and then poured into a mixture of ice slurry and 80 g. of sulfuric acid. The ethereal extracts were washed with sodium bicarbonate and water, dried with sodium sulfate, and distilled. Fraction, pressure (mm.), boiling range, $n^{25}D$, weight, C, H: 5, 760, 143–145°, 1.4319, 4.1, 72.8, 10.7; 6, 40, 68–72°, 1.4348, 8.8, 74.3 and 73.5, 10.7 and 10.6; 7, 40, 72–74°, 1.4365, 11.6, 73.7 and 73.7, 10.6 and 10.6; 8, 40, 74–78°, 1.4369, 6.1, 74.0 and 74.2, 10.7 and 10.7; 9, 40, 83–118°, 1.4442, 5.8, 73.3, 10.4; 10, 2, 100–103°, 1.4613, 8.0, 73.9, 10.3; 11, 2, 103–119°, 1.4658, 3.3, 73.5, 10.2; 12, 2, 126–150°, 1.4798, 6.8, 74.3, 10.5; 13, 2, 148–150°, 1.4842, 1.3, 75.0, 10.5; residue, —, —, 1.4971, 18.8, 75.3, 11.7.

Fraction 7 is fairly pure heptenone. It reacted with 2,4-DNP reagent to form an amorphous derivative with, however, correct analysis for heptenone–DNP.

Anal. Calcd. for heptenone DNP ($C_{13}H_{16}N_4O_4$): C, 53.4; H, 5.53; N, 19.15. Found: C, 53.0, 52.7; H, 5.5, 5.6; N, 19.0, 18.3.

Hydroxyl value (0.725 equiv./100 g.) and bromine number (127 g./100 g.) are in fair agreement with theory, 0.89 and 143, respectively.

Reaction of Methyl Propionate and Isoprene with Sodium in Ether.—Sodium (15 g.) was dispersed in 50 ml. of xylene. The xylene was decanted and the sodium pellets washed with absolute ether several times. Ether (200 ml.) was added and the mixture cooled to −25° and 50 ml. of isoprene added. A solution of 39 g. of methyl propionate in 50 ml. of ether was added and the reaction refluxed simultaneously (30 min.). The reaction was refluxed an additional hour and poured into a mixture of 35 g. of sulfuric acid and water. The upper layer was decanted and washed with sodium bicarbonate and dried with potassium carbonate. Fraction, pressure (mm.), boiling range, $n^{25}D$ weight: 1, 2.5, 34–40°, 1.4473, 8.7; 2, 2.5, 40–47°, 1.4485, 11.3; 3, 2.0, 49–62°, 1.4526, 2.5; 4, 1.0, 54–68°, 1.4686, 1.3; 5, 1.0, 68–102°, 1.4732, 1.4; 6, 1.0, 102–128°, 1.4850, 2.3.

The lower boiling fractions (1–4) from several runs were combined and redistilled at 12 mm. Fraction, boiling range, $n^{25}D$, weight, C, H: 1, 45–62°, 1.4530, 2.9, —, —; 2, 62–64°, 1.4478, 4.8, 75.3, 11.0; 4, 65–66°, 1.4498, 4.4, 74.7, 10.8; 4, 66–67°, 1.4516, 4.0, 74.1, 10.9; 5, 67–68°, 1.4520, 4.1, —, —; 6, 68–74, 1.4480, 3.7, 70.7, 10.4; 7, 74–87°, 1.4332, 3.9, —, —.

Fractions 2 and 4 were treated with 2,4-dinitrophenylhydrazine reagent and yielded solid derivatives. They were both recrystallized twice from ethanol–water solutions but yielded material melting over a range (fraction 2, DNP, m.p. 80–85; fraction 4, DNP, m.p. 80–90°). They both had correct analyses for an octenone.

Anal. Calcd. for DNP of octenone ($C_{14}H_{18}N_4O_4$): C, 55.0; H, 5.93; N (Dumas), 18.3. Found (fraction 2, DNP): C, 54.9; H, 6.3; N, 18.0. (Fraction 4, DNP): C, 55.0; H, 6.1; N, 18.3.

Reaction of Benzalacetone and Butadiene with Sodium in Tetrahydrofuran.—A mixture of 23 g. of sodium ribbon in 350 ml. of tetrahydrofuran was cooled to −60° and 300 ml. of butadiene added. The temperature was raised to −10° and a solution of 90 g. of benzalacetone in 100 ml. of tetrahydrofuran was added at such a rate to maintain the temperature at 12–14° (1 hr.). The reaction was stirred for 3 hr. at 14° and became quite viscous. It was poured into ice–water and separated as a very viscous, ether soluble, mass. It was not worked up.

Reaction of Acrolein and Butadiene with Sodium.—Sodium wire (30 g.) in 350 ml. of tetrahydrofuran was cooled to −70° and 350 ml. of butadiene added. A solution of 100 ml. acrolein in 100 ml. of tetrahydrofuran solvent was added dropwise at −70° and the addition continued until the temperature reached −10° (30 min.). The solution became opaque and as the acrolein was added a solid material separated (disacryl?). The sodium was not apparently consumed as evidence by its dull surface.

Reaction of Acetaldehyde and Butadiene with Sodium.—Sodium wire (30 g.) in 350 ml. of tetrahydrofuran was cooled to −70° and 350 ml. of butadiene added. An aliquot (20 ml.) of a solution of 100 ml. of acetaldehyde and 100 ml. of tetrahydrofuran was added and the reaction allowed to warm to −10°. The surface of the sodium was shiny, but, as the addition of the acetaldehyde solution was continued, the solution became opaque and the sodium surface became dull. After all the aldehyde had been added the sodium was less than 10% consumed. Addition of more acetaldehyde did not appear to activate the sodium. The reaction was stirred for 1 hr. at room temperature at which time most of the sodium wire remained unchanged. It was worked up in the usual manner by decanting the solution into ice–water. It yielded no material boiling where hexenol is expected.

The reaction was repeated with the simultaneous addition of acetic acid (100 ml.) with the acetaldehyde solution. After approximately half the solution was added (temperature, 0°, 1 hr.) the solution became opaque. After the acetaldehyde and acetic acid were added approximately 50% of the sodium was still unchanged. The reaction was stirred for an additional hour at 5°, but no visible reaction occurred. Approximately 10 g. of 3-mm. diameter glass beads was added and the reaction became exothermic (temperature rise to 20°). The mixture was cooled to 10° and after 0.5 hr. of stirring the sodium was completely dissipated. It was poured into sulfuric acid–ice mixture and extracted with ether. The ethereal extract, after washing three times with sodium bicarbonate and drying over sodium sulfate, was distilled to remove the ether. The residue (approximately 50 ml.) was vacuum distilled. Fraction, pressure, boiling range, $n^{25}D$, weight, C, H: 1, 70, 31–41°, 1.4192, 1.5, —, —; 2, 70, 45–46°, 1.4282, 3.5, 81.1, 12.4; 3, 30, 39–42°, 1.4322, 4.6, 82.8, 12.6; 4,[20a] 10, 36–84°, 1.4362, 6.3, 73.8, 12.1; 5,[20b] 10, 84–92°, 1.4613, 1.0, 73.7, 11.2; residue, —, —, 1.5003, 1.2, —, —.

A reaction was also run in which acetic anhydride (80 ml.) was used to replace the acetic acid in the previous reaction (23 g. of sodium, 75 ml. of acetaldehyde, 300 ml. of butadiene in 350 ml. of tetrahydrofuran). The products were distilled into the following fractions. Fraction, pressure (mm.), boiling range, weight (g.), $n^{25}D$, C, H: 3, 3, 25–42°, 2.9, 1.4341, —, —; 4, 2, 42–49°, 8.6, 1.4426, 66.8, 9.8; 5, 2, 52–66°, 5.3, 1.4469, 64.4, 9.3; 6, 2, 66–83°, 1.5, 1.4576, 64.3, 8.7; 7, 2, 83–91°, 7.8, 1.4574, —, —; 8, 2, 91–99°, 4.9, 1.4663, 64.4, 8.8; 9, 2, 100–106°, 4.8, 1.457, —, —; residue, —, —, 32.2, 1.5012, 71.7, 9.4.

Reaction of Ethyl Acetate and Butadiene with Sodium and Acetic Anhydride in Tetrahydrofuran.—A mixture of 30 g. of sodium wire in 350 ml. of tetrahydrofuran reacted with 350 ml. of butadiene and 122 ml. of acetic anhydride in the usual manner. The addition took approximately 1 hr. and the reaction was stirred an additional 2 hr. at 5°. The consumption of the sodium occurred very slowly. The work-up yielded products distilling over a wide range. Fraction, pressure, boiling range, weight, $n^{25}D$, C, H: 1, 8, 26–28°, 1.5, 1.4279, —, —; 2, 5, 28–37°, 2.1,

(20)(a) Hydroxyl value (equiv./100 g., acetic anhydride), 0.86, 0.88; (b) hydroxyl value (equiv./100 g., acetic anhydride), 0.66, 0.64.

1.4492, 68.5, 9.1; 3, 2.5, 41–42°, 17.9, 1.4632, 69.5, 9.0; 4, 2; 42–47°, 10.6, 1.4697, 69.5, 9.0; 5, 2, 47–58°, 1.9, 1.4670, —, —; 6, 2, 58–70°, 2.5, 1.4662, —, —; 7, 2, 70–84°, 4.1, 1.4700, —, —; 8, 2, 84–117°, 1.9, 1.4832, —, —; 9, 2, 117–124°, 7.9, 1.5035, —, —; residue, —, —, 32.6, 1.5150, 70.6, 8.7.

Fraction 4 on treatment with 2,4-DNP reagent yielded an orange-red DNP (recrystallized from absolute ethanol), m.p. 158–160°.

Anal. Calcd. for hexenone DNP ($C_{12}H_{14}N_4O_4$): C, 51.8; H, 5.07; N, 20.1. Found: C, 51.9, 52.1, 51.6; H, 4.9, 4.9, 5.0; N, 19.8, 19.8, 19.7. That fraction 4 was not pure hexenone also was indicated by its bromine number (137) and hydroxyl value (208).

Reaction of 2-Methylbutene-1 and Hexene-1 and Acetone with Sodium in Tetrahydrofuran.—A mixture of 30 g. of sodium wire and 400 ml. of tetrahydrofuran was chilled to −20° and 150 ml. of 2-methylbutene-1 was added. Acetone was added dropwise at such a rate to maintain the temperature at 30° (2.5 hr.). The clear homogeneous solution was quenched with 100 ml. of acetic acid and water and poured into an ice–water slurry. The mixture was extracted three times with ether and the ethereal solutions washed with sodium bicarbonate and dried over sodium sulfate. The distillation of the ethereal extracts yielded in addition to isopropyl alcohol, mesityl oxide, and isophorone. In addition there was formed a high boiling ketonic product(s) (b.p. 98–147° (1 mm.); $n^{25}D$ 1.5053–1.5231; 7.1 g.) which showed hydroxyl absorption in the infrared spectrum (2.80, strong; 5.80, strong, 6.05, strong; 6.4, weak μ). The distillation pattern from the reaction of acetone with 2-methylbutene-1 is given below. Boiling range, $n^{25}D$, weight (g.), C, H, hydroxyl value: 49.3–53.0°, 1.4705, 6.5, —, —, —; 53.0–53.5°, 1.4745, 8.5, 76.2, 10.2, —; 53.5–62.0°, —, 3.3, 77.5, 10.3, 0.624; 84–86°, 1.5089, 2.4, —, —, —; 86–88°, 1.5122, 3.0, —, —, —; 88–89°, 1.5158, 2.8, 79.9, 10.2, 0.500; 89–98°, 1.5156, 1.5, 79.2, 10.2, —; 98–128°, 1.5053, 3.3, —, —, —; 128–147°, 1.511, 3.0, —, —, —. A similar spectrum of products was obtained from the reaction of hexene-1 with acetone and sodium.

Reaction of Styrene and Methyl Propionate with Sodium in Ether.—To a mixture of 30 g. of sodium wire in 400 ml. of ether at −40° was added 10 ml. of methyl propionate and 150 ml. of styrene. Methyl propionate (150 ml.) was then added dropwise at 5–10° (0.5 hr.) and the reaction allowed to stir at 30–40° for 2 hr. (12 g. of unchanged sodium remained). The solution was decanted into a mixture of acetic acid and water and worked up in the usual manner. Distillation of the ether left approximately 100 g. of material which on distillation was primarily styrene. The reduction products although not isolated were probably monomeric products such as ethyl benzene and propanol. There was less than 3 g. of material boiling higher than styrene. It appeared thus that no condensation between methyl propionate and styrene occurred.

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Steroids. CCXXI.[1] Syntheses of Some Steroid Dienes

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Novel syntheses are outlined of $\Delta^{1,3}$- and $\Delta^{2,4}$-androstadien-17β-ols, $\Delta^{2,4}$-pregnadien-20-one, and $\Delta^{2,5}$-pregnadien-17α-ol-20-one 17-acetate. $\Delta^{2,5}$-Pregnadiene-11β,17α,21-triol-20-one 21-acetate was obtained, but with the $\Delta^{3,5}$-isomer as a contaminant. Diagnostic features of ultraviolet absorption, infrared absorption, and nuclear magnetic resonance spectra, and optical rotatory dispersion are discussed.

Until very recently an oxygen atom at C-3 of the steroid nucleus was considered mandatory for biological activity. However, in 1959 biological activity was demonstrated for steroids carrying either no substituent at C-3[2] or a nitrogen substituent.[3] There rapidly followed reports of other active steroids devoid of a C-3 oxygen atom,[4–6] and further extensive investigations were initiated in the Syntex Laboratories. As a result there was discovered a new class of highly active androstenes, sp^2 hybridized at C-2 or C-3, or at both positions.[7] Substitution at the C-2 position of these steroid ring A olefins by methyl[8] or substituted methyl[9,10] led to further variations in activity, and some of these derivatives displayed an unusually favorable separation of androgenic and anabolic (myotrophic) activity. It was of distinct interest, therefore, to study the activity coincident upon the introduction of further unsaturation into the electron-rich ring A of these steroid olefins.

Accordingly, syntheses of such compounds have been developed by routes which also should prove applicable to other cyclic systems.

3β-Chloro-Δ^1-androsten-17β-ol acetate[7b] (Ia), from the reaction of the 3β-alcohol Ib with thionyl chloride, was converted smoothly in 80% yield into $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa) by treatment with boiling dimethylformamide containing calcium carbonate or a little pyridine. Alternatively, boiling dimethyl sulfoxide alone, or in conjunction with a small quantity of pyridine, eliminated hydrogen chloride from Ia to give IIa. Earlier preparations of steroid $\Delta^{1,3}$-dienes proceeded in substantially inferior yields.[11] Hydrolysis of the acetate IIa furnished the corresponding 17β-alcohol IIb, which on oxidation with chromic acid[14]

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(11) Henbest and Wilson[12] reported $\Delta^{1,3}$-cholestadiene as a minor non-isolated contaminant of Δ^1-cholestene formed through reductive dehalogenation of 3β-chloro-Δ^1-cholestene. Our synthesis of Δ^1-androstenes by the same experimental method furnished no trace of a $\Delta^{1,3}$-diene elimination reaction product.[7b] $\Delta^{1,3}$-Cholestadiene was obtained in 4.3% yield by the action of alumina on, or pyrolysis of, Δ^1-cholestene-3β-ol benzoate.[13]

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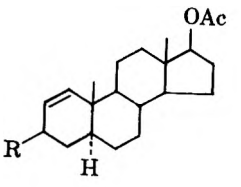
yielded $\Delta^{1,3}$-androstadien-17-one (IIc). Treatment of the latter with methyl- or ethynylmagnesium bromide led to 17α-methyl-$\Delta^{1,3}$-androstadien-17β-ol (IId) or the 17α-ethynyl analog IIe, respectively. Brief treatment with 60% formic acid under reflux converted the $\Delta^{1,3}$-diene acetate IIa into a $\Delta^{3,5}$-diene, probably IIIa admixed with its 17-formate.

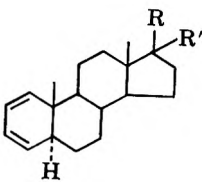
$\Delta^{2,4}$-Cholestadiene was prepared by Bergmann and his associates[15,16] by high temperature vacuum distillation of cholesterol from alumina, but the product is thermolabile, and it was considered essential, therefore, to develop a more attractive synthetic method. A synthesis of $\Delta^{2,4}$-estradienes from a 2α-acetoxy-Δ^4-3-ketone[17] was announced recently after the completion of our work.

Bromination of androstan-17β-ol-3-one acetate furnishes the 2α,4α-dibromo derivative IVa.[18,19] The latter when treated with sodium iodide in acetone afforded 2α-iodotestosterone acetate (Va)[20] in which the α-configuration of the iodine is equatorial as evidenced by the rotatory dispersion curve and infrared spectrum.[21] Reduction of the α-iodo ketone Va proceeded with sodium borohydride in aqueous dioxane to yield 2α-iodo-Δ^4-androstene-3,17β-diol 17-acetate (Vb).[22] A modified Cornforth reaction[23] on the iodohydrin Vb with a zinc–copper couple[24] in buffered acetic acid solution led to $\Delta^{2,4}$-androstadien-17β-ol acetate (VIa) in 35% over-all yield. This diene proved to be thermolabile, a hot solution in heptane developing ultraviolet absorption at 235 mμ characteristic of the isomeric $\Delta^{3,5}$-diene IIIb. Reductive cleavage of the acetate VIa furnished the corresponding 17β-alcohol VIb, from which the 17-ketone VIc was derived by oxidation in a two-phase system by the procedure of Brown and Garg.[25] Treatment of this ketone VIc with methylmagnesium iodide made available 17α-methyl-$\Delta^{2,4}$-androstadien-17β-ol (VId).

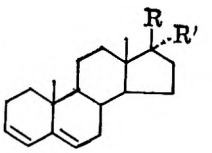
In a similar manner 5α-pregnan-20β-ol-3-one acetate[26] when brominated gave 2α,4α-dibromo-5α-pregnan-20β-ol-3-one acetate[26] (IVb), a crystalline compound, which upon treatment with sodium iodide furnished 2α-iodo-Δ^4-pregnen-20β-ol-3-one acetate (Vc). The latter was reduced by sodium borohydride in aqueous dioxane to afford the corresponding iodohydrin Vd[22] which, without further purification, was converted into $\Delta^{2,4}$-pregnadien-20β-ol acetate (VIe) by a modified Cornforth reaction.[23] Reductive cleavage of the 20β-acetate VIe with lithium aluminum hydride led to the derived 20β-alcohol VIf. Oxidation[25] of this alcohol VIf yielded the required $\Delta^{2,4}$-pregnadien-20-one (VIg). With hot acetic acid–hydrochloric acid the $\Delta^{2,4}$-diene VIe underwent conversion to a product showing ultraviolet maxima at 242, 235, and 227 mμ, which is considered to be mainly the isomeric $\Delta^{3,5}$-diene (IIId).



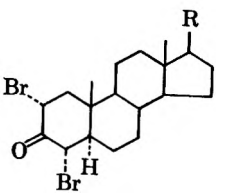
Ia, R = Cl
b, R = OH



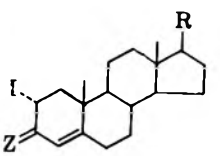
IIa, R = OAc; R′ = H
b, R = OH; R′ = H
c, R and R′ = =O
d, R = OH; R′ = Me
e, R = H; OR′ = C≡CH



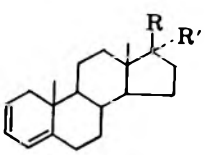
IIIa, R = OH; R′ = H
b, R = OAc; R′ = H
c, R = Ac; R′ = OAc
d, R = CH(OAc)Me; R′ = H



IVa, R = OAc
b, R = CH(OAc)Me



Va, Z = =O; R OAc
b, Z = H; R = OAc
c, Z = =O; R = CH(OAc)Me
d, Z = H, OH; R = CH(OAc)Me



VIa, R = OAc; R′ = H
b, R = OH; R′ = H
c, R and R′ = =O
d, R = OH; H′ = Me
e, R = CH(OAc)Me; R′ = H
f, R = CHOH·Me; R′ = H
g, R = Ac; R′ = H

Pyrolysis of cholesteryl-2-naphthyl carbonate at 280° gives, besides conjugated dienes, a diene which shows no strong absorption in the ultraviolet spectrum and which is considered to be $\Delta^{2,5}$-cholestadiene in spite of the absence of any supporting evidence.[27] In view of this a more definitive synthesis was sought.

Epoxidation of Δ^5-pregnene-3β-17α-diol-20-one 17-acetate[28] with monoperphthalic acid furnished a mixture of α- and β-epoxides which proved separable by chromatography over alumina. The major product was assigned the α-configuration from a consideration of molecular rotation differences[29] and its nuclear magnetic resonance spectrum.[30] Tosylation of this α-epoxide VIIa gave the 3β-tosylate VIIb which underwent an elimination reaction when heated with lithium carbonate in dimethylacetamide to afford 5α,6α-epoxy-Δ^2-5α-pregnen-17α-ol-20-one acetate (VIIc). A Cornforth reaction[23,24] upon the Δ^2-5α,6α-epoxide VIIc furnished $\Delta^{2,5}$-pregnadien-17α-ol-20-one acetate (VIII).

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Isomerization of this $\Delta^{2,5}$-diene VIII occurred on exposure to acetic acid containing hydrochloric acid, whereupon $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate (IIIc) was obtained with ultraviolet absorption spectrum resembling closely that of an authentic sample.[31]

By similar method 17,20:20,21-bismethylenedioxy-Δ^5-pregnen-3β-ol-11-one (IX)[33] was epoxidized and the α-epoxide Xa converted to the 3β-tosylate Xb which underwent elimination to afford the Δ^2-5α,6α-epoxide Xc. A Cornforth reaction then provided the $\Delta^{2,5}$-diene XIa. Lithium aluminum hydride reduced the corticoid 11-ketone XIa to the 11β-alcohol XIb. The free corticoid side chain was regenerated by brief acid hydrolysis of the bismethylenedioxy protecting group in XIb to furnish a mixture. This mixture was subjected to mild alkaline hydrolysis, acetylation, and chromatography over silica, but, in spite of repeated attempts, $\Delta^{2,5}$-pregnadiene-11β,17α,21-triol-20-one 21-acetate (XII) and its $\Delta^{3,5}$-isomer proved inseparable. Ultraviolet spectra analysis indicated that the mixture contained roughly equal proportions of the two isomers.

Physical Properties.—Ultraviolet absorption spectral data for some of the conjugated dienes and related compounds are collected in Table I. The molecular extinction coefficient of the $\Delta^{1,3}$-androstadienes (II) is less than one-half of that of $\Delta^{1,3}$-cyclohexadiene. Examination of Dreiding molecular models[34] suggests that this is due to the much greater difficulty in attainment of coplanarity of the double bonds in these $\Delta^{1,3}$-steroids than in the monocyclic compound. An unaccountable discrepancy exists between the ϵ values reported by Tamm and Albrecht[13] for $\Delta^{1,3}$-cholestadiene and the analogs described in this paper. Models[34] also reveal ring A of $\Delta^{2,4}$-steroid dienes to be more flexible than the $\Delta^{1,3}$-isomers, in keeping with their higher ϵ values.

TABLE I

ULTRAVIOLET ABSORPTION OF CYCLIC CONJUGATED DIENES

Compound	λ_{max}	ϵ
$\Delta^{1,3}$-Cyclohexadiene[a]	256.5	8000
$\Delta^{1,3}$-Cholestadiene[c]	262	5500
IIa	262	3800
IIb	262	3720
IIe	262	3800
$\Delta^{2,4}$-Estradien-17β-ol-3-one acetate[d]	259, 268, 279[b]	4450, 5270, 4620
VIa	266	6030
VIf	266	6450
VIg	266	6600

[a] V. Henri and L. W. Pickett, *J. Chem. Phys.*, **7**, 439 (1939). [b] Only a single maximum was observed for the $\Delta^{2,4}$-dienes prepared in the current work, though all showed a shoulder at 271–274 mμ. $\Delta^{2,4}$-Cholestadiene is reported as having maxima at 267 and 275 mμ [W. Bergmann and F. Hirschmann, *J. Org. Chem.*, **4**, 40 (1939)]. [c] See ref. 13. [d] See ref. 17.

In the infrared spectra all of the conjugated dienes show two absorption bonds characteristic for =C—H deformations of *cis*-disubstituted olefins. Both $\Delta^{1,3}$- and $\Delta^{2,4}$-dienes absorb strongly in the region 693–703 cm.$^{-1}$. For the $\Delta^{1,3}$-dienes the second absorption, of medium intensity, occurs at 735–740 cm.$^{-1}$, whereas in the $\Delta^{2,4}$-dienes this second absorption is observed in the range 719–728 cm.$^{-1}$.

The nuclear magnetic resonance (n.m.r.) spectra[35] clearly distinguish between the diene systems. Long range deshielding of the 19-angular methyl protons by the double bonds leads to characteristic shifts, $\Delta\delta$, relative to 5α-androstane (Table II), for each diene type. The olefinic proton resonance patterns (Fig. 1), though complex, are quite distinctive. For the $\Delta^{1,3}$-dienes, the only steroid nuclear conjugated dienes which carry four vinyl protons, the integrated areas are diagnostic. The $\Delta^{2,5}$-dienes show a two-proton absorption *ca.* 336 c.p.s. as a "hump," typical of the olefinic protons in a ring A unsubstituted Δ^2-steroid.[36]

TABLE II

N.M.R. FREQUENCIES OF THE ANGULAR METHYL PROTONS OF $\Delta^{1,3}$-, $\Delta^{2,4}$-, AND $\Delta^{2,5}$-STEROID DIENES[35]

Compound	Diene	19-H	$\Delta\delta$[a]	18-H
Androstane (in $CDCl_3$)[b]	...	46.5	0	40.4
IIb (in $CDCl_3$)	$\Delta^{1,3}$	47.5	+1.0	44.1
IIa (in CCl_4)[c]	$\Delta^{1,3}$	46.1	−0.4	46.1
VIII (in $CDCl_3$)	$\Delta^{2,5}$	59.2	+12.7	38.7
VIa (in CCl_4)[c]	$\Delta^{2,4}$	54.1	+7.6	46.6
VIe (in $CDCl_3$)[d]	$\Delta^{2,4}$	55.7	+9.2	39.7
VIf (in $CDCl_3$)[d]	$\Delta^{2,4}$	56.6	+10.1	47.0
VIg (in $CDCl_3$)[d]	$\Delta^{2,4}$	56.2	+9.7	39.2

[a] Positive values of $\Delta\delta$ indicate shifts downfield from the TMS reference and are caused by over-all deshielding. [b] R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961). [c] For steroids a change of solvent from carbon tetrachloride to deuteriochloroform generally causes small downfield frequency shifts. These shifts are largest for the resonances of protons which are part of, or adjacent to, polar groups (*e.g.*, acetate methyl). Values of $\Delta\delta$ should not be used for calculating angular methyl proton frequencies unless the solvent employed was the same for all $\Delta\delta$ determinations. [d] The small variations of the 19-H frequency in $\Delta^{2,4}$-dienes reflects small differences in the shielding contributions of substituents at C-17, as well as experimental error.

The rotatory dispersion curves (Fig. 2) of the $\Delta^{2,4}$-dienes VI (right-handed helices) all show a strong positive Cotton effect,[37] that of the 17-ketone VIc being the strongest due to the positive contribution of the cyclopentanone.[38] In the $\Delta^{1,3}$-dienes II the helicity of the diene is left-handed, and in consequence a negative Cotton effect curve is obtained.[37] The $\Delta^{1,3}$-17-ketone IIc, however, shows a positive Cotton effect curve since the amplitude of the cyclopentanone considerably outweighs that due to the diene.

(31) Prepared by the following unambiguous route. Oppenauer oxidation of Δ^5-pregnene-3β,17α-diol-20-one ethylene ketal[32] gave Δ^4-pregnen-17α-ol-3,20-dione 20-ethylene ketal, which was treated successively with lithium aluminum hydride, then acid, to yield $\Delta^{3,5}$-pregnadien-17α-ol-20-one, acetylation of which gave the diene IIIc. O. Halpern and J. A. Zderic, *Chem. Ind.*, (London), 1540 (1962).

(32) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).

(33) Prepared from cortisone BMD by successive conversion to the $\Delta^{3,5}$-enol acetate, borohydride reduction to the Δ^5-3β,11β-diol, selective acetylation at C-3, and oxidation to the 11-ketone X. We thank J. Zderic and H. Carpio for this information in advance of their publication.

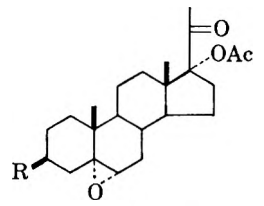
(34) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(35) N.m.r. spectra were taken with dilute deuteriochloroform or carbon tetrachloride solutions and a tetramethylsilane (TMS) internal reference on a Varian A-60 spectrometer. Calibration was checked against a Varian HR60 spectrometer suitably equipped for calibration by the standard sideband technique. Chemical shifts, δ, are quoted as c.p.s. downfield from the TMS reference and are accurate to ± 1 c.p.s.

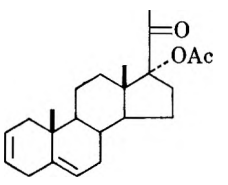
(36) A. D. Cross, forthcoming publication.

(37) *Cf.* A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4660 (1961); A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *ibid.*, **83**, 4661 (1961).

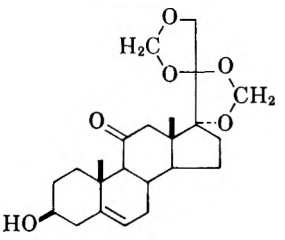
(38) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, p. 45.



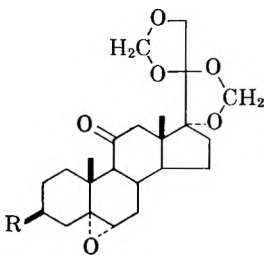
VIIa, R = OH
b, R = OTs
c, R = H; Δ^2



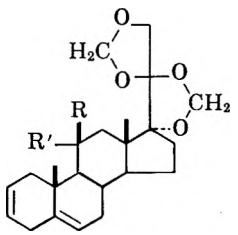
VIII



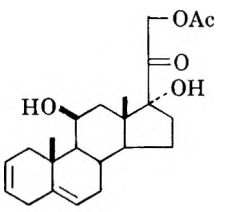
IX



Xa, R = OH
b, R = OTc
c, R = H; Δ^2



XIa, R and R' = = O
b, R = OH; R' = H



XII

Experimental[39]

$\Delta^{1,3}$-Androstadien-17β-ol Acetate (IIa).—(a) 3β-Chloro-Δ^1-androsten-17β-ol acetate[7b] (Ia) (1 g.) was dissolved in 40 ml. of dimethylformamide and 2 ml. of pyridine, and the solution was boiled under reflux during 16 hr. Dilution with water was followed by extraction with ethyl acetate, and the latter solution was washed well with dilute hydrochloric acid, water, sodium bicarbonate solution, with water to neutrality, and dried. Filtration, then evaporation to dryness, afforded 810 mg. of solid residue which was recrystallized from aqueous methanol to furnish 730 mg. of $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa), m.p. 115–118°. Further recrystallizations from the same solvent pair yielded a pure specimen, m.p. 124–125°; $[\alpha]_D$ +62°; λ_{max} 262 mμ, log ϵ 3.58; ν_{max} 3020 (w), 1738 (s), 1655 (w), 1250 (s), 738 (m), and 703 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +179°, $[\alpha]_{320}$ −24°, $[\alpha]_{295}$ −153°, $[\alpha]_{290}$ −82° (*c* 0.034 in dioxane).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.11; H, 9.21; O, 10.53.

On a 7.5-g. scale the yield was 80%.

(b) A solution of 0.3 g. of 3β-chloro-Δ^1-androsten-17β-ol acetate (Ia) in 5 ml. of dimethylformamide was heated under reflux for 4 hr. together with 0.60 g. of calcium carbonate and then poured cautiously into 5% hydrochloric acid. Extraction with ethyl acetate led to the $\Delta^{1,3}$-diene IIa, λ_{max} 262 mμ, log ϵ 3.56, for the crude product. Recrystallization from methanol afforded 110 mg. of sample indistinguishable from the compound described previously.

(39) Except where stated otherwise rotations are for chloroform solutions, ultraviolet spectra are for ethanol solutions, and infrared spectra are for potassium bromide disks. Melting points were taken on the Fisher-Johns block and are uncorrected. Rotatory dispersion measurements were made on a Rudolph automatic spectropolarimeter. We are indebted to J. Matthews and his staff for these measurements. Microanalyses are by either Mid-West Microlaboratories, Indianapolis 20, Ind., or by A. Bernhardt, Mulheim (Ruhr), Germany. Alumina used for chromatography was neutralized by stirring with ethyl acetate and reactivated by heating at 120° for 72 hr. Unless stated otherwise the alumina had activity grade III, as defined by H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

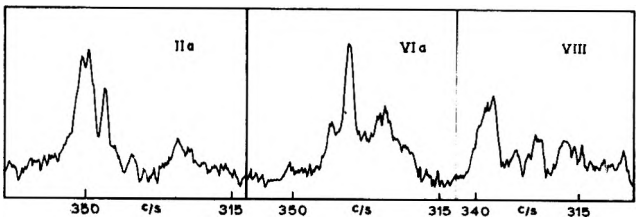


Fig. 1.—N.m.r. olefinic proton resonance patterns.

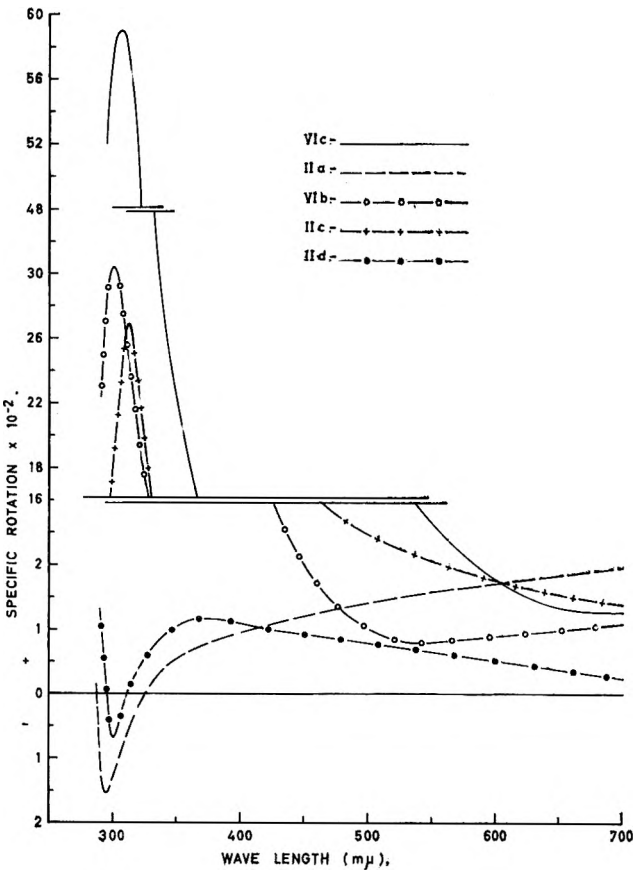


Fig. 2.—Optical rotatory dispersion curves of $\Delta^{1,3}$- and $\Delta^{2,4}$-androstenes.

(c) Replacement of dimethylformamide in method a by dimethyl sulfoxide gave the $\Delta^{1,3}$-diene IIa in 60% yield.

(d) Repetition of method c, but omitting the pyridine, again furnished the diene IIa in 60% yield.

$\Delta^{1,3}$-Androstadien-17β-ol (IIb).—The acetate IIa (2 g.) and 2 g. of sodium hydroxide were dissolved in 100 ml. of methanol, the solution kept 1.5 hr. under reflux, and then poured into ice-water. Ethyl acetate extracts were washed with hydrochloric acid and with water, dried, and evaporated to afford 1.57 g. of $\Delta^{1,3}$-androstadien-17β-ol (IIb) (91%), m.p. 143–145°. Several recrystallizations from methanol–water furnished a pure specimen, m.p. 147–148°; $[\alpha]_D$ +79°; λ_{max} 262 mμ, log ϵ 3.57; ν_{max} 3300 (s), 3025 (w), 1640 (w), 735 (m), and 700 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O \cdot 1/2H_2O$: C, 81.09; H, 10.39; O, 8.53. Found: C, 81.33; H, 10.25; O, 8.30.

$\Delta^{1,3}$-Androstadien-17-one (IIc).—A solution of 1.5 g. of the 17β-alcohol IIb in 15 ml. of pyridine was added to a stirred ice-cold slurry of 1.5 g. of chromic oxide in 15 ml. of pyridine. After being kept 18 hr. at room temperature, the mixture was diluted with 120 ml. of ethyl acetate and filtered through Celite, washing well with more ethyl acetate. The filtrate was passed quickly through an alumina column and evaporated to a solid mass. Upon further chromatographic separation hexane removed 770 mg. of $\Delta^{1,3}$-androstadien-17-one (IIc) (52%) and elution with benzene afforded unchanged alcohol. Several recrystallizations of the ketone from methanol yielded a pure sample, m.p. 129–130°; $[\alpha]_D$ +184°; λ_{max} 262 mμ, log ϵ 3.57; ν_{max} 3020 (w), 1745 (s), 735 (m), 712 (m), and 698 (s) cm.$^{-1}$; R.D.,

$[\alpha]_{589}$ +182°, $[\alpha]_{320}$ +2265°, $[\alpha]_{312.5}$ +2685°, $[\alpha]_{300}$ +1870°, (*c* 0.064 in methanol).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.36; H, 9.47; O, 5.92.

17α-Methyl-Δ^{1,3}-androstadien-17β-ol (IId).—To a solution of the above 17-ketone IIc (250 mg.) in 30 ml. of anhydrous ether was added 5.9 ml. of 4 *N* methylmagnesium bromide in ether. The mixture was boiled under reflux during 15 hr. and then poured into aqueous ammonium chloride. Ethyl acetate extracts were washed to neutrality, dried, and evaporated. The resultant oil was subjected to chromatography over alumina. Hexane eluents furnished upon evaporation 120 mg. of 17α-methyl-Δ^{1,3}-androstadien-17β-ol (IId) which, after several recrystallizations from aqueous acetone, had m.p. 118–119°; $[\alpha]_D$ +48°; λ_{max} 262 mμ, log ε 3.55; ν_{max} 3350 (s), 3020 (w), 1645 (w), 739 (m), and 698 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ −48°, $[\alpha]_{320}$ +37°, $[\alpha]_{300}$ −67°, $[\alpha]_{297.5}$ −31°, $[\alpha]_{295}$ +31° (*c* 0.065 in methanol).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.62; H, 10.55; O, 5.85.

17α-Ethynyl-Δ^{1,3}-androstadien-17β-ol (IIe).—A solution of Δ^{1,3}-androstadien-17-one (660 mg.) in tetrahydrofuran (10 ml.) was added to an excess of ethynylmagnesium bromide in the same solvent. After being kept under reflux during 3.5 hr., the solution was stirred a further 18 hr. at room temperature and then poured into ice-cold aqueous ammonium chloride. Ethyl acetate extracts were washed with water to neutrality, dried, and evaporated, Chromatography of the residue over 26 g. of alumina (grade IV) afforded, by elution with 10:1 hexane–benzene, 17α-ethinyl-Δ^{1,3}-androstadien-17β-ol (IIe) (330 mg.) which, after recrystallization from acetone–water, showed m.p. 142–143°; $[\alpha]_D$ +17°; λ_{max} 262 mμ, log ε 3.58; ν_{max} 3560 (m), 3280 (m), 3020 (m), 736 (m), 711 (s), 700 (s), and 668 cm.$^{-1}$; R.D., $[\alpha]_{589}$ +10°, $[\alpha]_{320}$ −148°, $[\alpha]_{298}$ −315°, $[\alpha]_{295}$ −271° (*c* 0.052 in dioxane).

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52; O, 5.40. Found: C, 84.76; H, 9.60; O, 5.78.

Action of Acid on Δ^{1,3}-Androstadien-17β-ol Acetate (IIa).—A solution of 20 mg. of Δ^{1,3}-androstadien-17β-ol acetate (IIa) in 5 ml. of 60% aqueous formic acid was brought rapidly to reflux and 1-ml. aliquots were removed at intervals of 5 min. and added to aqueous sodium hydroxide. Ethyl acetate extracts of the alkaline solutions were washed, dried, and evaporated. The residual oils were examined for absorption in the ultraviolet. Substantial absorption at 235 mμ (Δ^{3,5}-diene) was recorded for the second aliquot.

2α-Iodo-Δ^4-androsten-17β-ol Acetate (Va).—A solution of 30 g. of 2α,4α-dibromoandrostan-17β-ol-3-one acetate [18,19] and 30 g. of sodium iodide in 750 ml. of acetone was refluxed for 21 hr. Sodium bromide which precipitated from the dark-colored solution was filtered off and the color discharged from the filtrate by the addition of 5% sodium thiosulfate solution. Dilution with ice–water afforded a solid which was collected, washed with water, and crystallized from methylene chloride–heptane to furnish 20 g. of 2α-iodo-Δ^4-androsten-17β-ol acetate, m.p. 113–124° dec. Further recrystallization from the same solvent mixture gave the analytical sample, m.p. 126–130° dec.; $[\alpha]_D$ +80°; λ_{max} 244 mμ, log ε 4.15; ν_{max} 1732 (s), 1677 (s), and 1250 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ −44°, $[\alpha]_{400}$ +171°, $[\alpha]_{362.5}$ +285°, $[\alpha]_{335}$ +117°, $[\alpha]_{320}$ +348°, $[\alpha]_{307.5}$ +629°, $[\alpha]_{290}$ +308° (*c* 0.06 in methanol).

Anal. Calcd. for $C_{21}H_{29}O_2I$: C, 55.26; H, 6.40; I, 27.80. Found: C, 55.56; H, 6.53; I, 27.77.

2α-Iodo-Δ^4-androstene-3,17β-diol 17β-Acetate (Vb).—A solution of 20 g. of previous 2α-iodo-3-ketone Va in 300 ml. of dioxane was mixed with a solution of 10 g. of sodium borohydride in 30 ml. of water and then kept for 18 hr. at 10° before diluting with ice–water. The solid which separated was collected (19 g.) and 3 g. subjected to chromatography over neutral alumina. Benzene eluted 1.3 g. of 2α-iodo-Δ^4-androstene-3,17β-diol 17β-acetate which was crystallized several times from methylene chloride–isopropyl alcohol to furnish the analytical sample, m.p. 105–110° dec.; $[\alpha]_D$ +19°; λ_{max} 258 mμ, log ε 2.94; ν_{max} 3320 (m), 1740 (s), and 1260 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}O_3I$: C, 55.02; H, 6.81; I, 27.68. Found: C, 55.40; H, 6.51; I, 27.26.

Δ^{2,4}-Androstadien-17β-ol Acetate (VIa).—A mixture of 1.0 g. of the iodohydrin (Vb), 6.0 g. of copper–zinc couple,[24] and 2.5 g. of sodium acetate in 30 ml. of glacial acetic acid was stirred at or below room temperature for 6 hr. Temperature control was ensured by initial placement of the reaction vessel in a bath at 10°, the temperature of which slowly rose to 20°. Thereafter inorganic materials were removed by filtration and washed well with hexane. After being diluted with water the filtrate was extracted with hexane, and the extracts were washed to neutrality, dried, concentrated *in vacuo* at 40° to small volume, and passed through alumina. Elution with hexane furnished 610 mg. of product which after four recrystallizations from methylene chloride–pentane gave an analytical sample of Δ^{2,4}-androstadien-17β-ol acetate (VIa), m.p. 102–104°; $[\alpha]_D$ +158°; λ_{max} 266 mμ, log ε 3.78, with a shoulder at 272–274 mμ, log ε 3.74; ν_{max} 1732 (s), 1250 (s), 725 (s), and 696 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +135°, $[\alpha]_{320}$ +1682°, $[\alpha]_{295}$ +3430°, $[\alpha]_{292.5}$ +3325° (*c* 0.052 in methanol).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.24; H, 9.74; O, 10.28.

Δ^{2,4}-Androstadien-17β-ol (VIb).—To 300 mg. of lithium aluminum hydride in 80 ml. of anhydrous ether was added 1.0 g. of Δ^{2,4}-androstadien-17β-ol acetate (VIa) in 70 ml. of the same solvent. Addition was complete in 2 min., and the mixture was then stirred at room temperature for 0.5 hr. Destruction of the excess of lithium aluminum hydride was effected with a saturated solution of sodium sulfate, and the ethereal layer was separated and dried (anhydrous sodium sulfate). Removal of the solvent under reduced pressure left a solid residue, m.p. 152–158°, which was chromatographed over neutral alumina (grade II). Methylene chloride–hexane (1:1) eluent afforded upon evaporation 620 mg. of Δ^{2,4}-androstadien-17β-ol, further purified by crystallization from methylene chloride–hexane mixture and then sublimation, to give the analytical sample, m.p. 171–173°; $[\alpha]_D$ +209°; λ_{max} 266 mμ, log ε 3.77, with a shoulder at 271–275 mμ, log ε 3.72; ν_{max} 3260 (m), 721 (m), and 694 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +93°, $[\alpha]_{350}$ +1042°, $[\alpha]_{295}$ +3225°, $[\alpha]_{290}$ +2790° (*c* 0.0075 in methanol).

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36; O, 5.87. Found: C, 84.00; H, 10.36; O, 6.21.

Δ^{2,4}-Androstadien-17-one (VIc).—Concentrated sulfuric acid (1.87 ml.) was added to a solution of 2.6 g. of potassium dichromate in 50 ml. of water, and the resultant mixture was cooled to room temperature before the further addition of a solution of 700 mg. of Δ^{2,4}-androstadien-17β-ol (VIb) in 200 ml. of ether. The two-phase system was stirred efficiently during 2 hr. at room temperature after which time the ether layer was separated and washed successively with water, aqueous sodium bicarbonate, and water, before being dried. Evaporation under reduced pressure led to a crystalline mass, m.p. 103–110°, which was purified by chromatography over neutral alumina. Methylene chloride–pentane (1:9) eluent on evaporation yielded Δ^{2,4}-androstadien-17-one, further purified by recrystallization from methylene chloride–pentane to prisms, m.p. 134–136°; $[\alpha]_D$ +292°; λ_{max} 266 mμ, log ε 3.79, with a shoulder at 271–275 mμ; ν_{max} 1740 (s), 728 (m), and 698 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +182°, $[\alpha]_{350}$ +2170°, $[\alpha]_{307.5}$ +5900°, $[\alpha]_{290}$ +4330° (*c* 0.01 in methanol).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.40; H, 9.79; O, 5.81.

17α-Methyl-Δ^{2,4}-androstadien-17β-ol (VId).—To a solution of methylmagnesium iodide (prepared from 540 mg. of magnesium) in 600 ml. of anhydrous ether was added, in one portion, 790 mg. of the 17-ketone VIc in 600 ml. of anhydrous ether, and the mixture was kept 1 hr. at room temperature. Destruction of the excess of Grignard reagent was achieved through the cautious addition of ammonium chloride solution to the stirred reaction mixture. After being washed with water and then dried, the ethereal solution was evaporated to dryness. The residual solid was subjected to chromatography over neutral alumina from which methylene chloride–hexane (1:1) removed 510 mg. of 17α-methyl-Δ^{2,4}-androstadien-17β-ol. An analytical sample, prepared by four crystallizations from aqueous acetone, and sublimation, had m.p. 166–168°; $[\alpha]_D$ +128°; λ_{max} 266 mμ, log ε 3.75 with a shoulder at 271–275 mμ; ν_{max} 3300 (m), 722 (m), and 695 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +132°, $[\alpha]_{350}$ +1182°, $[\alpha]_{292.5}$ +4050°, $[\alpha]_{290}$ +3735° (*c* 0.009 in methanol).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.51; H, 10.42; O, 6.05.

2α,4α-Dibromopregnan-20β-ol-3-one Acetate (IVb).—To a solution of 5.52 g. of pregnane-20β-ol-3-one acetate[26] in 55 ml. of glacial acetic acid, 5.5 g. of bromine in 50 ml. of glacial acetic acid was added dropwise in 10 min. at room temperature. The mixture was kept at room temperature for 1 hr. and then poured

into ice–water. The precipitate which formed was collected and washed with water. Crystallization from methylene chloride–isopropyl alcohol afforded 5.4 g. of the dibromopregnane, IVb, from which an analytical sample was obtained by recrystallization from the same solvent pair, m.p. 184–186° dec.; $[\alpha]_D$ +18°; λ_{max} 264–268 mμ, log ε 2.05; ν_{max} 1750 (s), 1735 (s), 1245 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +4°, $[\alpha]_{305}$ +454°, $[\alpha]_{300}$ +443° (*c* 0.001 in dioxane).

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.28; H, 6.61; Br, 30.84. Found: C, 53.54; H, 6.59; Br, 31.22.

2α-Iodo-Δ^1-pregnen-20β-ol-3-one Acetate (Vc).—The mixture of 3.8 g. of the dibromopregnane, IVb, and 4.6 g. of sodium iodide in 160 ml. of acetone was refluxed for 7 hr. Sodium bromide was removed from the dark-colored solution by filtration and washed with acetone. The iodine color of the filtrate was discharged through the addition of 10% sodium thiosulfate solution. Addition of ice–water caused the precipitation of 2α-iodo-Δ^4-pregnen-20β-ol-3-one acetate (Vc), which was filtered, washed with water, and dried (yield, 3.8 g.), m.p. 124–128° dec. An analytical sample crystallized several times from methylene chloride–isopropyl alcohol exhibited m.p. 127–129° dec.; $[\alpha]_D$ +136°; λ_{max} 246 mμ, log ε 4.15; ν_{max} 1736 (s), 1683 (s), and 1612 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +110, $[\alpha]_{374}$ +579, $[\alpha]_{345}$ +267°, $[\alpha]_{341}$ +247°, $[\alpha]_{330}$ +380°, $[\alpha]_{295}$ +1328°, $[\alpha]_{290}$ +1019° (*c* 0.001 in dioxane).

Anal. Calcd. for $C_{23}H_{33}O_3I$: C, 57.02; H, 6.87; O, 9.91; I, 26.20. Found: C, 57.21; H, 7.13; O, 10.03; I, 26.47.

Δ^{2,4}-Pregnadien-20β-ol Acetate (VIc).—To a solution of 14 g. of sodium borohydride in 42 ml. of water, 27.8 g. of 2α-iodo-Δ^4-pregnen-20β-ol-3-one acetate (Vc) dissolved in 43 ml. of dioxane was added and the two-phase mixture kept at 5° for 17 hr. Precipitation from the above mixture with ice–water and filtration afforded 23.9 g. of the iodohydrin, m.p. 113–117° dec. A mixture of 5 g. of this crude iodohydrin, 9.25 g. of sodium acetate, and 10 g. of zinc–copper couple[24] in 275 ml. of glacial acetic acid was stirred efficiently at room temperature for 6 hr. Filtration followed by addition of ice–water to the filtrate afforded a milky precipitate which was extracted with hexane. The hexane solution was washed with water, 5% sodium bicarbonate solution, and finally with water until the washings were neutral. After being dried, the hexane solution was filtered and evaporated to furnish a crystalline mixture. This was chromatographed over neutral alumina and the fractions eluted with benzene–hexane (1:4) were collected to afford 1.3 g. of Δ^{2,4}-pregnadien-20β-ol acetate (VIe). An analytical sample was obtained by crystallization from acetone, m.p. 140–142°; $[\alpha]_D$ +209°; λ_{max} 266 mμ, log ε 3.80 (shoulder at 271–274 mμ); ν_{max} 1735 (s), 1245 (s), 721 (m), 695 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +255°, $[\alpha]_{292.5}$ + 4380°, $[\alpha]_{290}$ +4160° (*c* 0.04 in methanol).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 80.66; H, 9.92; O, 9.11. Found: C, 80.72; H, 10.10; O, 9.28.

Δ^{2,4}-Pregnadien-20β-ol (VIIf).—To a suspension of 900 mg. of lithium aluminum hydride in 1500 ml. of ether 3.0 g. of Δ^{2,4}-pregnadien-20β-ol acetate (VIe) was added, and the mixture was kept at room temperature for 2 hr. The excess of the hydride was destroyed with a saturated solution of sodium sulfate and the ethereal solution dried and filtered. Evaporation afforded 2.9 g., m.p. 110–116°, of Δ^{2,4}-pregnadien-20β-ol (VIf), from which an analytical sample was obtained by recrystallization from methylene chloride–hexane, m.p. 121–122°; $[\alpha]_D$ +182°; λ_{max} 266 mμ, log ε 3.81 (shoulder at 271–274 mμ); ν_{max} 3400 (m), 719 (m), and 684 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +284°, $[\alpha]_{292.5}$ +4190°, $[\alpha]_{290}$ +3845° (*c* 0.04 in methanol).

Anal. Calcd. for $C_{21}H_{32}O$: C, 84.01; H, 10.75; O, 5.44. Found: C, 84.00; H, 10.78; O, 5.60.

Δ^{2,4}-Pregnadien-20-one (VIg).—A two-phase system of 2000 ml. of ether containing 1.77 g. of Δ^{2,4}-pregnadien-20β-ol (VIf) and 260 ml. of water containing 13.4 g. of potassium dichromate and 9.6 ml. of concentrated sulfuric acid was stirred efficiently for 24 hr. at room temperature. Thereafter the ether solution was washed with water, 5% sodium bicarbonate solution, and finally with water until the washings were neutral. The solution was dried over sodium sulfate and evaporated to give the crude diene, VIg, m.p. 99–107°, which was chromatographed over neutral alumina. Elution with chloroform–hexane (1:9) afforded 930 mg. of Δ^{2,4}-pregnadien-20-one (VIg). An analytical sample crystallized from acetone–hexane had m.p. 116–118°; $[\alpha]_D$ +296°; λ_{max} 266 mμ, log ε 3.82 (shoulder at 271–274 mμ); ν_{max} 1700 (s), 728 (m), and 702 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +541°, $[\alpha]_{292.5}$ +7740° $[\alpha]_{290}$ +7230° (*c* 0.001 in methanol).

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13; O, 5.36. Found: C, 84.48; H, 10.17; O, 5.48.

Action of Acid on Δ^{2,4}-Pregnadien-20β-ol Acetate (VIe).—A solution of 26 mg. of Δ^{2,4}-pregnadien-20β-ol acetate (VIe) in 5 ml. of acetic acid and one drop of 15% hydrochloric acid was refluxed for 2 hr. The mixture was then extracted with ethyl acetate and washed with water, 5% sodium bicarbonate solution, and finally with water. Evaporation of the solvent led to an oil which exhibited λ_{max} 242, 235, 227 mμ.

5α,6α-Epoxy-pregnane-3β,17α-diol-20-one 17-Acetate (VIIa).—To 50 g. of 17α-acetoxy-Δ^5-pregnen-3β-ol-20-one[28] in solution in 250 ml. of chloroform was added, in one portion, an excess (900 ml.) of monoperphthalic acid solution[40] and the mixture kept at 0° for 16 hr. Ethyl acetate was added and the solution washed successively with water (enough ethyl acetate was used to ensure a good separation into two layers with water), sodium bicarbonate solution, water, sodium thiosulfate solution, and water. Distillation of the washed and dried solution gave a crystalline mass which was delivered (in benzene solution) to a column of neutral alumina. Elution with chloroform–benzene (1:1) furnished 25 g. of the epoxide VIIa, which was purified through recrystallization from methylene chloride–heptane to obtain the analytical sample, m.p. 252–254°; $[\alpha]_D$ −57°; ν_{max} 3420 (m), 1735 (s), 1720 (s), and 1250 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 71.21; H, 8.56; O, 20.15.

5α,6α-Epoxypregnane-3β,17α-diol-20-one 3-Tosylate 17-Acetate (VIIb).—To a solution of 7.0 g. of previous epoxide VIIa in 200 ml. of dry pyridine was added 7.0 g. of *p*-toluenesulfonyl chloride, and the mixture was kept at room temperature for 20 hr. Work-up in the normal manner furnished the tosylate VIIb as a solid which was purified by chromatography over neutral alumina. Elution with benzene provided 6 g. of the tosylate which, after several recrystallizations from isopropyl alcohol, had m.p. 184–186° dec.; $[\alpha]_D$ −54°; λ_{max} 226, 262, and 274 mμ, log ε 4.10, 2.76, and 2.69, respectively; ν_{max} 1735 (s), 1712 (s), 1250 (s), and 668 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{40}O_7S$: S, 5.88. Found: S, 5.73.

5α,6α-Epoxy-Δ^2-pregnen-17α-ol-20-one Acetate (VIIc).—A mixture of 1 g. of the 5α,6α-epoxide 3β-tosylate VIIb and 1 g. of lithium carbonate in 50 ml. of dimethylacetamide was kept under reflux during 3.5 hr. Thereafter the inorganic salts were removed by filtration and washed well with ethyl acetate. The combined washings and filtrate were washed with water, dried, and evaporated. Chromatography of the residue over alumina and elution with benzene led to 200 mg. of the Δ^2-5α,6α-epoxide VIIc. Crystallization from methylene chloride–heptane followed by sublimation gave a sample with m.p. 214–216°; $[\alpha]_D$ −40°; ν_{max} 1735 (s), 1715 (s), 1250 (s), and 750 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 73.90; H, 8.77; O, 17.14.

Δ^{2,5}-Pregnadien-17α-ol-20-one Acetate (VIII).—A mixture of 1.2 g. of 5α,6α-epoxy-Δ^2-pregnen-17α-ol-20-one acetate (VIIc), 1.5 g. of sodium iodide, 400 mg. of sodium acetate, and 280 mg. of zinc, in 20 ml. of acetic acid containing 0.25 ml. of water, was stirred at room temperature for 6 hr. Solid material was collected by filtration, and the filtrate was diluted with water and extracted with ethyl acetate. These extracts were washed with water, with 5% aqueous sodium bicarbonate, and with water again. Evaporation of the dried extracts and subsequent chromatography of the residual solid over neutral alumina gave from the benzene eluent 845 mg. of the Δ^{2,5}-diene VIII, further purified by recrystallization from ethyl alcohol to obtain the analytical sample, m.p. 176–178°; $[\alpha]_D$ −47°; ν_{max} 1740 (s), 1715 (s), 1250 (s), and 798 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.25; H, 9.30; O, 13.54.

Acid-Catalyzed Isomerization of Δ^{2,5}-Pregnadien-17α-ol-20-one Acetate (VIII).—(a) A solution of the Δ^{2,5}-diene VIII in acetic acid containing 1% hydrochloric acid was kept at room temperature 24 hr. Isolation of the diene by dilution with water and extraction furnished a solid with weak ultraviolet absorption, λ_{max} 235 mμ, log ε 2.05.

(b) A solution of 20 mg. of the Δ^{2,5}-diene VIII in 5 ml. of acetic acid containing 4 drops of concentrated hydrochloric acid and 3 drops of water was boiled under reflux during 3 hr. Dilution with water and ethyl acetate extraction led to a gum from which

(40) E. E. Royals and L. L. Harrell, *J. Am. Chem. Soc.*, **77**, 3405 (1955).

was obtained by chromatographic separation over alumina and elution with benzene 15 mg. of a product, m.p. 130–145°.

Recrystallization from aqueous acetone furnished a sample, m.p. 155–163°; λ_{max} 235 mμ, log ε 4.24, with shoulders at 243 and 229 mμ. The infrared spectrum and chromatographic behavior were very similar to those of authentic $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate[31] (IIIc) (λ_{max} 228, 235, and 243 mμ, log ε 4.30, 4.35, and 4.15, respectively).

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxy-pregnan-3β-ol-11-one (Xa).—To 10 g. of 17α,20:20,21-bismethylenedioxy-Δ^5-pregnen-3β-ol-11-one[33] (IX) in 150 ml. of chloroform was added an excess (1000 ml.) of monoperphthalic acid solution, and the mixture was kept at 0° for 18 hr. Some crystalline material separated and was collected (1.03 g.) by filtration. The filtrate was diluted with ethyl acetate, sufficient to ensure formation of a two-phase system, after which the organic solution was washed with water, 5% sodium bicarbonate solution, and water again. Traces of monoperphthalic acid which persisted in the ethyl acetate solution were destroyed with 5% sodium iodide solution, and the liberated iodine was then discharged with 5% sodium thiosulfate solution. Finally, the dried ethyl acetate solution was evaporated to dryness, and the crystalline residue was then combined with the precipitate obtained earlier and subjected to chromatography over neutral alumina. Benzene–chloroform (1:3) eluted 9.0 g. of the 5α,6α-epoxide (Xa) which, after several crystallizations from isopropyl alcohol, had m.p. 260–261°; $[\alpha]_D$ −116°; ν_{max} 3280 (m) and 1705 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67; O, 26.64. Found: C, 65.73; H, 7.75; O, 26.09.

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxypregnan-3β-ol-20-one Tosylate (Xb).—*p*-Toluenesulfonyl chloride (5.0 g.) was added to a solution of 5 g. of preceding 5α,6α-epoxy 3β-alcohol Xa in 100 ml. of anhydrous pyridine, and the mixture was then kept 17 hr. at room temperature. When the mixture was poured into ice–water, a precipitate formed which was collected, washed with water, and purified by chromatography over alumina. Chloroform–benzene (3:7) eluent removed the tosylate Xb which was recrystallized from chloroform–isopropyl alcohol to furnish 3.9 g. of the pure material, m.p. 192–194°; $[\alpha]_D$ −96°; λ_{max} 226, 256, 262, 267, and 274 mμ, log ε 4.08, 265, 2.75, 2.70, and 2.61, respectively; ν_{max} 1699 (s), 1600 (m), 1500 (w), and 668 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_9S$: C, 62.69; H, 6.66; S, 5.57. Found: C, 63.02; H, 6.66; S, 5.62.

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxy-Δ^2-pregnen-11-one (Xc).—A mixture of 3.8 g. of the tosylate Xb and 2.0 g. of lithium carbonate in 25 ml. of dimethylacetamide was boiled under reflux for 5 hr. After filtration the solution was poured into water, and the precipitate was collected and subjected to chromatographic purification over alumina. Benzene eluted 950 mg. of the Δ^2-5α,6α-epoxide Xc containing impurities which absorbed in the ultraviolet (λ_{max} 320, 308, and 297 mμ). Rechromatography over silica gel sequestered these impurities and ethyl acetate–benzene (1:4) eluted 780 mg. of the Δ^2-5α,6α-epoxide Xc. Further recrystallization from isopropyl alcohol and sublimation gave the analytical sample, m.p. 213–214°; $[\alpha]_D$ −76°; ν_{max} 1700 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; O, 23.85. Found: C, 68.38; H, 7.47; O, 23.72.

17α,20:20,21-Bismethylenedioxy-$\Delta^{2,5}$-pregnadien-11-one (XIa).—A Cornforth reaction was carried out, as described before, on a mixture consisting of 700 mg. of the Δ^2-5α,6α-epoxide Xc, 400 mg. of sodium acetate, 1 g. of sodium iodide, and 320 mg. of zinc–copper couple[24] in 10 ml. of acetic acid containing 2 drops of water, for 1.5 hr. at room temperature. Work-up as before followed by chromatography of the crude product over alumina led to 530 mg. of the $\Delta^{2,5}$-diene XIa from evaporation of the benzene–hexane (1:1) eluent. Recrystallization from isopropyl alcohol afforded the analytical sample, m.p. 155–158°; $[\alpha]_D$ −113°; ν_{max} 1700 (s) and 803 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.39; H, 7.92; O, 20.42.

17α,20:20,21-Bismethylenedioxy-$\Delta^{5,2}$-pregnadien-11β-ol (XIb).—The $\Delta^{2,5}$-diene 11-ketone XIa (400 mg.) in 30 ml. of dry tetrahydrofuran was added during 5 min. to a suspension of 400 mg. of lithium aluminum hydride in 40 ml. of the same solvent. The mixture was then stirred for 1 hr. at room temperature before being worked up as described earlier for a similar reduction with this reagent. Chromatography of the crude product over silica gel gave 360 mg. of the $\Delta^{2,5}$-diene-11β-ol XIb in the chloroform–benzene (1:9) eluent. An analytical sample prepared by several recrystallizations from isopropyl alcohol had m.p. 219–220°; $[\alpha]_D$ −61°; ν_{max} 3450 (m) and 800 (s) cm.$^{-1}$; and no detectable absorption in the ultraviolet, at 235 mμ.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.14; H, 8.45; O, 20.42.

Acid Hydrolysis of 17α,20:20,21-Bismethylenedioxy-$\Delta^{2,5}$-pregnadien-11β-ol (XIb).—The bismethylenedioxy compound XIb (200 mg.) in solution in 50 ml. of dioxane was added to a boiling solution of 70% aqueous formic acid, and the mixture was refluxed for 2 min. Thereafter the clear solution was poured into ice–water, and to the slightly turbid solution which resulted was added dropwise a cold solution of 20% sodium hydroxide to pH 7. The precipitate which formed was collected, washed with water, and dried (136 mg.; λ_{max} 236 mμ, log ε 3.10). A solution of this material in 5 ml. of dioxane was diluted with 10 ml. of methanol and then treated with 10 ml. of 2% methanolic potassium hydroxide at 0° for 1 hr., during which time dry nitrogen was slowly bubbled through the solution. When the solution was poured into ice–water a solid separated, which was collected, washed with water, and dried. To the dry product were added 5 ml. of pyridine and 2 ml. of acetic anhydride, and the mixture was kept for 16 hr. at room temperature then poured into ice–water. The solids which were precipitated were filtered off, washed with water, and dried (80 mg.), m.p. 100–210°. Paper chromatography revealed the presence of at least three products. Chromatography of the mixture over silica gel and elution with chloroform–hexane, chloroform, and acetone–chloroform afforded a succession of heterogeneous oily fractions all of which absorbed in the ultraviolet at 235 mμ and gave strong positive tests for the free corticoid side chain. Only traces of crystalline product resulted.

A New Synthesis of 5-Benzylpyrimidines[1]

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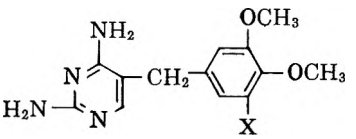
Aromatic aldehydes undergo base-catalyzed condensations with propionitriles having electron-withdrawing substituents in the β-position to give mixtures of isomers resulting from condensation α to the nitrile function. The condensation products react with guanidine to give 2,4-diamino-5-benzylpyrimidines in fair to good yields. It is shown that losses are mainly due to nucleophilic attack of the base on the *para* position of the arylidene propionitrile when that position is substituted by an alkoxy group.

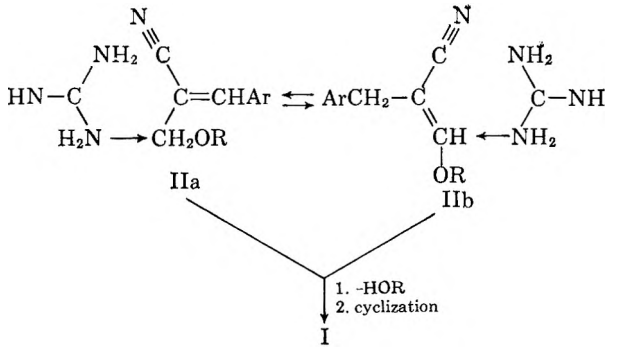
A number of 2,4-diamino-5-benzylpyrimidines, especially Ia and Ib, possess marked antibacterial activity.[2] Utilization of these compounds has been limited by expense, since the previously known synthesis[3] involves seven steps, some of them rather unsatisfactory, with an over-all yield of 20% or less. The synthesis of the closely related 5-arylpyrimidines,[4] on the other hand, is quite efficient. The superiority of the latter synthesis depends on the availability of α-aryl-β-alkoxyacrylonitriles, which are readily prepared by several methods[4] not applicable to the intermediates for benzylpyrimidine synthesis.



Ia, X = H
b, X = OCH_3

If an aldehyde could be condensed with a suitable propionitrile (such as the readily available β-ethoxypropionitrile), the expected product would have the structure IIa which would be in tautomeric equilibrium with IIb. The latter is a homolog of enol ethers used in 5-arylpyrimidine synthesis (IIb, Ar in place of CH_2Ar) and would be expected to cyclize with guanidine along the line of Reaction Scheme A. Alternatively, attack might be initiated on IIa itself which possesses an allylic carbon atom.

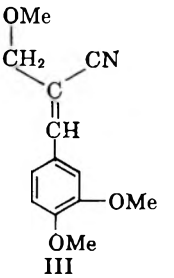
REACTION SCHEME A



In a preliminary experiment veratric aldehyde and β-ethoxypropionitrile were refluxed in a benzene suspension of sodium methoxide and an ethanolic solution of guanidine was added thereto. From the reaction mixture Ia was isolated in about 7% yield. As a result it was decided to investigate the two steps separately and systematically.

The results of condensations of aromatic aldehydes with propionitriles having electron-withdrawing substituents in the β-position are shown in Table I. The reaction appears to be fairly general but no conditions were found that were superior to simple condensations in lower alcohols with alkoxide ion as the base. The products were oils, boiling higher than the parent aldehydes, and appeared to be mixtures of isomers, presumably IIa and IIb, each of which can have two geometrical forms. These crude products are referred to as "benzal nitriles." From three of these "benzal nitriles," namely those derived from veratric aldehyde, piperonaldehyde, and 3,4,5-trimethoxybenzaldehyde, crystalline substances were obtained which are believed to have the structure IIa.

In Fig. 1 is shown the absorption curve 2 for α-veratrylidene-β-methoxypropionitrile (III), which is formed by condensation of veratric aldehyde with β-methoxypropionitrile (or by refluxing the β-ethoxy homolog with catalytic amounts of sodium methylate in methanol). Comparison with the absorption curve 1 of *p*-methoxycinnamonitrile indicated conjugation between the aromatic ring and the nitrile function.[5] While no clear evidence as to the geometry is available, the *trans* position of ring and cyano group seems probable.



III

(1) Presented in part before the Organic Division, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) For a discussion of these activities, see B. Roth, E. A. Falco, G. H. Hitchings, and S. R. M. Bushby, *J. Med. Pharm. Chem.*, **5**, 1103 (1962).

(3) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

(4) (a) P. B. Russell and G. H. Hitchings, *ibid.*, **73**, 3763 (1951); (b) P. B. Russell and N. Whittaker, *ibid.*, **74**, 1310 (1952); (c) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951); (d) B. H. Chase and J. Walker, *ibid.*, 3518 (1953); (e) R. Baltzly and P. B. Russell, *J. Org. Chem.*, **21**, 912 (1956).

(5) The additional methoxymethyl substituent would be expected to product a bathochromic shift comparable to that observed (15 mμ) while the lowered absorption coefficient could be caused by steric interference with complete co-planarity.

TABLE I

"BENZAL NITRILES" FROM ArCHO AND XCH_2CH_2CN

Substitution in Ar	X	Catalyst and reaction conditions[a]	Time, hr.	B.p. of product, °C. (pressure)[b]	Yield, %
3,4-$(MeO)_2$	EtO	1.25 eq. of NaOEt in EtOH[c]	2	155–175 (0.45 mm.)	76[d]
3,4-$(MeO)_2$	EtO	0.75 eq. of $NaNH_2$ in benzene. Reflux	5	150–200 (2 mm.)	27
3,4-$(MeO)_2$	EtO	1 eq. of $NaNH_2$ in liq. NH_3	4	160–180 (0.5 mm.)	29
3,4-$(MeO)_2$	EtO	0.6 eq. of NaOMe in dioxane at 100°	4	172–186 (0.9 mm.)	16
3,4-$(MeO)_2$	EtO	0.5 eq. of NaOMe in MeOH. Reflux	24		38
3,4-$(MeO)_2$	MeO[e]	0.33 eq. of NaOMe + $Mg(OMe)_2$ in MeOH at reflux[f]	7	125–130 (0.1 mm.)	80[d]
3,4-$(MeO)_2$	EtO	0.5 eq. of $NaOC_3H_7$ in n-C_3H_7OH at reflux	24		20
3,4-$(MeO)_2$	EtO	0.5 eq. of $NaOC_4H_9$ in n-C_4H_9OH at reflux	4		20
3,4-$(MeO)_2$	Br	1.5 eq. of NaOEt in EtOH. Reflux[c,g]	3	170–180 (1 mm.)	49
3,4-$(MeO)_2$	Me_2N—	0.5 eq. of NaOEt in EtOH. Reflux[c]	6	150–175	32[h]
3,4-$(MeO)_2$	n-C_3H_7S—	0.67 eq. of NaOEt in EtOH. Reflux[c]	4	(0.7 mm.)	73[i]
None	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3	160–180 (5 mm.)	49
4-Cl	EtO	0.3 eq. of NaOEt in EtOH. Reflux[c]	4		75
4-Me_2N	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3	170–190 (0.5 mm.)	24
3-EtO	EtO	1 eq. of NaOEt in EtOH. Reflux[f,j]	8	140–165 (1 mm.)	50
2-MeO	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	2	148–154 (1.5 mm.)	31
3-MeO-4-C_4H_9O	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3		67
3-MeO-4-C_4H_9O-5-Br	EtO	0.25 eq. of NaOEt in EtOH. Reflux[c]	3		80
3-MeO-4-s-C_4H_9O	EtO	1 eq. of NaOEt in EtOH. Reflux[f,j]	6		80
3-MeO-4-n-$C_8H_{17}O$	EtO	1 eq. of NaOEt in EtOH. Reflux[f,j]	6		70
3,4,5-$(MeO)_3$	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3		87[d]
3,4-OCH_2O—	MeO[e]	0.33 eq. of NaOMe in MeOH + $Mg(OMe)_2$. Reflux[f]	7	135–180 (1 mm.)	75[d]

[a] Except where otherwise stated, the amount of β-substituted propionitrile was equivalent to that of aldehyde. The equivalence of catalyst is reckoned on amount of aldehyde used. [b] Where no boiling point is given, product, in ethereal solution, was washed free of aldehyde, dried, and evaporated *in vacuo* on the steam bath. [c] Azeotropic distillation to remove water. [d] Crystalline isomer obtained. [e] By addition of 2 eq. of acrylonitrile to the methylate solution before addition of aldehyde. [f] Product freed of residual aldehyde by bisulfite treatment. [g] Rapid separation of salt (NaBr) was observed. [h] The product was a mixture of ethoxy and dimethylamino derivatives. [i] Mercaptan odors were noted during the reaction. The product probably was not homogeneous. [j] Azeotropic distillation with added benzene.

The distilled oil from which no more of III could be isolated had the absorption shown by curve 3 in Fig. 1. Assuming that the oil could still contain 25% of III (from comparison of the absorption coefficients at 340 mμ) another curve can be reconstructed for the remaining components of the oil [curve 4, $E_{IV} = {}^4/_3 (E_{III} - {}^1/_4 E_{II})$]. This strongly suggests that the oil contains at least two components of which at least one lacks conjugation between the ring and the CN group. When the oil was refluxed in methanol with a catalytic amount of sodium methylate a further amount of III could be recovered. We take this to indicate that the base-catalyzed tautomeric change between III and its isomers does actually exist. As will be seen later, complete and efficient conversion is probably prevented by other factors.

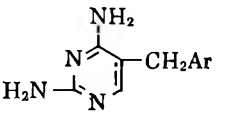
Both the solid III and the unseparated mixture of isomers reacted with guanidine to yield Ia. Yields from III were somewhat the better, reaching a maximum of 40–45% under optimal conditions. The *two* steps together, therefore, afford an over-all yield of about 30%. Cyclization is best accomplished in relatively concentrated solution with methanol as solvent and a considerable excess of guanidine (2–3 equivalents[6]). The best yields were obtained by warming about twenty-four hours at 56° but a shorter reaction period at reflux is not significantly inferior. Use of an inert atmosphere gave no gain in yield. The quantity of ammonia volatilized during such a reaction was found to be somewhat in excess of that produced by heating a methanolic solution of guanidine for the same period, but the quantity was too small to be significant as regards the yield of pyrimidine.

Referring to the proposed Reaction Scheme A, if the bulk of the pyrimidine is formed by attack of guanidine on tautomer IIb present initially as *ca.* 25% of the "benzal nitrile" mixture and replenished by isomeriza-

(6) Higher alcohols are usable but give inferior results both in yield and in rapidity of reaction. One experiment was tried in dimethyl sulfoxide using "guanidine base." Reaction was rapid at room temperature and the only product was the yellow polymer discussed later. "Guanidine base" was the syrup obtained by evaporating a methanolic solution of guanidine *in vacuo*, finally at 0.1-mm. pressure with a Dry Ice trap. The weight of the sirup was consistent not with "guanidine base" but with guanidinium methoxide.

TABLE II

2,4-DIAMINO-5-BENZYLPYRIMIDINES



Ar	M.p., °C.	Yield in cyclization, %	Empirical formula	Anal. % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
2-$MeOC_6H_4$	154	25	$C_{12}H_{14}N_4O$	62.6	62.9	6.1	6.3	24.4	24.4
3-$EtOC_6H_4$	173.5–174	75	$C_{13}H_{16}N_4O$	63.9	63.7	6.6	6.9	22.9	23.3
3-MeO-4-EtO-C_6H_3	188–190	30	$C_{14}H_{18}N_4O_2$	61.3	61.3	6.6	6.6	20.5	20.6
3,4-(O-CH_2O)C_6H_3	255–256	35	$C_{12}H_{12}N_4O_2$	59.0	58.9	5.0	5.1	22.9	22.6
3-MeO-4-s-C_4H_9O-C_6H_3	181–181.5	20	$C_{16}H_{22}N_4O_2$	63.6	63.2	7.3	7.1	18.5	18.2
3-MeO-4-$C_8H_{17}OC_6H_3$	155.5–156	30	$C_{20}H_{30}N_4O_2$	67.0	67.2	8.4	8.6	15.6	15.7
α-$C_{10}H_7$	240–241	80	$C_{15}H_{14}N_4$	72.0	72.6	5.6	5.7	22.2	22.4
			$C_{15}H_{14}N_4 \cdot HCl$	62.8	63.0	5.3	5.5		

tion during the reaction, it is rather surprising that the actual cyclization is so slow in comparison to the 5-arylpyrimidine synthesis (complete in good yield in less than one hour). The unseparated isomer mixture should give a better result than pure IIa. Furthermore, the "benzal nitrile" from *m*-ethoxybenzaldehyde and β-ethoxypropionitrile, whose absorption spectrum suggested presence of a smaller proportion of conjugated isomer, reacted much less rapidly than usual, though eventually giving a good yield. Accordingly we believe that the cyclization is initiated predominantly by attack on IIa.

The other "benzal nitriles" of Table I were cyclized with guanidine to give the corresponding 2,4-diamino-5-benzylpyrimidines. The yields were mainly from 25 to 45%, deviations from which range being critical to the following discussion. Most of the products were known previously. Properties of the new pyrimidines are presented in Table II. Their antibacterial properties have already been reported.[2]

The major loss in these cyclizations is due to development of a yellow gummy material, soluble in hot methanol and in aqueous acid and corresponding roughly to about half the starting nitrile. Attempts to separate it effectively into fractions were unsuccessful. Its intractable nature suggests that it is a polymer. Any further considerable improvement in the synthesis must be dependent on an understanding of the nature of this material and its mode of origin. Its formation evidently is not due to oxidation or to reactions of ammonia present or to a reaction involving the elimination of ammonia.

Further information bearing on the side reaction that produces polymer came from experiments with the "benzal nitriles" derived from α-naphthaldehyde and *m*-ethoxybenzaldehyde. Although crystalline components could be obtained from neither of these condensation products, both gave high yields (80% and 75%) of pyrimidines. In both cases considerable amounts of apparently unchanged "benzal nitrile" could be found when the reactions were stopped while with III not more than traces were present. With neither of these compounds was there any sign of polymer formation. Clearly the formation of polymer is a function of the *p*-alkoxyl group.

Two obvious side reactions that involve a 4-alkoxyl group are possible with such compounds as these "benzal nitriles." These are nucleophilic attacks on the ether alkyl group (1) and on the ring in the *para* position to the conjugated system (2). Both of these points should be made somewhat vulnerable by electron-shift toward the nitrile grouping. It is believed that both these processes do occur, the presumptive nucleophilic reagents being methoxide ion and guanidine base.[7] (See p. 1986, top of col. 1.)

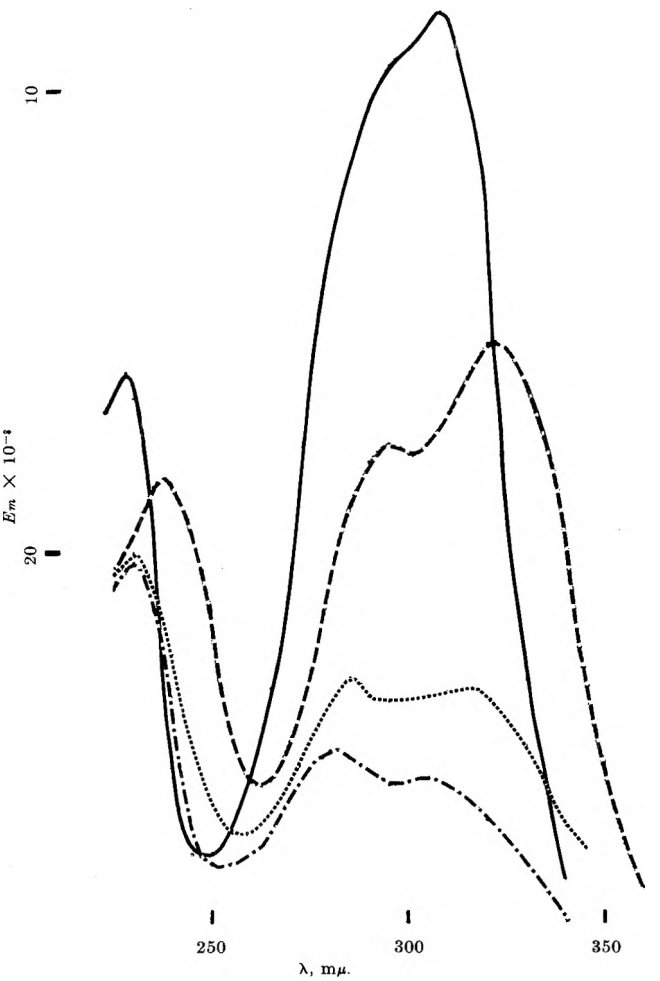
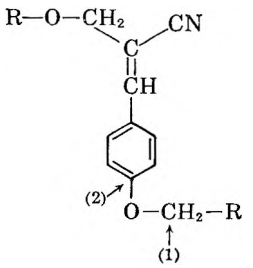


Fig. 1.—Curves 1 ———, *p*-methoxycinnamonitrile; 2, – – – –, compound III; 3, ... , isomer mixture remaining after removal of III; 4, – · – · –, reconstructed curve for other components of isomer mixture.

(7) The relative concentrations of these are uncertain due to lack of precise information as to the acidities of either guanidinium ion or methanol.



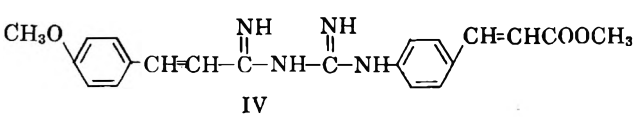
(1) **Attack on the Ether Alkyl Group.**—The products would be phenolic material plus dimethyl ether and methylguanidine. However, it is not apparent why small amounts of phenolic material should lead to formation of polymers under conditions unfavorable to electrophilic substitution.

(2) **Attack on the Ring.**—If methoxide ion engaged in this attack, no alteration would result in III, though compounds with *different* alkoxyl groups would be modified (resulting in diminished yield of the main product). Attack by guanidine base would result in an N-phenyl substituted guanidine. Since that would be a weaker base than guanidine itself, it should be present extensively as base rather than conjugate acid, and should, therefore, enjoy a favored opportunity for further attacks on other molecules of III. Such an operation would thus lead to a polymeric product.

Consideration of such processes involves the effectiveness of guanidine as a nucleophile. On this point exact information is lacking although guanidine is employed extensively in syntheses most readily formulated as involving nucleophilic attack (usually on unsaturated systems and resulting in cyclic products). Experiments involving substitution in 2,4-dichlorobenzyl chloride suggest that, for substitution in aliphatic systems, guanidine is about as active as methoxide ion and much more active than ammonia.

It was possible to demonstrate *both* of these modes of attack through methoxide ion by conducting the cyclization in methanol enriched by $C^{14}H_3OH$. Radioactivity in the isolated pyrimidine Ia corresponded to about 3.5% of exchange, and a radioactive dimethyl ether fraction was obtained corresponding to about two-thirds as much exchange at the methyl group.

Attempts to demonstrate similar substitution on simpler compounds unlikely to cyclize were partially successful. From refluxing solutions of guanidine in methanol, *p*-methoxybenzonitrile and 4-methoxy-α-naphthonitrile were recovered unchanged. However, *p*-methoxycinnamonitrile was largely converted to a yellow polymeric gum similar to that found in the pyrimidine syntheses. Two crystalline substances were isolated in trace amounts during the working up of the reaction product. The first was a hydrochloride with a composition consistent with that of *p*-guanidinocinnamide. The second was obtained as base and as hydrochloride and is formulated as IV.



IV

Both of these structures correspond to probable transformations of primary products from displacement attack of guanidine in the *para* position of *p*-methoxycinnamonitrile.

It, consequently, is believed that diversion of *p*-alkoxy "benzal nitriles" does occur by processes 1 and 2 essentially as outlined earlier. Reactions of this sort have not often been invoked in the past but an analogy can be found in Bunnett's demonstration of attack by methoxide ion on the ester methyl group of methyl benzoate.[8] Such examples will doubtless be multiplied in course of time when suitable techniques are applied to their demonstration.

Experimental

Two main variations were employed in the condensations of aldehydes with β-alkoxy propionitriles. The following illustrate each of these variations. On the subject of the related condensations (in nonalcoholic solvents) it may be said that optimal conditions for reaction have not been determined.

β-Ethoxy-α-veratrylidenepropionitrile.—To a solution of 2.8 g. of sodium methoxide in 140 ml. of absolute ethanol were added 33 g. (0.2 mole) of veratric aldehyde and 20 g. of β-ethoxypropionitrile. The reaction mixture was heated under a fractionating column allowing about 40 ml. to distil each half hour and replacing these quantities with absolute ethanol. After 2 hr., the solution was concentrated *in vacuo* to a thick sirup and partitioned between ether and cold water. Much of the color went into the aqueous layer. The ethereal layer was washed with water until the washings were neutral and then dried over sodium sulfate. The ethereal solution was filtered, the solvent was evaporated, and the residue was distilled at 0.45-mm. pressure, the fraction (37.7 g.) coming over from 155–175° being saved. From a portion of this distillate a solid was obtained. The solid could be recrystallized from ethanol, methanol, or ether–hexane mixture. It melted at 57.5–58° when pure. The absorption spectrum in alcohol showed maxima at 324 mμ (ε 13,600), 295 mμ (ε 10,900), and 238 mμ (ε 10,000). (This curve is virtually identical with curve 2 of Fig. 1.)

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.1; H, 6.9; N, 5.2.

β-Ethoxy-α-(3,4,5-trimethoxybenzylidene)propionitrile.—The condensation was carried out as in the previous preparation. After evaporation of solvent, cold water was added and acetic acid to bring the pH to 6. Ammonia was then added until a pH of 8.5 was reached. The oily product separated and crystallized on further washing with ice–water. After one crystallization from ethanol, the product melted at 74–75°. Further crystallization from methanol raised the melting point to 79–80°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9. Found: C, 65.3; H, 6.9.

Conversion of β-Ethoxy-α-veratrylidenepropionitrile to β-Methoxy-α-veratrylidenepropionitrile.—The preceding solid isomer (4 g.) melting at 57° was added to 50 ml. of methanol in which 0.1 g. of sodium had been dissolved. The solution was heated on the steam bath for 1 hr. and then cooled. Overnight, a solid separated that melted at 45–48°. The entire material was heated a second hour and a solid again was obtained; melting point was now 61–68.5°. After 2 hr. further heating (at or close to reflux) the solid obtained melted at 69.5–72°. This was identical with the β-methoxy derivative whose preparation is described later.

β-Methoxy-α-veratrylidenepropionitrile.—A solution of magnesium methylate was prepared from 3.5 g. of magnesium and 100 ml. of methanol. To it was added 100 ml. of methanol in which 1.5 g. of sodium had been dissolved. The combined solution was placed in a three-necked flask equipped with a mechanical stirrer and a reflux condenser. To this was added 13 ml. of acrylonitrile rather cautiously. After stirring 15 min., 33.2 g. (0.2 mole) of veratric aldehyde was added and the solution was heated rapidly to reflux. By the time boiling had begun, the solution had become markedly turbid. Methanol was allowed to evaporate until the volume had diminished to about 150 ml., after which the reaction mixture was refluxed 6 hr. and allowed to stand overnight.

Ice was added to the stirred reaction mixture, 150 ml. of 2 *N* hydrochloric acid and about 150 ml. of ether. A considerable

(8) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950).

amount of crystalline solid separated. This was filtered off and washed with water and ether, the ethereal layers being combined and separated. The solid was dissolved in 50:50 ether–benzene and was washed successively with water, potassium bisulfite solution, water, dilute sodium hydroxide solution, and again with water. It was then dried over potassium carbonate. The ethereal layers from the original filtration were treated in the same way, bisulfite washing being continued until no more aldehyde was removed. In all, about 3 g. of aldehyde was recovered.

Both solutions, after removal of the desiccant, were put through a short (2 cm.) column of alumina, which removed a small amount of dark impurity, and were evaporated to small volume and diluted with hexane. Several crops of solid were obtained from each, total 26 g.

The mother liquors were combined and distilled at 0.1-mm. pressure (bath temperature, 125–130°). There was obtained 12 g. of a nearly colorless oil. When dissolved in methanol and cooled, this afforded 3 g. more of the solid.

The combined crops of solid were recrystallized from methanol, m.p. 73.5–74°. The absorption spectrum in alcohol is shown in Fig. 1 (curve 2).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 66.9; H, 6.5. Found: C, 66.7; H, 6.4.

The oil obtained when the solvent was evaporated from the last mother liquors had the absorption shown in curve 3 of Fig. 1. Two grams of this oil was dissolved in 10 ml. of methanol in which a trace of sodium (*ca.* 0.05 g.) had been dissolved. After refluxing 6 hr. the solution was cooled and seeded. One-half gram more of the 74° melting solid separated.

β-Methoxy-α-(3,4,5-trimethoxybenzylidene)propionitrile.—In 20 ml. of methanol was dissolved 0.1 g. of sodium. To this was added 3.5 g. of the β-ethoxy derivative, m. p. 79–80°, in 50 ml. of methanol. The solution was refluxed 4 hr. and cooled. The solid that separated was recrystallized twice from methanol. It weighed 1.5 g. and melted at 85–85.5°. The mixture melting point with the starting compound showed a large depression.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.5. Found: C, 64.1; H, 6.5.

The absorption spectrum of this compound was simpler than those of the 3,4-disubstituted derivatives, showing λ_{max} at 232 mμ (ε 15,140) and 308 mμ (ε 15,060) and λ_{min} at 260 mμ (ε 2760).

β-Methoxy-α-piperonylidenepropionitrile.—The preparation followed the procedure described for the veratrylidene analog. Since the product did not crystallize during the early working up, it was distilled after washing and drying. About half of the distillate was obtained as a solid, m.p. 50–51°, after crystallization from methanol.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1. Found: C, 66.6; H, 4.9.

The absorption curve of this compound was virtually identical with that of its veratrylidene analog (curve 2, Fig. 1), λ_{max} 237 mμ (ε 11,200), 291 mμ (ε 9500), 327 mμ (ε 13,500); and λ_{min} 265 mμ (ε 3700), 301 mμ (ε 8100).

Preparation of 2,4-Diamino-5-(3′,4′-dimethoxybenzyl)pyrimidine from β-Methoxy-α-veratrylidenepropionitrile.—One-tenth g.-atom (2.3 g.) of sodium was dissolved in 40 ml. of methanol. Ten grams (0.102 mole) of guanidine hydrochloride was dissolved in 25 ml. of warm methanol. The solution was allowed to cool and added to the sodium methylate solution. The sodium chloride was filtered off and the filtrate was made up to 100 ml. A 5-ml. portion was diluted with water and titrated electrometrically against standard hydrochloric acid. From the curve it was deduced that the guanidine solution was 0.83 *M* in guanidine and 0.05 *M* in ammonia.

Forty milliliters of the preceding guanidine solution and 4.7 g. (0.02 mole) of β-methoxy-α-veratrylidenepropionitrile were placed in a flask heated by boiling acetone.[9] A slow stream of nitrogen was passed through the reaction mixture and thereafter through a gas-wash bottle containing water acidified by 1 ml. of 1.75 *N* perchloric acid and containing methyl red indicator. As the reaction solution became concentrated by evaporation of methanol it was replenished by adding more of the standard guanidine solution. In all, 25 ml. of this solution was added. Heating was continued through 26 hr. During this time the evolution of ammonia was followed, a total of 5.8 mmoles being collected. Since the guanidine solution originally contained 3.3 mmoles of ammonia 2.5 mmoles in excess had developed. (Similar aeration of 30 ml. of the guanidine solution for 21 hr. resulted in collection of 1.7 mmoles of excess ammonia.)

The reaction mixture was initially colorless but was markedly yellow within 2 hr. and solid had begun to precipitate. After 26 hr., the contents of the flask were filtered hot and the precipitate was washed with hot methanol. It weighed 2.3 g. (calcd. 5.4 g.) and, though still yellow, was almost pure Ia.

A duplicate experiment employing 30 ml. of a guanidine solution initially 2.03 *M* in guanidine and 0.05 *M* in ammonia resulted in collection of 6 mmoles of ammonia. The yield of product was 2.4 g. (44% yield). Comparable runs with 1 and 2 equiv. of guanidine to 1 of nitrile gave 25% and 40% yields of Ia, respectively.

No difficulties have been observed in preparation on a much larger scale.

Preparation of Ia Using $C^{14}H_3OH$.—The same apparatus was employed as in the experiment described before. No gas was passed through the reaction chamber but the outlet was connected to a Dry Ice trap.

One-tenth g.-atom (2.3 g.) of sodium was dissolved in 40 ml. of methanol and added to a solution of 10 g. guanidine hydrochloride in 25 ml. of methanol. After filtration, the solution was taken down *in vacuo* to about 15 ml. and filtered into a 25-ml. volumetric flask. After making up to volume, 1 ml. was removed and titrated against standard acid. The solution was 3.8 molar. Fourteen milliliters of this solution was placed in the reaction chamber together with 4 g. (0.017 mole) of β-methoxy-α-veratrylidenepropionitrile. To this was added in 5 ml. of ordinary methanol 8 mg. (0.5 mc.) of $C^{14}H_3OH$. The acetone in the outer chamber of the apparatus was brought to reflux and heating was continued for 23 hr. After cooling for an hour, a boiling chip and 5 ml. of ethyl ether were introduced into the reaction chamber and heating was resumed for 1 hr. The Dry Ice trap was then opened, attached to a vessel containing ordinary dimethyl ether, and 4 g. of that was distilled into the trap. This was closed and left in the Dry Ice bath overnight.

The contents of the reaction vessel was filtered and washed with hot methanol, the filtrate and washings being saved for recovery.

The precipitate (Ia) was dissolved in 10% acetic acid, treated with charcoal, and re-precipitated by ammonia. The solid was filtered off, washed with water, and recrystallized from 80% ethanol. It was subjected to counting at this stage and recrystallized twice more with re-counting at each stage. The average of the counting values corresponded to $1.3 \pm 0.3 \times 10^{-6}$ μc./mg. or to 3.5 ± 1% exchange of the *p*-methoxyl group.

The trap containing the dimethyl ether was removed from the Dry Ice dewar and connected to a vial immersed in Dry Ice. A portion (0.88 g.) of the liquid was distilled by placing the original trap in cold water. The vial was sealed and dispatched for counting.[10] The value obtained was 0.21 μc. for the 0.88 g. = 2.3×10^{-4} mc./g. corresponding to 2.3% exchange at the methyl group of the 4-methoxyl moiety (in relation to the total amount of nitrile used).

β-Methoxy-α-(naphthylmethylene)propionitrile.—The procedure was the same as that described for the veratrylidene analog. When the product could not be induced to crystallize, purification was attempted by chromatography on alumina. This removed much of the color but none of the fractions could be induced to crystallize. The collected material was then distilled at 1-μ pressure. Most of the material came over at 90–100° (bath temperature). Thirty-four grams of distillate was collected (from a 0.2-mole run: a quantity of α-naphthoic acid equivalent to 7% of the starting aldehyde was recovered—it was presumably contained in the aldehyde).

The absorption spectrum of this material in ethanol showed a medium peak at 280 mμ (ε 6360 calcd. for mol. wt., 223) and a strong peak (ε 36,700) at 226 mμ. There is a possible shoulder at about 290 mμ.

2,4-Diamino-5-(α-menaphthyl)pyrimidine.—Twelve grams of this nitrile was added to 100 ml. of methanol containing guanidine base from 15 g. of guanidine hydrochloride. The solution was heated with stirring and methanol allowed to evaporate until the volume had been diminished to about 75 ml. Refluxing was continued for 22 hr. Solid began to separate after about 3 hr. refluxing, but no increase in depth of color was noted at any

(9) The apparatus consists of a 1-l. round-bottom flask having a 24:40 joint available for a condenser. Sealed into it with only the outlet protruding is a 50-ml. spherical flask whose outlet is a female 14:35 joint.

(10) Counting was done by the New England Nuclear Assay Corp.

time. The reaction mixture was filtered hot and the precipitate was washed with water, methanol, and finally with ether; weight, 9.8 g. From the mother liquors 0.4 g. more was obtained. Recrystallization from a rather large volume of 80% ethanol gave material melting at 240–241°. On titration in 50% methanol, the pK_a appears to be about 7 (the situation was complicated by the sparing solubility of both the base and its hydrochloride). The neutral equivalent was 250. The hydrochloride is moderately soluble in alcohol and very sparingly soluble in water.

Condensation of *m*-Ethoxybenzaldehyde with β-Ethoxypropionitrile.—Twenty milliliters of β-ethoxypropionitrile and 22.5 g. (0.15 mole) of *m*-ethoxybenzaldehyde were added to 160 ml. of absolute ethanol in which 2.5 g. of sodium had been dissolved. Forty milliliters of benzene was added and the solution was boiled under a fractionating column for 6 hr., about half of the solvent being allowed to distil during that time. The solution was allowed to stand overnight, concentrated rapidly, and the residue was partitioned between ether and water. The ethereal layer was washed with water, bisulfite solution, and again with water. It was dried briefly over a little calcium chloride, passed through a short alumina column (which removed most of the color), concentrated, and distilled at 1-mm. pressure. A 17.5-g. sample was obtained over the range 140–165°. This oil showed λ_{max} 224 mμ (ε 11,300), 275 mμ (ε 3050); and λ_{min} 259 mμ (ε 2000), from which it is concluded that much of the material was not conjugated completely.

2,4-Diamino-5-(*m*-ethoxybenzyl)pyrimidine.—A guanidine solution was prepared from 30 g. of guanidine hydrochloride and sodium methylate (from 7.2 g. of sodium). After filtration of salt, the solution was concentrated *in vacuo* to 150 ml. To it was added 12.8 g. (0.055 mole) of the described nitrile; the solution was stirred and refluxed for 20 hr. Stirring was continued while the solution (still nearly colorless) was allowed to cool and 100 ml. of water was added. A solid separated that was filtered off, washed with ether, and dried. It melted at 164–166° and weighed 3.5 g. Further evaporation of the mother liquors gave 1 g. more of this solid but there was also obtained 8 g. of an ether-soluble neutral oil, spectrometrically identical with the starting nitrile.

This recovered nitrile together with a further portion to make a total of 11 g. (0.048 mole) was recyclized with a guanidine solution as before, except that the refluxing period was 48 hr. and the solution was allowed to stand overnight. The product, washed with methanol, water, acetone, and ether, weighed 8.3 g. and melted at 166–167.5°. The mother liquors afforded 0.7 g. more of this solid, m.p. 164–166°, and also about 3 g. of neutral, ether-soluble oil.

For analysis, the main crop was recrystallized from 150 ml. of methanol, 6.8 g. being obtained and with melting point unchanged.

4-*n*-Octyloxy-3-methoxybenzaldehyde.—This was prepared from vanillin with octyl iodide and alkali in alcoholic solution. It boils at 165–167° at 1 mm. and melts at 40–42° after crystallization from pentane.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found: C, 72.8; H, 9.4.

Reactions of 2,4-Dichlorobenzyl Chloride with Guanidine and Other Nucleophiles. (a) Guanidine at Room Temperature.—A solution of 0.2 mole of guanidine and 0.3 mole of 2,4-dichlorobenzyl chloride in 140 ml. of methanol was allowed to stand 8 days at room temperature. There were obtained 2.5 g. of a base hydrochloride soluble in cold water and 1.5 g. of an insoluble one. The former proved to be 2,4-dichlorobenzylguanidine hydrochloride, m.p. 146–147°.

Anal. Calcd. for $C_8H_9Cl_2N_3 \cdot HCl$: C, 37.7; H, 4.0; N, 16.5. Found: C, 37.6; H, 4.1; N, 16.3 (Kjeldahl).

The sulfate crystallized from water, m.p. 219°.

Anal. Calcd. for $C_8H_9Cl_2N_3 \cdot 0.5H_2SO_4$: C, 36.0; H, 3.7. Found: C, 35.9; H, 3.8.

The less soluble hydrochloride appeared to be a mixture of more highly alkylated bases. About 100 mg. of one component, probably N,N′-bis(2,4-dichlorobenzyl)guanidine hydrochloride, m.p. 180–181°, was isolated by repeated crystallization from hot water.

Anal. Calcd. for $C_{15}H_{13}Cl_4N_3 \cdot HCl$: C, 43.6; H, 3.4; N. 10.2. Found: C, 43.3; H, 3.7; N, 10.0 (Kjeldahl).

The total amount of the bases corresponded to 7% of the original guanidine.

(b) **Ammonia at Room Temperature.**—A solution of 0.2 mole of 2,4-dichlorobenzyl chloride and 1.5 moles of ammonia in 200 ml. of methanol was allowed to stand 21 days at room temperature. The bases formed were separated as a water-insoluble hydrochloride (5.2 g.) and a water-soluble hydrochloride. The latter (6.5 g.) was identified as the hydrochloride of 2,4-dichlorobenzylamine by melting point and conversion to the guanidine described above. The water-insoluble hydrochloride melted at 212–215° and is the salt of bis(2,4-dichlorobenzyl)amine.

Anal. Calcd. for $C_{14}H_{11}Cl_4N \cdot HCl$: C, 45.3; H, 3.3; N, 3.8. Found: C, 44.7; H, 3.0; N, 3.9 (Kjeldahl).

(c) **Guanidine in Methanol at Reflux.**—One-half mole of "guanidine" and 50 g. (0.255 mole) of 2,4-dichlorobenzyl chloride were refluxed 16 hr. in methanol (total volume 300 ml.). The reaction mixture, after partial evaporation of solvent, was partitioned between water and hexane. Analysis of the aqueous layer showed the presence of chloride equivalent to 0.233 mole (90% of the original dichlorobenzyl chloride). The hexane layers were evaporated and 2,4-dichlorobenzylguanidine equivalent to 0.04 mole isolated by conversion to the hydrochloride and sulfate described before. It is evident that about one-sixth of the dichlorobenzyl chloride had reacted with guanidine and most of the rest with methoxide ion. As mentioned previously, the concentrations of these nucleophiles cannot be calculated. On the assumption that pK_a values for guanidinium ion and methanol are the same, the concentration of methoxide would have been much larger.

(d) **Guanidine in Dimethyl Sulfoxide.**—"Guanidine base" (0.5 mole obtained by evaporation of a methanolic solution *in vacuo*) was dissolved in 130 ml. of dimethyl sulfoxide (it is substantially insoluble in ether, benzene, and dioxane). On addition of 0.25 mole of 2,4-dichlorobenzyl chloride, an exothermic reaction ensued and the temperature was around 50° despite cooling under the tap. The reaction product was a mixture of bases whose hydrochlorides were largely insoluble in water. The only substance that could be isolated in pure form (by crystallization from dimethyl sulfoxide) melted at 279–280° dec. and had the composition of tris(2,4-dichlorobenzyl)guanidine hydrochloride.

Anal. Calcd. for $C_{22}H_{17}Cl_6N_3 \cdot HCl$: C, 45.1; H, 3.2; N, 7.3. Found: C, 45.2; H, 3.5; N, 7.4 (Dumas). About 12 g. of this compound was isolated.

Reaction of Guanidine with *p*-Methoxycinnamonitrile.—To a solution of guanidine (0.15 mole) in methanol was added 8 g. (0.05 mole) of *p*-methoxycinnamonitrile (wt. of solution, 55 g.). The solution was refluxed for 30 hr.; it was then a deep yellow. Most of the methanol was boiled off and water and ether were added to the residue from which a yellow gum precipitated. The gum was collected, redissolved in methanol, and reprecipitated by dilution with water. The ethereal washes were evaporated; the residue weighed less than 0.5 g.

The yellow gum was largely soluble in acetone. After filtering off a small amount of undissolved material, dilute hydrochloric acid was added to bring the pH to about 4, water was added, and the solution was allowed to stand. By gradual evaporation small amounts of two crystalline compounds were obtained (A and B) but the bulk of the material remained gummy and reminiscent of the polymeric by-product of the benzylpyrimidine syntheses.

Compound A was a yellow solid melting at 284–288° and at 286–288° after recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{12}N_4O \cdot HCl$: C, 50.1; H, 5.5; N, 23.3. Found: C, 50.4; H, 5.9; N, 23.0 (Dumas).

Compound B forms a hydrochloride crystallizing in yellow needles from methanol. The color deepens to an orange-red in concentrated hydrochloric acid. When made basic the color disappeared and a colorless base crystallizing from methanol in needles was isolated. It had no useful melting point.

Anal. (of base). Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.7; H, 5.8; N, 14.8. Found: C, 67.2; H, 5.7; N, 14.8 (Dumas).

Anal. (of hydrochloride). Calcd. for $C_{21}H_{22}N_4O_3 \cdot HCl \cdot CH_4O$: C, 59.1; H, 6.1; N, 12.5; CH_4O, 7.2. Found: C, 58.5; H, 5.9; N, 12.5; loss in weight at 90° and 1-μ pressure, 7.1%.

Acknowledgment.—The authors wish to express their gratitude to Dr. S. W. Blackman, Mrs. Veronica Purdy, and Mr. F. J. McMurray for the microanalyses here recorded, to Dr. Samuel Bieber for determinations of radioactivity, and to Drs. Barbara Roth and George H. Hitchings for their advice on special aspects of this problem.

Photochromic Nitrobenzylpyridines

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The synthesis of several nitrobenzylpyridines is presented. These compounds are all photochromic in solution and some are photochromic in the crystalline form. The visible spectra of the irradiated isomers are shown.

A kinetic study on the photoisomerization of 2-(2,4-dinitrobenzyl)pyridine and 2-(2-nitro-4-cyanobenzyl)-pyridine recently was reported.[1] When pale yellow crystals of 2-(2,4-dinitrobenzyl)pyridine or colorless crystals of 2-(2-nitro-4-cyanobenzyl)pyridine are exposed to light the crystals change to blue and green, respectively. When stored in the dark the crystals fade to their original color. Chilled solutions of these compounds also exhibit reversible photochromism.

In order to study this phenomenon, we have prepared a number of substituted benzylpyridines. All of these new compounds show a reversible photochromism in the solution phase and some also exhibit photochromism in the solid state.

The benzylpyridines synthesized are listed in Table I. Compounds I–III were prepared directly from 2-(2-nitro-4-cyanobenzyl)pyridine (VIII), the preparation of which was described by Sousa and Weinstein.[1] Amide III was obtained initially by alkaline peroxide treatment of VIII similar to a procedure reported by Radziszewski.[2] The amide also was obtained when cyano compound VIII was heated with isopropyl alcohol saturated with hydrogen chloride gas. It was not possible to prepare 2-(2-nitro-4-carboxybenzyl)pyridine (IV) by extended hydrolysis of VIII with either 50% sulfuric or 18% hydrochloric acid. However, treatment of the methyl ester (I) with hot 18% hydrochloric acid furnished the acid in good yield. Esters I and II were prepared by the acid-catalyzed alcoholysis of VIII. The azoxy compound V was obtained when 2-(2-nitro-4-aminobenzyl)pyridine was exposed at room temperature to a peroxidic glacial acetic acid solution containing a trace of sulfuric acid. This procedure has been utilized to oxidize aromatic amines to nitroso compounds.[3] It is likely that an intermediate nitroso compound is formed which then reacts with unchanged amine to form an azo compound which in the peroxidic medium oxidizes to the azoxy form.

$$RNH_2 \longrightarrow R{-}N{=}O + RNH_2 \longrightarrow RN{=}NR \xrightarrow{[O]} RN(\uparrow O){=}NR$$

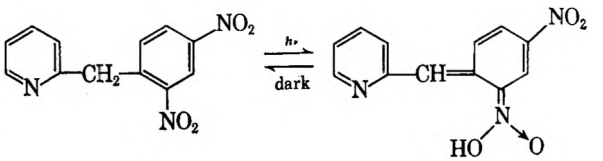
Holmes and Bayer[3] reported that their nitroso compounds precipitated from the reaction mixture. However, in our preparation no material precipitated during the reaction, due to the solubility of the pyridine entity in the acid medium. This solubility factor most likely permits any intermediate nitroso compound to condense with unreacted amine.

The hydroxy compound VI was prepared by the reduction of 2-(2,4-dinitrobenzoyl)pyridine with sodium borohydride in methanol. The benzoyl compound was prepared by the procedure of Nunn and Schofield.[4]

The cyano compound VII was obtained from diazotization of 4-(2-nitro-4-aminobenzyl)pyridine[4] similarly to the preparation of VIII.[1]

Photochromic Properties

The reversible photochromic change from a pale yellow to a deep blue color observed when crystals of 2-(2,4-dinitrobenzyl)pyridine are exposed to light was first reported by Tschitschibabin and co-workers.[5] Since then other workers[1,6,7] have reported the reversible photochromism of cooled solutions of some benzylpyridines. It is believed that the color change shown by these compounds on irradiation is due to the formation of the tautomeric *aci*-nitro structure.[1,7,8]



This view is consistent with the observation that in compounds of this type the requirement for photochromism is the presence of a nitro and —C—H group *ortho* to each other.[1,9] The criterion which is responsible for the apparent lack of photochromism in the crystalline form of some of the benzylpyridines is not clear at this time. In Table I are shown the colors obtained when the crystalline forms are irradiated with a Hanovia lamp. Compounds I–III give a colored form on irradiation at room temperature. In order to observe the photochromism of IV and V, the solid was cooled on Dry Ice. Compounds VI and VII did not show photochromism in the solid phase even when cooled.

The visible spectra of the irradiated colored forms of the benzylpyridines in solution are shown in Fig. 1. Their maxima are given in Table I. The benzylpyridine solutions are essentially colorless before irradiation and revert to the colorless form in the dark. The kinetics of the fading reaction are being investigated and will be the subject of a future paper.

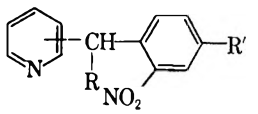
Experimental[10]

Visible Absorption Measurements.—A Cary Model 14 spectrophotometer was used. Solutions were measured in absolute

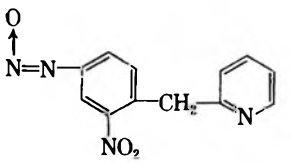
(1) J. A. Sousa and J. Weinstein, *J. Org. Chem.*, **27**, 3155 (1962).
(2) R. Radziszewski, *Ber.*, **18**, 355 (1885).
(3) R. R. Holmes and R. P. Bayer, *J. Am. Chem. Soc.*, **82**, 3454 (1960).
(4) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 5813 (1952).
(5) A. E. Tschitschibabin, B. M. Kuindshsi, and S. W. Benewolenskaja *Ber.*, **58**, 1580 (1925).
(6) R. Hardwick, H. S. Mosher, and P. Passailaigue, *Trans. Faraday Soc.*, **56**, 44 (1960).
(7) H. S. Mosher, C. Souers, and R. Hardwick, *J. Chem. Phys.*, **32**, 1888 1960).
(8) R. Hardwick and H. S. Mosher, *J. Chem. Phys.*, **36**, 1402 (1962).
(9) G. Wettermark, *Nature*, **194**, 677 (1962).
(10) Melting points were taken on a Fisher-Johns block and are not corrected.

TABLE I

WAVE LENGTHS OF THE VISIBLE ABSORPTION BANDS OF IRRADIATED BENZYLPYRIDINES IN ETHANOL SOLUTION AND COLOR OF THE IRRADIATED CRYSTALLINE FORMS



2-Benzylpyridines

Compound	R	R′	Color (solid)	λ_{max}, mμ
I	H	$COOCH_3$	Dark blue-green	405, 460, 485, 575
II	H	$COOCH_2CH_3$	Pale blue-green	410, 460, 485, 585
III	H	$CONH_2$	Pale green	403, 450, 485, 580
IV	H	COOH	Pale gray[a]	405, 450, 470, 580
V	H		Med. blue-green[a]	610
VI	OH	NO_2	...	600

4-Benzylpyridine

VII	H	CN	...	448, 555, 590

[a] Observed by cooling solid on Dry Ice.

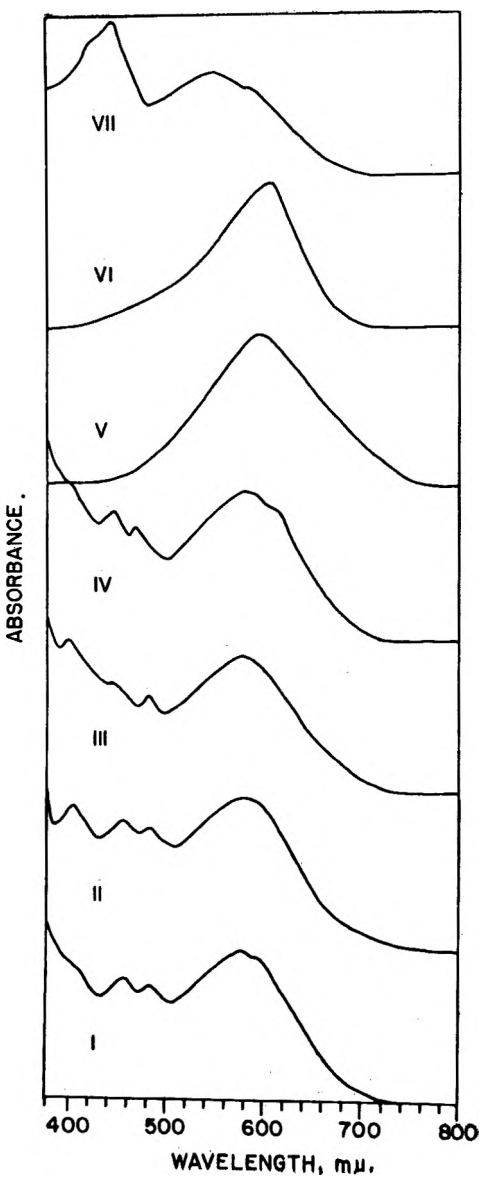


Fig. 1.—Visible absorption spectra of irradiated ethanol solutions measured at −91.0°. The ordinate is in arbitrary units.

"Spectro Grade" ethanol in a cryostated 2.5-cm. cell,[11] against a reference of pure solvent. The solutions at −91.0° were exposed for 2 min. to the unfiltered radiation from a Hanovia Type 16200 lamp with a quartz envelope.

2-(2-Nitro-4-cyanobenzyl)pyridine (VIII).—This cyano compound was prepared according to the procedure of Sousa and Weinstein.[1] The colorless crystals melted at 102–103°.

2-(2-Nitro-4-carbomethoxybenzyl)pyridine (I).—Dry hydrogen chloride gas was passed through 3 ml. of commercial absolute methanol in a 10-ml. round-bottom flask fitted with a condenser protected with a calcium chloride drying tube and a gas inlet tube, for 10 min. To this solution 0.20 g. of the preceding cyano compound VIII was added and the solution heated over a steam bath for 3 hr. On cooling a solid (the hydrochloride) deposited. To this mixture 3 ml. of water was added and the solution made alkaline with 28% ammonium hydroxide. The crystals which deposited were filtered after chilling and washed with water. Recrystallization from aqueous methanol furnished colorless lancelets melting at 67–68° in 75% yield. The infrared spectrum showed no C≡N group and the presence of a carboxylate group.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.49; H, 4.32; N, 10.33.

2-(2-Nitro-4-carboethoxybenzyl)pyridine (II).—The procedure was similar to the preceding reaction, starting with 0.20 g. of VIII. Recrystallization of the product from aqueous ethanol furnished white crystals melting at 72–73° in 83% yield.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.63; H, 4.70; N, 9.65.

2-(2-Nitro-4-carbamylbenzyl)pyridine (III).—In a 50-ml. erlenmeyer flask 0.30 g. of cyano compound VIII was dissolved in 15 ml. of acetone. Two ml. of 10% hydrogen peroxide and 0.10 ml. of 10% sodium hydroxide were added. The solution was placed in the dark at room temperature for 2 days and then evaporated in a current of air. Pale yellow crystals deposited which were filtered and washed with water. Recrystallization from 50% aqueous ethanol furnished cream colored needles melting at 169–170.5° in 70% yield. The infrared spectrum showed absence of C≡N group, and the presence of a carbonyl group at 1685 $cm.^{-1}$. The NH_2 group was observed at 3120 and 3305 $cm.^{-1}$ in a halocarbon mull and at 3411 and 3528 $cm.^{-1}$ in chloroform solution.

Anal. Calcd. for $C_{13}H_{11}O_3N_3$: C, 60.69; H, 4.31; N, 16.33. Found: C, 60.40; H, 4.43; N, 16.40.

2-(2-Nitro-4-carboxybenzyl)pyridine (IV).—2-(2-Nitro-4-carbomethoxybenzyl)pyridine (I) (0.25 g.) was refluxed with 18% hydrochloric acid for 8 hr. The cooled solution deposited fine white needles (hydrochloride) which were filtered and washed with a little ice–water. This product was dissolved in 15 ml. of

(11) J. A. Sousa and J. Weinstein, *Rev. Sci. Instr.*, **34**, 150 (1963).

warm water and just neutralized with 5% sodium hydroxide. The white solid which precipitated was filtered and washed with a small amount of ice–water and recrystallized from 95% ethanol, m.p. 208–210°, white, 0.10 g.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.26; H, 3.91; N, 10.98.

3,3′-Dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene (V).—In a 125-ml. erlenmeyer flask 5 g. of 2-(2-nitro-4-aminobenzyl)pyridine (m.p. 118.5°, prepared according to the procedure of Nunn and Schofield[4]), 40 ml. of glacial acetic acid, 10 ml. of 30% hydrogen peroxide, and 2 drops of concentrated sulfuric acid were combined. The mixture was kept at room temperature for 48 hr., and 50 ml. of water was added followed by treatment with 20% sodium hydroxide. An oil which separated was extracted with toluene, the toluene extract washed with water and dried over anhydrous magnesium sulfate. After removal of the drying agent, the toluene was removed in a current of warm air. The solid yellow residue was recrystallized with a charcoal treatment from aqueous ethanol. The pure compound was yellow and melted at 135–136° (70% yield). The infrared spectrum showed no NH absorption bands.

Anal. Calcd. for $C_{24}H_{18}N_6O_5$: C, 61.27; H, 3.86; N, 17.87; mol. wt., 470.43. Found: C, 61.36; H, 3.97; N, 18.01; mol. wt., 464.0 (vapor pressure method).

2-(2,4-Dinitrobenzoyl)pyridine.—This material was prepared from 2-(2,4-dinitrobenzyl)pyridine by a procedure utilized by Nunn and Schofield[4] to oxidize analogous benzylpyridines. The 2-(2,4-dinitrobenzoyl)pyridine was obtained as white crystals melting at 149.5–151° (lit.[5] m.p. 148°).

2-(2,4-Dinitro-α-hydroxybenzyl)pyridine (VI).—In a 500-ml. round-bottom flask fitted with a condenser, stirrer, and addition funnel, a suspension of 2.75 g. (0.010 mole) of 2-(2,4-dinitrobenzoyl)pyridine in 150 ml. of commercial absolute methanol was cooled to 0° and an ice-cold solution of 1.04 g. (0.028 mole) of sodium borohydride in 15 ml. of methanol was quickly added. The reddish purple mixture was stirred at 0° for 1 hr. and then the temperature allowed to rise. After 1.5 hr. at room temperature the reaction mixture was heated at 50° for 1 hr. Dilute sulfuric acid was added and the inorganic material filtered. The filtrate was evaporated to one-fifth its original volume, an equal volume of water added, and the solution made basic with 2% sodium hydroxide. This mixture was extracted with ether, the ether extracts dried over anhydrous magnesium sulfate, and the drying agent removed. Evaporation of the ether afforded a yellow solid. Recrystallization from ethanol furnished pale yellow crystals melting at 134.5–135° dec. The infrared spectrum showed absence of C=O band and presence of OH band.

Anal. Calcd. for $C_{12}H_9N_3O_5$: C, 52.37; H, 3.30; N, 15.27. Found: C, 52.62; H, 3.36; N, 15.13.

4-(2-Nitro-4-cyanobenzyl)pyridine (VII).—A magnetically stirred solution of 1.5 g. (0.0065 mole) of 4-(2-nitro-4-aminobenzyl)pyridine (m.p. 129–130°, lit.[4] m.p. 130–131°) and 1.68 ml. (0.020 mole) of concentrated hydrochloric acid in 5 ml. of water was cooled to 0° and the amine diazotized by gradual addition of 0.45 g. (0.0065 mole) of sodium nitrite in 4 ml. of water. The diazonium solution was then added to a magnetically stirred mixture of 0.58 g. (0.0065 mole) of cuprous cyanide, 0.85 g. (0.013 mole) of potassium cyanide, 5 ml. of water, and 75 ml. of toluene at 5–10°. The reaction mixture was heated at 80° for 2.5 hr., cooled, and made basic with 5% sodium hydroxide. Solids were collected on a filter. They and the water layer of the filtrate were extracted several times with toluene. The combined extracts were washed with 3% sodium hydroxide, water, and then dried over anhydrous magnesium sulfate. Evaporation of the toluene afforded 0.63 g. of amber residue which rapidly crystallized. Several crystallizations from toluene–ligroin (charcoal treatment) furnished pale yellow crystals melting at 73–74°. The infrared spectrum showed the presence of C≡N group.

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79. Found: C, 64.89; H, 3.95.

Acknowledgment.—The authors wish to thank Mr. C. DiPietro for the chemical analyses.

Michael-Type Addition Reactions of 4-Chloropyrrolo[2,3-*d*]pyrimidines

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4-Chloropyrrolo[2,3-*d*]pyrimidines react with acrylonitrile and ethyl acrylate under strong base catalysis giving N-7 adducts. These addition compounds are shown to be valuable synthetic intermediates.

It previously has been reported that 4-chloropyrrolo-[2,3-*d*]pyrimidine and its 2-methyl relative were readily alkylated on the pyrrole nitrogen (N-7) using alkyl halides under alkaline conditions at room temperatures.[1]

The present investigation deals with the addition of these chloropyrrolopyrimidines, presumably as their anions, to acrylonitrile and to ethyl acrylate. These additions proceeded in excellent yields in refluxing ethanol with a catalytic amount of sodium ethoxide using excesses of the acrylic reagents (Table I). Paper chromatographic studies revealed that, with three moles of either ethyl acrylate or acrylonitrile to each mole of the pyrimidine, the additions were essentially complete after two hours. However, with four or five reactant molar ratios, much troublesome polymeric material resulted. With one or two reactant molar ratios of the acrylic reagents, unchanged materials were detected chromatographically even after four hours at reflux temperatures.[2]

Paper chromatographic studies failed to detect any di- or tri- addition products even after twenty-four hours at reflux. Further paper chromatographic studies revealed that strong base and moderately elevated temperatures were absolute requirements for these addition reactions to proceed within a reasonable length of time (twenty-four hours). The additions did not proceed in glacial acetic acid as shown by chromatography and by quantitative recovery of unchanged pyrrolopyrimidine.

Reaction of these adducts in alkaline media showed them to be reasonably stable. No retrogression was evident when they were heated in aqueous potassium hydroxide solutions (see experimental data and Reaction Scheme II) or when refluxed with an equimolar amount of sodium ethoxide for several hours. The chloro ester compounds under the former conditions yielded the chlorocarboxylic acids, however, as expected. The chloronitrile derivatives did not react under these

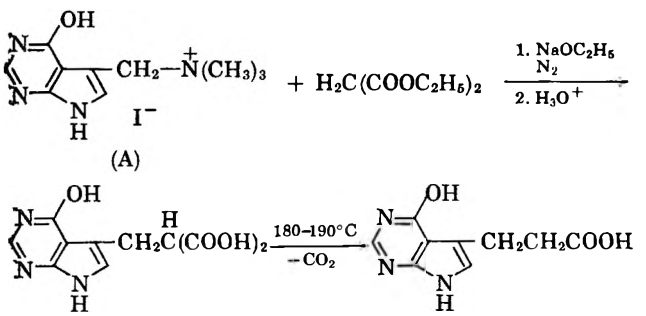
(1) R. A. West and L. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961).

(2) The solvent system employed in these chromatographic studies was a mixture of 5 ml. of isopropyl alcohol and 95 ml. of a 5% aqueous ammonium sulfate solution using 1.5-in.-wide Whatman no. 1 paper strips using the ascending technique. The spots were detected on the dried papers, in a darkroom, using a Fisher Mineralite ultraviolet lamp (2537 Å.).

conditions; there was no evidence of nitrile hydrolysis, chlorine displacement, or retrogression. Retrogression does occur, however, if 2 *M* sodium ethoxide is used at reflux temperatures for short periods, however, even after five to six hours at reflux, retrogression is not complete.

Although simple alkylations of 4-chloropyrrolo[2,3-*d*]-pyrimidines yielded N-7 derivatives, it could not be assumed that such would be the case with these addition reactions. The heat requirement for the addition reactions as well as the excessive molar proportions of the acrylic reagents required as optimum reaction conditions evoked speculation that the modes of attack differed. The reaction mechanisms differ somewhat. The simple alkylations are SN2 reactions, whereas these additions are, presumably, the addition of the pyrrolopyrimidine anion to the electron-deficient β-carbon of the α,β-unsaturated acceptor moleculer. By resonance considerations, the pyrrolopyrimidine anion hybrid should receive contributions from a β-carbanion structure through which C-5 addition might occur.[3] To prove that such C-5 addition did not occur, a C-5 derivative was prepared by the Reaction Scheme I. The

REACTION SCHEME I



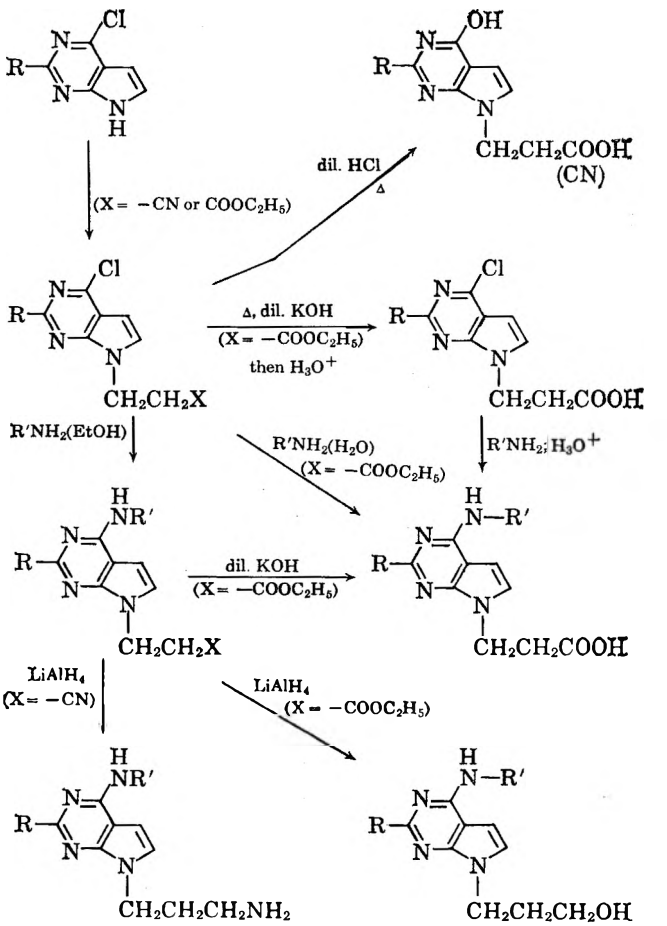
structure of the Mannich base methiodide (A) has been established previously.[4]

The 4-hydroxy-5-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidine (B) arising from this reaction sequence proved to be isomeric (analyses) with that product obtained by the aqueous acid hydrolysis of the 4-chloropyrrolopyrimidine–ethyl acrylate adduct (see Reaction Scheme II and Experimental). The isomers proved to be distinctly different by ultraviolet absorption spectra, paper chromatography, and by melting point properties as described later. The adducts, therefore, were assigned the structures as indicated in Table I and in Reaction Scheme II.

These addition compounds proved to be valuable synthetic intermediates. Being bifunctional, by virtue of a displaceable chlorine and an aliphatic-type of nitrile or ester group, they give rise to a variety of interesting derivatives which would be difficultly accessible by other routes. Reaction Scheme II indicates the facile transformations which may be effected thereby. Benzylamine was chosen as a model amine (being of intermediate nucleophilicity) in these chlorine displacement reactions. These reactions proceed readily in water using a slight excess of the amine with potassium carbonate as the proton acceptor. With the chloronitrile adducts only the halogen was displaced, the nitrile group being unaffected. However, the chloro esters yielded the 4-benzylamino-7-carboxylic acid derivatives. These latter derivatives also are obtained by similar treatment of the corresponding 4-chloro-7-carboxylic acid compounds with benzylamine in water. The 4-benzylamine-7-carboxylic esters could be obtained, however, by the reaction of the chloro ester adduct in ethanol with three molar equivalents of the amine at elevated temperatures in sealed containers. These esters are readily saponified to the corresponding carboxylic acids without affecting the benzylamino moiety as described in the Experimental. Despite the elevated temperatures and excess of amine employed, there was no evidence of amide formation in these reactions.

REACTION SCHEME II

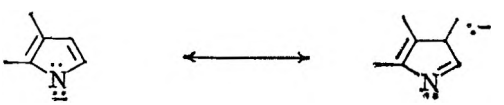
(R = H or CH_3 throughout, R′ = benzyl throughout)



Excesses of lithium aluminum hydride were used to reduce the 4-benzylamino esters and nitriles to their 7-γ-hydroxypropyl and 7-γ-aminopropyl derivatives, respectively. There was no evidence of ring reduction or reductive debenzylation in these reactions. These derivatives were best isolated and purified as their anhydrous monohydrochlorides as noted in Table II.

All of these 4-benzylamino compounds have quite characteristic ultraviolet absorption spectra. The peaks of maximum absorption are between 274–282 mμ with molar absorptivity coefficients on the order of

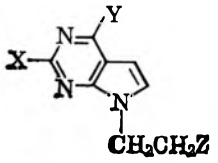
(3) The following structures, among others, contribute to the anion hybrid.



(4) R. A. West, *J. Org. Chem.*, **26**, 4959 (1961).

TABLE I

ADDITION COMPOUNDS AND DERIVATIVES



X	Y	Z	M.p.,[a] °C.	Yield, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
H	Cl	CN	110–111[c]	90	$C_9H_7N_4Cl$	52.1	52.0	3.4	3.5	27.1	26.9
H	Cl	$COOC_2H_5$	[b]	92	$C_{11}H_{12}N_3O_2Cl$	52.3	52.1	4.7	4.7	..	..
CH_3	Cl	CN	99–100[c]	84	$C_{10}H_9N_4Cl$	54.4	54.3	4.1	3.8	25.3	25.1
CH_3	Cl	$COOC_2H_5$	27[c]	84	$C_{12}H_{14}N_3O_2Cl$	53.8	54.0	5.3	5.2	15.7	15.7
H	Cl	COOH	169–171	92	$C_9H_8N_3O_2Cl$	47.8	47.9	3.6	3.7	18.6	18.2
CH_3	Cl	COOH	155–157	98	$C_{10}H_{10}N_3O_2Cl$	50.1	50.3	4.2	4.4	17.5	17.8
H	OH	COOH	250–253	86	$C_9H_9N_3O_3$	52.2	52.3	4.4	4.5	20.2	19.9
CH_3	OH	COOH	265–267	72	$C_{10}H_{11}N_3O_3$	54.3	53.9	5.0	5.0	19.0	18.8
H	$C_6H_5CH_2N$(H)—	COOH	189–190	81	$C_{16}H_{16}N_4O_2$	64.9	64.6	5.4	5.4	18.9	19.1
CH_3	$C_6H_5CH_2N$(H)—	COOH	233–234	83	$C_{17}H_{18}N_4O_2$	65.7	65.4	5.8	5.6	18.1	17.9
H	$C_6H_5CH_2N$(H)—	CN	110–111[c]	82	$C_{16}H_{16}N_6$	69.3	69.3	5.5	5.6	25.2	24.8
CH_3	$C_6H_5CH_2N$(H)—	CN	114[c]	82	$C_{17}H_{17}N_5$	70.2	70.0	5.8	5.8	24.0	23.7
H	$C_6H_5CH_2N$(H)—	$—CH_2NH_2$	149–150	76	$C_{16}H_{19}N_5$	68.3	68.2	6.8	7.0	24.9	24.8
CH_3	$C_6H_5CH_2N$(H)—	$—CH_2NH_2$	193–194[d]	80[d]	$C_{17}H_{21}H_5 \cdot HCl$	61.5	61.5	6.7	6.8	21.1	21.0
H	$C_6H_5CH_2N$(H)—	$—CH_2OH$	180–181[d]	73[d]	$C_{16}H_{18}N_4O \cdot HCl$	60.2	60.3	5.9	5.7	17.6	17.5
CH_3	$C_6H_5CH_2N$(H)—	$—CH_2OH$	163–164[d]	84[d]	$C_{17}H_{24}N_4O \cdot HCl$	61.2	60.9	6.3	6.7	16.8	16.8

[a] Uncorrected. Köfler hot plate. From aqueous ethanol unless noted otherwise. [b] Oil at room temperatures. [c] From ether-pentane. [d] Isolated and purified as these salts.

1.5×10^4 and 1.8×10^4 in acid and base buffers, respectively (pH 1.0 and 13.0).

Experimental[5]

4-Hydroxy-5-(β,β-dicarboxyethyl)pyrrolo[2,3-*d*]pyrimidine.—To 70 ml. of absolute ethanol containing 0.042 mole of sodium ethoxide were added 0.036 mole (11.5 g.) of 4-hydroxy-5-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidine methiodide and 0.039 mole (6.2 g.) of diethyl malonate. The reaction mixture was refluxed under a stream of nitrogen until amine was no longer liberated (16 hr.). The solvent was removed *in vacuo*, and the residue was taken up in 75 ml. of water containing 3.5 g. of potassium hydroxide and heated on low steam for 1 hr. After chilling and acidifying to pH 2.0 a flocculent precipitate formed. It was refrigerated overnight, filtered, and dried *in vacuo* giving 6.0 g. (67% yield) of the expected dicarboxylic acid which required no further purification. It decomposed slowly above 220° and became a black tar between 290–300°.

Anal. Calcd. for $C_{10}H_9N_3O_6$: C, 47.8; H, 3.6; N, 16.7. Found: C, 47.7; H, 3.7; N, 16.7.

4-Hydroxy-5-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidine (Compound B, Reaction Scheme I).—The dicarboxylic acid was best decarboxylated in a dry state as described later. Earlier attempts at aqueous alkali decarboxylations were only partially successful.

Two grams of this preparation was heated in an open flask at 185–190° for 2 hr. Most of the carbon dioxide was evolved during the first hour of heating. The remaining residue was recrystallized from water using a small amount of Darco yielding 1.5 g. (91%) of the desired product. It turned tan at 270°, black at 285°, and decomposed further to a dark oil at 310°.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.1; H, 4.4; N, 20.1. Found: C, 52.4; H, 4.7; N, 20.1.

(5) All melting points were taken on a Köfler hot plate and are uncorrected.

Compound B was compared chromatographically and spectrophotometrically with its isomer, compound C, which is described in Table II and later in these experimental details. The data (Table II) serve to differentiate between the two isomers. The isomers were chromatographed in duplicate in two different solvent systems. They were applied along opposite sides of the same paper strip in each case and detected as previously described. The solvent systems employed were *n*-butyl alcohol saturated with 0.1 *N* acetic acid at room temperature (solvent A) and the same alcohol saturated with 0.1 *N* hydrochloric acid at room temperature (solvent B).

TABLE II

	R_f solvents A	B	Ultraviolet spectral data: pH 1.0 λ_{max} (mμ)	ϵ (10^3)	pH 13.0 λ_{max} (mμ)	ϵ (10^3)
Isomer C	0.33	0.43	263	8.7	267	7.3
Isomer B	.21	.56	270	7.9	272	8.9

Preparation of the Adducts (Table I).—A small piece of sodium metal (25–35 mg.) was allowed to react with 100 ml. of absolute ethanol. To this were added 0.03 mole of the appropriate 4-chloropyrrolopyrimidine and 0.09 mole of either ethyl acrylate or acrylonitrile. After 3 hr. at reflux under anhydrous conditions, the solvent was driven off and the thick oils remaining were extracted with 200 ml. of ether leaving a small amount of tarry residue. The ether solution was dried over anhydrous sodium sulfate overnight, filtered, and two volumes of pentane were added. After chilling overnight, the pure adducts were filtered off and air dried.

4-Chloro-7-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidines.—One gram of the appropriate chloro ester addition compound in 25 ml. of a 70% aqueous ethanol solution containing 1.5 g. of potassium hydroxide was warmed for 0.5 hr. on low steam. After the addition of two volumes of cold water and acidifying to pH 2.0, the carboxylic acids were obtained quantitatively almost in a pure

4-Hydroxy-7-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidines.—One and one-half grams of the appropriate 4-chloropyrrolopyrimidine ethyl acrylate adduct was refluxed for 3 hr. in 60 ml. of 3.0 *N* hydrochloric acid. The solution was taken to dryness with water pump vacuum in a 60° water bath. The residues were triturated with 5 ml. of water, filtered, and recrystallized from ethanol yielding 0.7–0.8 g. of the desired products. The 4-hydroxy-7-carboxylic compound (referred to as compound C) was compared to its isomer, compound B, for structural proof.

4-Benzylamino-7-(β-cyanoethyl)pyrrolo[2,3-*d*]pyrimidines.—To 0.0113 mole of the appropriate 4-chloro-7-cyanoethyl derivative in 75 ml. of water containing 0.0115 mole (1.6 g.) of anhydrous potassium carbonate was added 0.0123 mole of benzylamine. After heating at slow reflux for 3 hr., the suspension was chilled and the solid was taken up in 200 ml. of ether and dried overnight over anhydrous sodium sulfate. Addition of an equal volume of pentane to the filtered ethereal solutions yielded the pure desired compounds.

4-Benzylamino-7-(β-carbethoxyethyl)pyrrolo[2,3-*d*]pyrimidines.—To 0.0113 mole of the appropriate chloro ester adduct in 100 ml. of absolute ethanol was added 0.034 mole of benzylamine and then heated at 130° for 3 hr. in sealed containers. The solvent was driven off and the thick oils were taken up in ether and dried over anhydrous sodium sulfate. (Paper chromatography on these solutions revealed only one component present.) Addition of pentane to the filtered ethereal solutions gave gums which resisted all attempts to crystallize. They were used as such in the reductions described later. They also were hydrolyzed to the carboxylic acids by the method described earlier for the alkaline hydrolysis of the 4-chloro adducts except that the pH was adjusted carefully to 3.5 for maximum recovery. These 4-benzylamino-7-carboxylic acids also may be prepared as described subsequently.

4-Benzylamino-7-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidines.—These may be prepared likewise by the reaction of the 4-chloropyrrolopyrimidine–ethyl acrylate adducts using water as solvent and potassium carbonate with benzylamine as described before for the 4-benzylamino-7-(β-cyanoethyl)-compounds. They may be prepared also by similarly treating the 4-chloro-7-carboxylic acids with aqueous benzylamine and potassium carbonate. These compounds precipitate maximally at pH 3.5–3.8.

4-Benzylamino-7-(γ-hydroxypropyl and γ-aminopropyl)pyrrolo-[2,3-*d*]pyrimidines.—To rapidly stirred suspensions of 0.01 mole (0.38 g.) of lithium aluminum hydride in 300 ml. of anhydrous ether was added, dropwise over 20 min., 0.009 mole of the appropriate 4-benzylamino-7-β-carbethoxy or -β-cyanoethyl compound in 70 ml. of anhydrous ether. After stirring at room temperature for 0.5 hr. longer, 1.0 ml. of water was added dropwise to the vigorously stirred mixtures, followed by 2 ml. of a 25% aqueous sodium hydroxide solution, and finally 2 ml. more of water. After 30 min. of vigorous stirring, the inorganic materials were filtered off and extracted twice with 100 ml. of anhydrous sodium sulfate. The products were best obtained pure as monohydrochlorides by the addition of a slight excess (5–10%) of an ethanolic solution of hydrogen chloride to the previously filtered ethereal solutions and allowing them to stand overnight at room temperature.

Acknowledgment.—The author thanks Miss Lilia Beauchamp for her technical assistance and Dr. S. Blackman and Mrs. R. Purdey for their microanalytical contributions.

Synthesis and Reactions of Some 1,2,4-Pyrimido[4,5-*e*]thiadiazine 1,1-Dioxides[1]

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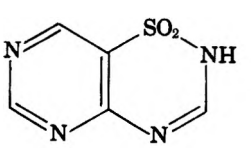
Synthesis of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide and 8-amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxide was effected by the cyclization of the corresponding 4-amino-5-pyrimidinesulfonamides with ethyl orthoformate. N-Alkylation of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide was observed giving evidence that the double bond is localized in the 3,4-position. Various reactions of the 1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxides are reported together with the preparation and reactions of some 5-pyrimidinesulfonic acids and their derivatives.

As a part of the intensive current effort to find more effective anticancer agents, considerable attention has been given to the fields of pyrimidine and purine chemistry in a search for potential antimetabolites of the naturally occurring pyrimidines and purines involved in biosyntheses. A large number of pyrimidine and purine derivatives containing sulfur have been reported and also tested for anticancer properties. 6-Mercaptopurine is one of the more effective of this group.[3] It is felt that pyrimidine and purine derivatives containing sulfur in some of its higher oxidation states have been neglected. The first synthesis of a purinesulfonamide was described recently by Beaman and Robins.[4] Kromov-Borisov and Karlinskaya[5] have shown that derivatives of pyrimidine-5-sulfonic acids display antileukemic activity. This prompted us to prepare various purine and pyrimidine derivatives containing sulfonic acid and sulfonamide groups so that their anticancer properties could be evaluated.

Two examples of a 1,2,4-thiadiazine 1,1-dioxide ring system fused to a heterocyclic system have been reported. Blicke and Lee[6] reported the fusion of this system to an imidazole ring while Yale, Losee, and Bernstein[7] have fused it to a pyridine ring. If the 1,2,4-thiadiazine 1,1-dioxide ring system also could be fused to a pyrimidine ring, two general types of derivatives could be formed (1 and 2).[8]



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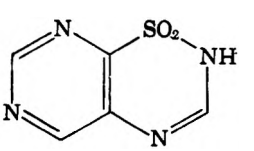

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(1) This investigation was supported by the National Cancer Institute, National Institutes of Health, contract no. CY-5252.

(2) Undergraduate Research Participant supported by a grant, NSF G-12070, from the National Science Foundation.

(3) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel Jr., *Cancer Res.*, **19**, No. 4, 425 (1959).

(4) A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc.*, **83**, 4038 (1961).

(5) N. V. Khromov-Borisov and R. L. Karlinskaya, *Zh. Obschch. Khim.*, **24**, 2212 (1954); *Chem. Abstr.*, **50**, 355 (1956).

(6) F. F. Blicke and C.-M. Lee, *J. Org. Chem.*, **26**, 1861 (1961).

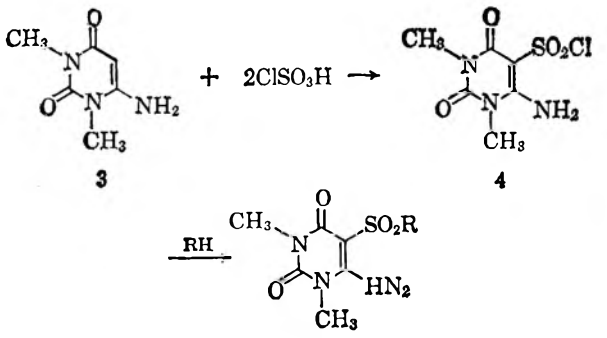
(7) H. L. Yale, K. Losee, and J. Bernstein, *J. Am. Chem. Soc.*, **82**, 2044 (1960).

(8) It has been shown by F. C. Novello, *et al.*, (ref. 15), Ekbom [*Bih. Svensk Velenskakad Handl.*, **27**, II, 3 (1902)], and H. L. Yale and J. T. Sheehan (ref. 14) that the 1,2,4-thiadiazine 1,1-dioxide system exists as a tautomeric equilibrium in which the hydrogen resides on either the 2- or 4-position. This would indicate that I and II also might exist as a tautomeric equilibrium; however, for simplicity only one of the tautomers is shown in each case.

The preparation of derivatives of **1** has been accomplished and will be reported here.

In order to obtain derivatives of **1** it appeared that the easiest approach would be the cyclization of some 4-amino-5-pyrimidinesulfonamides. Direct introduction of a sulfonyl chloride group in the 5-position of various pyrimidines has been reported by numerous authors.[5,9-12]

6-Amino-1,3-dimethyluracil (**3**) reacted with chlorosulfonic acid to form the relatively stable 5-sulfonyl chloride **4**. The 5-sulfonyl chloride **4** reacted with water, methanol, ammonia, methylamine, and ethylamine in a manner characteristic of sulfonyl chlorides to form **5**, **6**, **7**, **8**, and **9**, respectively.



5. R = OH
6. R = OCH_3
7. R = NH_2
8. R = $NHCH_3$
9. R = $NHCH_2CH_3$

Preparation of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]-thiadiazine-6,8-dione 1,1-dioxide (**10**) and 2,5,7-trimethyl-1,2,4-pyrimido[4,5-*e*]thidiazine-6,8-dione 1,1-dioxide (**11**) was effected by heating **7** and **8**, respectively, in an excess of triethyl orthoformate or trimethyl orthoformate. Cyclization could not be effected when the sulfonamides were heated with formic acid or formaldehyde. It also has been observed by Freeman and Wagner[13] that triethyl orthoformate can bring about cyclization more readily than does formic acid. N - Ethyl - 6 - amino - 1,3 - dimethyl - 5 - pyrimidinesulfonamide (**9**), when treated with triethylorthoformate, did not form the corresponding N-ethylthiadiazine **12**. Freeman and Wagner[13] and also Blicke and Lee[6] have observed similar difficulty in cyclization of N-alkylsulfamoyls.

When the cyclization reactions were run at higher temperatures both cyclization and N-alkylation of the thiadiazine nucleus occurred. For example, when **7** was heated with triethyl orthoformate at 150° instead of the usual 120–130°, a 74% yield of 2-ethyl-5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide (**12**) was formed. Similar treatment of **7** with trimethyl orthoformate yielded a 76% yield of 2,5,7-trimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide (**11**) together with a 15% yield of **10**. The fact that none of the 4-alkylthiadiazines was isolated in the reactions carried out and the relatively high yield of 2-alkylthiadiazines indicates that very little, if any, of the 4-alkyl product was formed in these cases. Yale and Sheehan have observed the reaction of triethyl orthoformate and benzothiadazines at 150° and report the formation of both the 2- and 4-alkylthiadiazines.[14]

Both **11** and **12** readily undergo cleavage of the thiadiazine ring when crystallized from water to form 1,3-dimethyl - 5 - methylsulfamoyl - 6 - uracilformamide (**13**) and 1,3-dimethyl-5-ethylsulfamoyl-6-uracilformamide (**14**), respectively. Cleavage of 2-alkylthiadiazines is known to take place with hydroxylic solvents; however, 4-alkylthiadiazines are stable to hydroxylic solvents[14] and are cleaved only under basic conditions.[15] This together with the fact that the preparation of **11** also was accomplished by the reaction of triethyl orthoformate and **8**, which was identical with the product obtained from the reaction of **7** and trimethyl orthoformate at the higher temperature, indicated that **11** and probably **12** were the 2-alkylthiadiazines and not the 4-alkylthiadiazines. The ultraviolet spectra of **11** and **12** were similar, also indicating that both thiadiazines were alkylated in the same position.

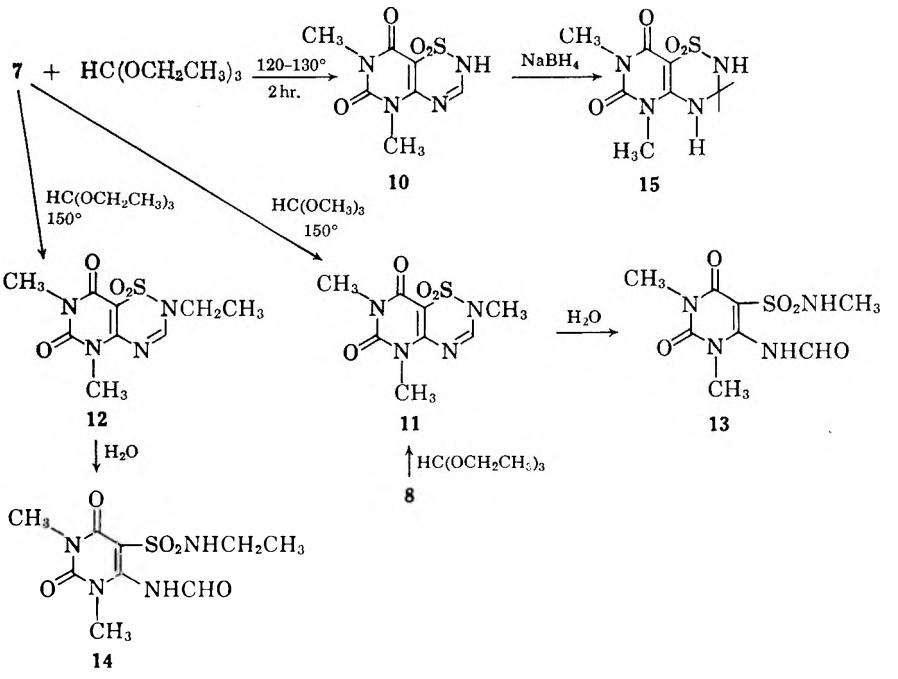
Cyclization of **7** with trimethyl orthoformate and triethyl orthoformate to form the corresponding 2-alkylthiadiazine in a 78 and 74% yield, respectively, indicates that the double bond of **10** exists predominantly, if not entirely, in the 3,4-position under these conditions. This is different from the results obtained with the benzothiadiazines where the major product was the 4-alkyl product.[14,15]

The ultraviolet spectra also support these findings since **10** shows maxima at 308 mμ and 258 mμ similar to the 2-alkylthiadiazine, **11** and **12**, both of which have maxima at 309 mμ and 263 mμ. This is in agreement with Yale and Sheehan[14] who found that the 1,2,4-thiadiazine with the double bond in the 2,3-position has only one absorption maximum at 278 mμ with a shoulder at 295 mμ.

The reaction of **7** with formaldehyde did not form the desired 5,7-dimethyl-3,4-dihydro-1,2,4-pyrimido[4,5-*e*]-thiadiazine-6,8-dione 1,1-dioxide (**15**). However, **15** was prepared by the reaction of **10** with an excess of sodium borohydride.

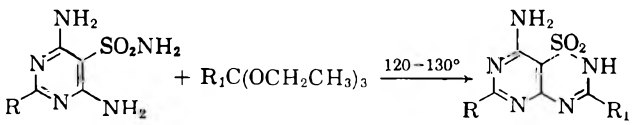
Preparation of other pyrimido-1,2,4-thiadiazines 1,1-dioxides was limited by the difficulty encountered in the preparation of other 4-amino-5-pyrimidinesulfonamides needed to form thiadiazines of type **1**. Pyrimidines such as 4,6-diamino-2-methylthiopyrimidine, 4,6-diamino - 2 - hydroxypyrimidine, 2,6 - diamino - 4 - hydroxypyrimidine, 4-amino-6-hydroxy-2-methylpyrimidine, or 2,6-diamino-4-chloropyrimidine were sulfonated with chlorosulfonic acid to form the corresponding 5-pyrimidinesulfonic acids. In no case was the corresponding sulfonyl chloride isolated. 4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid (**16**) was converted to 4,6-diamino-2-methylthio-5-pyrimidinesulfonyl chloride with phosphorus oxychloride. The relatively unstable sulfonyl chloride formed 4,5-diamino-2 - methylthio - 5 - pyrimidinesulfonamide (**18**) when treated with ammonia. None of the other sulfonic acids could be converted to the corresponding sulfonamides in this way.

(9) G. R. Barker, N. G. Luthy, and M. M. Dhar, *J. Chem. Soc.*, 4206, (1954).
(10) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **26**, 3863 (1961).
(11) R. R. Herr, T. Enklji, and R. J. Bardo, *J. Am. Chem. Soc.*, **78**, 401 (1956).
(12) N. V. Khromov-Borisov and R. S. Karlinskaya, *Zh. Obshch. Khim.*, **27**, 2518 (1957); *Chem. Abstr.*, **52**, 7327 (1958).
(13) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).
(14) H. L. Yale and J. T. Sheehan, *ibid.*, **26**, 4315 (1961).
(15) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *ibid.*, **25**, 970 (1960).



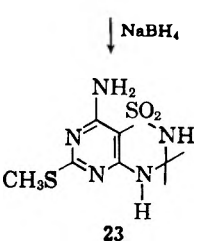
4,6 - Diamino - 5 - pyrimidinesulfonamide (**19**) was formed when the methylthio group of sulfonamide **18** was replaced by a hydrogen in refluxing Raney nickel. Oxidation of the methylthio group of **18** to the methylsulfonyl group with chlorine or hydrogen peroxide could also be effected without affecting the sulfonamide group. These reactions could not be carried out on the corresponding sulfonic acid or sulfonyl chloride.

When 4,6-diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) or 4,6-diamino-5-pyrimidinesulfonamide (**19**) was heated with an excess of triethyl orthoformate ring closure was effected to form 8-amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxide (**20**) and 8-amino - 1,2,4 - pyrimido[4,5-*e*]thiadiazine 1,1 - dioxide (**21**), respectively, with no N-alkylation being observed. Ring closure of **18** also was effected with refluxing trimethyl orthoformate to form **20** or with triethyl orthoacetate to form **22**. Sodium borohydride reduced **20** to form 8-amino-3,4-dihydro-6-methylthio-1,2,4-pyrimido-[4,5-*e*]thiadiazine 1,1-dioxide (**23**).



18. R = SCH_3
19. R = H

20. R = SCH_3, R_1 = H
21. R = H, R_1 = H
22. R = SCH_3, R_1 = CH_3



All of the sulfonamides prepared showed characteristic absorption bands at 1134–1177 cm.$^{-1}$ and at 1020–1043 cm.$^{-1}$. The sulfonamides of substituted uracils also showed characteristic bands at 1372–1385 cm.$^{-1}$. The sulfonic acids and the one methylsulfonate **6** showed characteristic absorption bands at 1030–1051 cm.$^{-1}$ and at 1204–1220 cm.$^{-1}$.[16]

Tests for anticancer activity of the compounds reported in this paper are being obtained by the National Cancer Chemotherapy Service Center, Bethesda, Maryland. Significant results of these tests will be reported elsewhere.

Experimental[17]

Sulfonation of Substituted Pyrimidines.—To 25 ml. of freshly distilled chlorosulfonic acid, which was cooled on ice, was added 10 g. of 6-amino-1,3-dimethyluracil (**3**) at such a rate so that the temperature of the reaction mixture did not go above 20°. After addition was complete the reaction mixture was heated on a water bath for 2 hr. or refluxed for 1 hr., cooled, and poured on 300 g. of crushed ice with vigorous stirring. The excess ice was removed and the sulfonyl chloride was rapidly filtered. The light tan precipitate was washed with a little cold water and sucked as dry as possible. This product was never purified but was used as such in subsequent reactions.

4,6-Diamino-2-methylthiopyrimidine, 4,6-diamino-2-hydroxypyrimidine, 2,6-diamino-4-hydroxypyrimidine, and 4-amino-6-hydroxy-2-methylpyrimidine were sulfonated by the same procedure as was **3**. In all cases the only product isolated was the 5-sulfonic acid. Analytical data for these sulfonic acids are given in Table I.

2,4-Diamino-6-chloropyrimidine (2.9 g.) could be sulfonated only when refluxed with chlorosulfonic acid (10 ml.) for 1 hr. When the reaction mixture was poured on ice an immediate precipitate of starting material formed. The filtrate yielded 2,4-diamino-6-chloro-5-pyrimidinesulfonic acid in a 31% yield (1.4 g.) on standing overnight. The sulfonic acid was crystallized from water to give a pure sample which did not melt below 330°. A satisfactory C–H analysis could not be obtained on 2,4-diamino-6-chloro-5-pyrimidinesulfonic acid, but it could be converted to 2,4,6-triamino-5-pyrimidinesulfonic acid by heating at 150° in an excess of alcoholic ammonia which did give acceptable analytical data (Table I).

6-Amino-1,3-dimethyl-5-uracilsulfonamide (**7**).—6-Amino-1,3-dimethyl-5-uracilsulfonyl chloride (**4**), obtained from the chlorosulfonation of 10 g. of **3**, was added to 200 ml. of anhydrous ammonia. Evaporation of the excess ammonia left a tan solid which was dissolved in a small amount of water, decolorized with animal charcoal, and cooled to give 5.05 g. (31% yield based on 10 g. of **3**) of the monohydrate as white needles, m.p. 117–119°. After several crystallizations from water the anhydrous product, m.p. 218–220°, was obtained when the monohydrate was heated at 150° under reduced pressure overnight.

Anal. Calcd. for $C_6H_{10}N_4O_4S$: C, 30.76; H, 4.30; N, 23.92; S, 13.69. Found: C, 30.60; H, 4.32; N, 23.71; S, 13.30.

6-Amino-N-methyl-1,3-dimethyl-5-uracilsulfonamide (**8**) **and 6-Amino-N-ethyl-1,3-dimethyl-5-uracilsulfonamide** (**9**).—6-Amino-1,3-dimethyl-5-uracilsulfonyl chloride (**4**), obtained from the chlorosulfonation of 10 g. of **3**, was added to 100 ml. of anhydrous methylamine, or 100 ml. of anhydrous ethylamine if **9** was the desired product, and kept at the temperature of Dry Ice. After all of the solid had gone into solution it was removed from the Dry Ice and the excess amine evaporated. (If the mixture is removed from the Dry Ice before all of the solid had gone into solution the mixture becomes hot and the product isolated is mainly the corresponding amine salt of the sulfonic acid.) A 25% yield (4.0 g.) of the pure N-methylsulfonamide

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 363, 364.

(17) All melting points are uncorrected. All ultraviolet spectra were made in water unless otherwise noted using a Beckman DB spectrophotometer. The infrared spectra were taken with potassium bromide pellets using a Perkin-Elmer Infracord spectrophotometer.

TABLE I

2,4,6-TRISUBSTITUTED 5-PYRIMIDINESULFONIC ACIDS AND DERIVATIVES

Compound	Yield, %	M.p.,[a] °C.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid	33	265–267	$C_5H_{10}N_4O_4S_2$[c]	23.62	23.57	3.96	3.73	22.04	22.23	25.22	25.44
4,6-Diamino-2-hydroxy-5-pyrimidinesulfonic acid	23	>330	$C_4H_6N_4O_3S$	23.30	23.49	2.94	3.10	27.17	27.18	15.55	15.64
2,4-Diamino-6-hydroxy-5-pyrimidinesulfonic acid	34	>330	$C_4H_9N_5O_4S$[d]	21.57	21.67	4.06	3.94	31.38	31.48	14.37	14.33
4-Amino-6-hydroxy-2-methyl-5-pyrimidinesulfonic acid	43	305–306	$C_5H_7N_3O_4S$	29.26	29.01	3.44	3.51	20.48	20.62	15.63	15.51
2,4-Diamino-6-chloro-5-pyrimidinesulfonic acid	31	>330	$C_4H_5ClN_4O_3S$	21.34		2.24		24.94	25.01	14.28	14.54
2,4,6-Triamino-5-pyrimidinesulfonic acid	82	>310	$C_4H_7N_5O_3S$	23.41	23.39	3.44	3.69	34.13	34.06	15.63	15.66
4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide	59	198–199	$C_5H_9N_5O_2S_2$	25.52	25.28	3.81	3.77	29.77	29.66	27.26	27.19
4,6-Diamino-5-pyrimidinesulfonamide	31	217–218	$C_4H_7N_5O_2S$	25.39	25.55	3.72	3.87	37.02	37.28	16.95	16.83
4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide	79	238–239	$C_5H_9N_5O_4S_2$	22.47	22.61	3.39	3.28	26.20	26.46	24.00	24.00

[a] All melting points are uncorrected. [b] All samples were crystallized from water except 4,6-diamino-2-hydroxy-5-pyrimidinesulfonic acid which was dissolved in 5% sodium hydroxide and precipitated by the addition of acetic acid. [c] Formula and calculations based on monohydrate. [d] Formula and calculation based on ammonium salt.

8 was obtained by decolorizing with animal charcoal and three crystallizations from water, m.p. 203–204°.

Anal. Calcd. for $C_7H_{12}N_4O_4S$: C, 33.87; H, 4.88; N, 22.57; S, 12.92. Found: C, 33.55; H, 4.86; N, 22.32; S, 12.96.

The N-ethylsulfonamide **9** was dissolved in methanol, decolorized with animal charcoal, and cooled to yield 4.5 g. (26% yield based on 10 g. of **3**), m.p. 260–263°.

Anal. Calcd. for $C_8H_{14}N_4O_4S$: C, 36.63; H, 5.38; N, 21.36; S, 12.23. Found C, 36.38; H, 5.68; N, 21.35; S, 12.52.

Methyl 6-amino-1,3-dimethyl-5-uracilsulfonate (**6**).—Crude **4**, obtained from 10 g. of **3**, was stirred in 350 ml. methanol overnight at room temperature. Enough methanol was added to the mixture so that on heating the ester went into solution. Upon cooling the crude methylsulfonate **6** was obtained in a 46% yield (7.4 g.), m.p. 204–206°. Further crystallization from methanol yielded a product which began to soften at 193°, m.p. 206–208°. When water was used as a solvent, only a very small portion of the ester could be reclaimed.

Anal. Calcd. for $C_7H_{11}N_4O_5S$: C, 33.73; H, 4.45; N, 16.88; S, 12.88. Found: C, 33.59; H, 4.63; N, 16.94; S, 13.07.

5,7-Dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-Dioxide (**10**).—6-Amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) (4 g.) was added to 50 ml. of triethyl orthoformate and kept at 120–130° for 2 hr. with stirring. It is best to carry out this reaction in an open container in order to allow the ethanol to escape as the reaction proceeds. After the reaction was complete, it was cooled and diluted with 50 ml. of ether to assure complete precipitation of the product. A 67% yield (2.8 g.) of the thiadiazine **10** was obtained by dissolving in N,N-dimethylformamide and then diluting with methanol, m.p. 271–272°. Further purification gave an analytical sample, m.p. 274–275°; ν_{max} 1219, 1162, 1134, and 1031 cm.$^{-1}$; λ_{max} 308 mμ (ε 7100) and 258 mμ (ε 8490).

Anal. Calcd. for $C_7H_8N_4O_4S$: C, 34.43; H, 3.30; N, 22.95; S, 13.13. Found: C, 34.53; H, 3.62; N, 22.82; S, 13.10.

2-Ethyl-5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-Dioxide (**12**).—6-Amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) (1 g.) was heated in 25 ml. of triethyl orthoformate for 3 hr. at 150°. Upon cooling a 74% yield (0.86 g.) of the N-ethylthiadiazine **12** was isolated, m.p. 180–181°. Two crystallizations from triethyl orthoformate yielded white needles, m.p. 182–183°; ν_{max} 1232, 1166, 1134, 1041, and 1022 cm.$^{-1}$; $\lambda_{max}^{HC(OEt)_3}$ 309 mμ (ε 4050) and 263 mμ (ε 12,200).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 39.70; H, 4.48; N, 20.58, S, 11.78. Found: C, 39.83; H, 4.43; N, 20.37; S, 12.03.

5-Ethylsulfamoyl-1,3-dimethyl-6-uracilformamide (**14**).—A 96% yield (0.31 g.) of formamide **14** was obtained when 0.30 g. of the thiadiazine **12** was dissolved in a minimum amount of hot water. The product melted 181–182° and showed a depression to 148–158° when mixed with **12**; λ_{max} 250 mμ (ε 17,300) and 230 mμ (ε 10,600).

Anal. Calcd. for $C_9H_{14}N_4O_4S$: C, 37.23; H, 4.86; N, 19.30; S, 11.12. Found: C, 37.09; H, 4.91; N, 19.38; S, 11.05.

2,5,7-Trimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-Dioxide (**11**).—N-Methyl-6-amino-1,3-dimethyl-5-pyrimidinesulfonamide (**8**) (1 g.) was heated with stirring at 120–130° for 6 hr. in 100 ml. of triethyl orthoformate. On cooling a 78% yield (0.82 g.), m.p. 235–237°, of the 2-alkylthiadiazine **11** was obtained. The analytical sample was crystallized twice from triethyl orthoformate, m.p. 243–244°; ν_{max} 1233, 1166, 1132, 1064, and 1088 cm.$^{-1}$; $\lambda_{max}^{HC(OEt)_3}$ 309 mμ (ε 4480) and 263 mμ (ε 12,300).

Anal. Calcd. for $C_8H_{10}N_4O_4S$: C, 37.22; H, 3.90; N, 21.70; S, 12.42. Found: C, 36.92; H, 4.04; N, 21.68; S, 12.64.

The 2-alkylthiadiazine **11** also was prepared by heating 0.5 g. of 6-amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) and 25 ml. of trimethyl orthoformate at 150° in a pressure bottle for 6 hr. Upon cooling 15% yield (0.08 g.) of the thiadiazine **10**, m.p. 273–275°, was obtained. The thiadiazine **10** was the same in all respects as the product obtained from the reaction of triethyl orthoformate and the sulfonamide **7**. When the filtrate was diluted with 75 ml. of ether a 76% yield (0.42 g.) of the 2-alkylthiadiazine **11** was obtained, m.p. 242–243°. Mixture melting point with the 2-alkylthiadiazine **11** obtained from the reaction of the N-methylsulfonamide **8** and triethyl orthoformate showed no depression.

1,3-Dimethyl-5-methylsulfamoyl-6-uracilformamide (**13**).—An 88% yield (0.39 g.) of the formamide **13** was obtained when 0.40 g. of the thiadiazine **11** was dissolved in a minimum amount of hot water. The product melted 238–239° and showed a depression to 213–227° when mixed with **10**; λ_{max} 250 mμ (ε 16,100) and 230 mμ (ε 9000).

Anal. Calcd. for $C_8H_{12}N_4O_5S$: C, 34.78; H, 4.38; N, 20.28; S, 11.61. Found: C, 34.74; H, 4.63; N, 20.34; S, 11.84.

3,4-Dihydro-5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-Dioxide (**15**).—To 0.1 g. of sodium borohydride dissolved in 2 ml. of water was added slowly 0.8 g. of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide (**10**). After 2 hr. a small amount of precipitate formed which was removed and then acidified with acetic acid. Upon filtration of the acidic mixture the dihydro product **15** was isolated in a 37% yield (0.3 g.). After one crystallization from water an analytical sample was obtained, m.p. 298–299°; ν_{max} 1240, 1148, 1089, 1065, 1022, and 1000 cm.$^{-1}$; λ_{max} 259 mμ (ε 11,500).

Anal. Calcd. for $C_7H_{10}N_4O_4S$: C, 34.14; H, 4.09; N, 22.76; S, 13.02. Found: C, 34.17; H, 4.31; N, 22.91; S, 13.19.

4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid trihydrate (**16**) (20 g.) was refluxed for 1 hr. with 75 ml. of phosphorus oxychlo-

ride. The excess phosphorus oxychloride was distilled by heating the sample on a water bath under reduced pressure. Heating was continued until the solution became a thick sirup. If heating was continued for a longer period of time the sulfonyl chloride decomposed to a crystalline material and the desired product was not obtained. The thick sirup was added to 400 ml. of ammonia. Evaporation of the ammonia left a tan solid which was decolorized with animal charcoal and crystallized from water yielding 9.7 g. (59% yield) of long white needles, m.p. 195–197°. Further crystallization from water increased the m.p. to 198–199°. Analytical data are given in Table I.

4,6-Diamino-5-pyrimdinesulfonamide (19).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2.5 g.) was dissolved in 50 ml. water to which 5 g. of Raney nickel[18] was added. This reaction mixture was refluxed for 3 hr. with vigorous stirring. Longer refluxing also will remove the sulfonamide group while a shorter reflux time leaves too much starting material. A 31% yield (0.63 g.) of **19** was obtained upon evaporation of the filtrate and crystallization of the residue from a small amount of water, m.p. 215–216.5°. Further crystallization from water gave an analytical sample, m.p. 221–222°. Analytical data are given in Table I.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide.—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2 g.) was added to 50 ml. water and cooled to 0° in an ice bath. Chlorine was slowly bubbled through this suspension until all of the solid went into solution and the solution was light yellow in color. (This takes a few minutes depending on how rapidly the chlorine is bubbled through the suspension. A large excess of chlorine should be avoided or the yield will be reduced greatly.) The product begins to separate shortly after the solid goes into solution. After standing in an ice bath for 0.5 hr. the mixture was filtered and after one crystallization from water yielded 1.6 g. (70% yield), m.p. 235–237°, with evolution of a gas. Further crystallization from water gave a sample that turns yellow at 235°, m.p. 249–250° dec.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide also was prepared by dissolving **18** (0.9 g.) in 10 ml. of acetic acid and 10 ml. of acetic anhydride. To this solution was added 1 ml. of 30% hydrogen peroxide. After a short time the reaction mixture became hot and the product separated from the solution. A 79% yield (0.81 g.) of crude product was obtained upon filtration. Two crystallizations from water gave material that was identical with that from the oxidation with chlorine. Analytical data are given in Table I.

8-Amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (20) and 8-Amino-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (21).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 2 hr. at 120–130° in 20 ml. of triethyl orthoformate. Upon cooling the thiadiazine **20** was obtained in an 86% yield (0.9 g.), m.p. 315–317°. An analytical sample was obtained by two crystallizations from N,N-dimethylformamide and water, m.p. 321–322° dec.; ν_{max} 1204, 1136, and 1079 cm.$^{-1}$; λ_{max} 249 mμ (ε 26,700).

Anal. Calcd. for $C_6H_7N_5O_2S_2$: C, 29.34; H, 2.86; N, 28.39; S, 26.15. Found: C, 29.16; H, 3.06; N, 28.24; S, 26.17.

Cyclization of sulfonamide **18** also was effected with refluxing trimethyl orthoformate yielding **20** in a 62% yield.

To 4,6-diamino-5-pyrimidinesulfonamide (**19**) (1.8 g.) was added 50 ml. of triethyl orthoformate and treated in a manner similar to **18**. Thiadiazine **21** was obtained in a 97% yield (1.76 g.). Two crystallizations from N,N-dimethylformamide and water gave an analytical sample, m.p. 308–309°; ν_{max} 1219, 1159, 1078, 1020, and 1002 cm.$^{-1}$; λ_{max} 244 mμ (ε 11,200) and 223 mμ (ε 22,000).

Anal. Calcd. for $C_5H_5N_5O_2S$: C, 30.15; H, 2.53; N, 35.16; S, 16.10. Found: C, 29.88; H, 2.71; N, 35.02; S, 16.30.

8-Amino-3-methyl-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (22).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 1 hr. at 120–130° with stirring in 15 ml. of triethyl orthoacetate. Upon cooling the thiadiazine **22** was obtained in a 54% yield, m.p. 314–315°; ν_{max} 1149, 1099, 1050, and 1020 cm.$^{-1}$; λ_{max} 247 mμ (ε 28,300).

Anal. Calcd. for $C_7H_9N_5O_2S_2$: C, 32.42; H, 3.50; N, 27.01; S, 24.73. Found: C, 32.27; H, 3.61; N, 27.29; S, 24.90.

8-Amino-3,4-dihydro-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (23).—8-Amino-6-methylthio-1,2,4-pyrimido [4,5-*e*]thiadiazine 1,1-dioxide (**20**) (0.5 g.) was added slowly to 0.1 g. of sodium borohydride in 5 ml. of water. After standing for 3 hr. the reaction mixture was filtered to obtain the dihydro product **23** in an 81% yield (0.41 g.). One crystallization from water gave an analytical sample, m.p. 261–262°; ν_{max} 1202 and 1148 cm.$^{-1}$; λ_{max} 230 mμ (ε 26,600) and 255 mμ (sh).

Anal. Calcd. for $C_6H_9N_5O_2S_2$: C, 29.14; H, 3.67; N, 28.32; S, 25.93. Found: C, 29.11; H, 3.69; N, 28.41; S, 25.81.

Acknowledgment.—The authors wish to thank F. C. Chang of the University of Tennessee, Medical Units, for the infrared spectra.

(18) X. A. Dominquez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

9-Aminoacridines and 4-Aminoquinolines. Steric Effects of N,N-Disubstitution[1]

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N,N-Disubstitution was found to labilize the aromatic amino bond of 9-aminoacridine to permit a previously unreported type of reaction with alcohols, yielding 9-acridinyl ethers. An analogous reaction in similarly N,N-disubstituted 4-aminoquinolines was not found; however, a pronounced effect on base strength and ultraviolet spectra upon increasing the bulk of the substituents was noted.

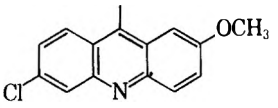
N,N-Disubstitution of 9-aminoacridine and 4-aminoquinoline derivatives was initially attempted to reduce intramolecular reactivity to other groups which were to be introduced at the end of an alkyl side chain; these objectives were abandoned in the quinoline series due to an unexpected rearrangement[2] and now in the acridine series due to inherent instability of the compounds to the conditions of subsequent reactions. In an attempt at synthesis of compound III, the reaction was carried out in refluxing Methyl Cellosolve, a procedure often found useful in moderating the sometimes destructively exothermic nature of such reactions,[3] and a compound subsequently identified as IV was isolated. Compound III was then synthesized in the absence of Methyl Cellosolve and its reactivity to or the alcohols near the boiling point of Methyl Cellosolve was investigated with a series of simple glycols, with ethylene chlorohydrin, and with diethylene glycol. The reactions all occurred rapidly near 115° and apparently were uncomplicated by side reactions, except in the case of ethylene chlorohydrin, where too long a reaction time led to alkylation of the nucleus. No attempt was made, however, to obtain optimum yields. Table I lists the products which are stable in the absence of active hydro-

(1) Supported in part by research grant CA-02975 from the National Cancer Institute, U. S. Public Health Service.

(2) R. M. Peck, *J. Org. Chem.*, **27**, 2677 (1962).

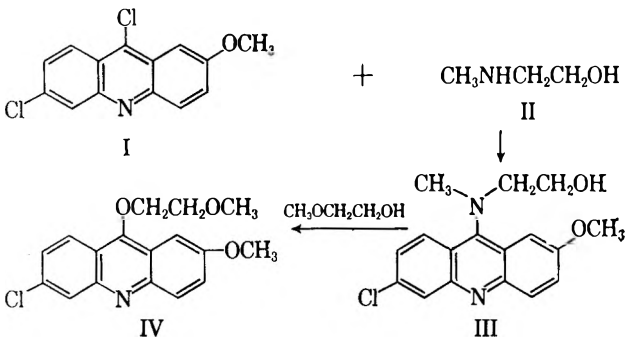
(3) R. M. Peck, R. K. Preston, and H. J. Creech, *ibid.*, **26**, 3409 (1961).

TABLE I



9-Acridinyl substituent	M.p., °C.	Anal.[a] Calcd. C	H	N	Cl	Found C	H	N	Cl
—OCH_2CH_2OH	216–217.5	63.30	4.65	4.62	11.69	63.51	4.67	4.68	12.3[illegible]
—$O(CH_2)_3OH$	157.5–159.5	64.38	5.08	4.41		64.66	5.22	4.52	
—$O(CH_2)_4OH$	166–168.5	65.18	5.46	4.22		65.56	5.84	4.27	
—$O(CH_2)_5OH$	131.5–132	66.03	5.83	4.05		66.18	5.95	4.09	
—$OCH_2CH_2OCH_3$	113–115	64.30	5.08	4.41	11.17	64.12	5.05	4.72	11.5[illegible]
—$OCH_2CH_2OCH_2CH_2OH$	131.5–134	62.19	5.22	4.02		62.71	5.29	4.11	
—OCH_2CH_2Cl	122–123.5	59.64	4.06	4.35	22.00	59.60	4.20	4.43	22.10

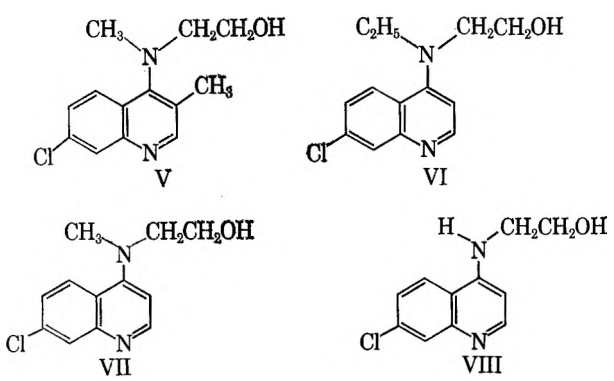
[a] Values are either single analyses or averages of checks.



gen compounds, but are quickly decomposed even by dilute acetic acid.[4]

To investigate whether other N,N-disubstituted 9-aminoacridines have the same property or whether the nature of the substituents is a factor, 6-chloro-2-methoxy-9-morpholinoacridine[5] was heated in the presence of ethylene glycol. It was found that no reaction occurred at 115°; reaction occurred, but did not go to completion, over a two-hour period at 140°. These results suggest that the degree of conjugation of the nitrogen at position 9 with the acridine nucleus is a function of the bulkiness of the nitrogen substituents which determine the ease with which that group is displaced by the alcohol.

To discover if a corresponding reaction was readily demonstrable in the quinoline series when a 3-substituent simulates the crowding effect of the second benzenoid ring of acridine, compounds V, VI, and VII were synthesized and compared with one another and with the reference compound VIII.[6]



None of these underwent a corresponding reaction with alcohols, even at elevated temperatures. With the most hindered compound, V, an hour's heating at 170° in ethylene glycol yielded only starting material and an approximately equal quantity of 7-chloro-3-methyl-4-quinolinol.

When the ultraviolet spectra and basicity of these compounds were determined, it was found that the presence of alkyl groups on the nitrogen and on the 3-position of the ring produced parallel and profound effects, additional substitution weakening the base strength and displacing the absorption maxima toward the visible (Fig. 1).

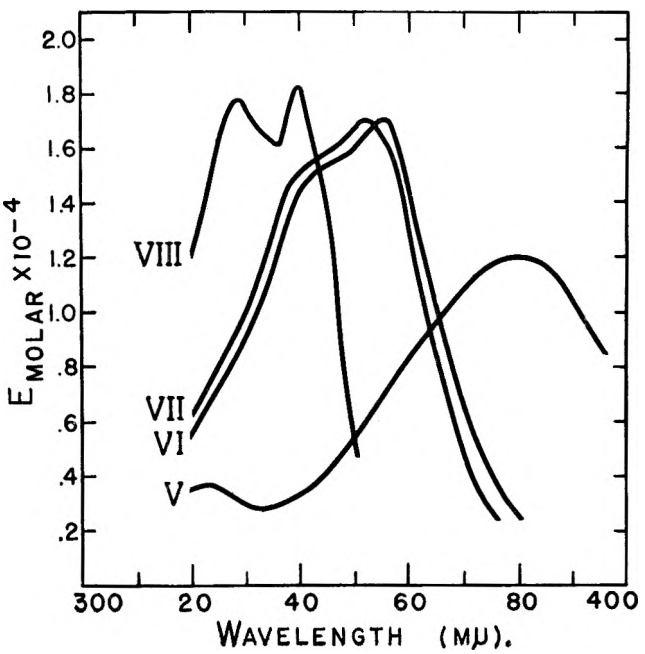


Fig. 1.—Roman numerals refer to designations in the text; the corresponding pK_a values (pH of one-half neutralization) were determined in 20% ethanol. VIII, pK_a 7.91; VII, pK_a 725; VI, pK_a 7.07; and V, pK_a 5.92. Spectra were determined in 0.01 *N* HCl.

In a pertinent comparison, Steck and Ewing[7] found that N,N-disubstitution *per se* produced no such shift in absorption spectrum where the substituents were small (methyl groups), and, in an even more interesting parallel with the present work, Irvin and Irvin[8] presented both absorption and base strength data on the antimalarial compounds SN-7618 and SN-6911 [7-

(4) R. O. Clinton and C. M. Suter, *J. Am. Chem. Soc.*, **70**, 491 (1948).

(5) O. Yu. Magidson, A. M. Grigorovskii, and E. P. Hal'perin, *J. Gen. Chem. USSR*, **8**, 56 (1938).

(6) R. C. Elderfield, W. J. Gensler, O. Birstein, F. J. Kreysa, J. T. Maynard, and J. Galbreath, *J. Am. Chem. Soc.*, **68**, 1250 (1946).

(7) E. A. Steck and G. W. Ewing, *ibid.*, **70**, 3397 (1948).

(8) J. L. Irvin and E. M. Irvin, *ibid.*, **69**, 1091 (1947).

TABLE II

DERIVATIVES OF 4-AMINOQUINOLINE

N,N-Substituents		Other substituents	Salt	M.p., °C.	Anal.[a] Calcd. C	H	N	Cl	Found C	H	N	Cl
CH_3	CH_2CH_2OH (VII)	7-Cl	HNO_3[b]	136–138	48.11	4.70	14.02		47.92	4.84	13.88	
CH_3	CH_2CH_2Cl	7-Cl	HCl	186–189	49.50	4.50	9.62	36.46	49.68	4.38	9.47	36.44
C_2H_5	CH_2CH_2OH (VI)	7-Cl	HNO_3[c]	137–139	49.85	5.14	13.40	11.30	49.97	5.28	13.46	11.59
C_2H_5	CH_2CH_2Cl	7-Cl	HCl	185–187	51.14	4.95	9.17	34.81	51.46	5.38	9.15	34.33
CH_3	CH_2CH_2OH (V)	7-Cl-3-CH_3	HNO_3[d]	133–138	49.85	5.14	13.40		50.27	5.19	13.24	
CH_3	CH_2CH_2Cl	7-Cl-3-CH_3	HCl	198–201	51.15	4.95	9.17	34.80	51.37	5.10	8.46	34.84

[a] Values are either single analyses or averages of checks. [b] Free base, m.p. 95–97°. [c] Free base, m.p. 85–87°. [d] Free base, m.p. 120–121°.

chloro-4-(4-diethylamino-1-methylbutylamino) - quinoline and 7-chloro-3-methyl-4-(4-diethylamino-1-methylbutylamino)quinoline, respectively], among others, which showed the effect of a 3-methyl substituent on these two parameters. Presence of a 3-methyl group lowered the base strength of the aromatic moiety by about 0.8 unit and displaced the absorption peak in acid solution to longer wave lengths by about 10 mμ. In the present work the parallel pair, V and VII, show significantly greater shifts, namely, 1.3 units and 30 mμ. This is consistent with ascribing the cause of these effects to steric hindrance which becomes more critical as crowding increases. The steric factor in this case arises from interference with molecular planarity of one of the resonance forms of the salt cation.[9]

Table II lists the constants and analyses for these compounds and their chloro derivatives which have been prepared in a project on the synthesis of antitumor agents.[3]

Experimental

6-Chloro-2-methoxy-9-[(2-hydroxyethyl)methylamino]acridine (III).—A mixture of 5.0 g. of 6,9-dichloro-2-methoxyacridine and 10.0 g. of redistilled methylaminoethanol was stirred in a heating bath maintained at 110–112°. An exothermic reaction was noted and the internal temperature rose a degree above the external while the solid dissolved (0.75 hr.). After an additional 0.25 hr. the product crystallized; after a further 0.5 hr., the mixture was cooled, diluted with 50 ml. of ethanol, filtered, washed, and dried. The yield was 4.4 g. (69%), m.p. 173–180°. An analytical sample melted at 185–186° on rapid heating; on slower heating, an intramolecular reaction apparently occurred and a high-melting product was formed.

(9) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 170.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.38; H, 5.41; N, 8.83; Cl, 11.17. Found: C, 64.59; H, 5.51; N, 8.63; Cl, 11.22.

(6-Chloro-2-methoxy-9-acridinyl)-2-hydroxyethyl Ether.—A mixture of 1.0 g. of the 9-amino compound and 10 ml. of ethylene glycol was stirred and heated in a bath held at 115 ± 2° for 15 min. The product precipitated from the solution, was removed by filtration and washed. It weighed 0.8 g. (83%), m.p. 212–217°. Recrystallization from ethanol gave the analytical sample reported in Table I.

The compounds in Table II were synthesized by well known methods of amination and chlorination.[3] An example of the former is included.

7-Chloro-4-(2-hydroxyethyl)methylaminoquinoline (VII).—A mixture of 20 g. (0.1 mole) of 4,7-dichloroquinoline and 15 g. of methylaminoethanol was stirred and heated. At 115° the reaction became exothermic and proceeded at 115–120° without further heating, and was complete after an hour's heating at 120°. The mixture was taken up in dilute acetic acid, filtered, and the nitric acid salt precipitated by addition of a large excess of saturated sodium nitrate (alternatively the base was precipitated with alkali and recrystallized). The crude material weighed 26 g.; recrystallization from water gave 16.5 g., m.p. 132–135° (55%).

Physical Measurements.—Ultraviolet spectra were determined on a Beckman Model DU spectrophotometer, the pH determinations on a Beckman pH meter with glass electrode. In the latter, an accurately weighed sample of 1 mmole of base was dissolved in a small amount of ethanol, 0.5 meq. of standardized 0.1 *N* hydrochloric acid was added, and the mixture made up immediately to 500 ml. containing in all 100 ml. of ethanol. The pH was measured immediately. As a check, a solution of 1 meq. of the nitric acid salt half-neutralized with standard sodium hydroxide was diluted to the same concentration and the pH measured immediately.

Acknowledgment.—The technical assistance in the determination of physical constants by Miss Evelyn R. Breuninger, Mr. Richard H. Creech, and Mrs. Ann J. Miller is gratefully acknowledged.

Oxidation of Steroidal α-Ketols to Glyoxals with Cupric Acetate[1]

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Received September 28, 1962

Catalytic amounts of copper acetate in methanol will convert the α-ketolic side chain of steroids to a glyoxal group. Oxidation is hastened by passing air over or through the solution, and retarded by addition of water. The reaction is general and gives high yields of steroidal glyoxals. In dry methylene chloride or benzene the glyoxals tend to polymerize; in aqueous ethyl acetate they are stable. With a ratio of copper acetate to ketolic steroid of 1:8, oxidation to the glyoxal is complete in an hour or less. With a longer reaction time the yield decreases because of a rearrangement of the glyoxal side chain to a methyl glycolate side chain. The glyoxals are characterized as hydrates, dimethyl acetals, and quinoxalines. The glyoxal from cortisone crystallizes from aqueous methanol as a stable 21-hemiacetal. The preparation of six 3α-hydroxy-5β-pregnanes with an α-ketolic function in the side chain and with variations in the molecule at C-9, C-11, and C-16 is described.

The finding that the α-ketolic side chain of steroids was altered in the presence of a trace of cupric ions[3] stimulated us to investigate this reaction in detail. One of the products of the reaction gave an immediate yellow color with the Porter–Silber[4] reagent, but did not reduce alkaline tetrazolium. These results indicated that the product contained a glyoxal (20-oxo-21-aldehyde) function. This oxidative process offered promise for the preparation of steroidal glyoxals which were needed for a study on the Porter–Silber reaction. The preparation of several α-ketolic steroids is described at the end of the discussion in this paper.

Various copper salts were tested for their ability to convert cortisone to the corresponding glyoxal. Of the salts investigated, copper acetate gave by far the most rapid and complete oxidation. Methanol was a satisfactory solvent for the reactants. At the time this work was done it was not known that Conbere[5] and Weijlard[6] had assigned patents to Merck and Company dealing with the preparation of steroidal glyoxals from α-ketols using copper acetate as the oxidant in both catalytic and stoichiometric amounts. Our results are presented since they are a confirmation and extension of the findings described in the patents.

3α,21-Dihydroxy-5β-pregnane-11,20-dione (I) was used as a model α-ketol in preliminary studies. The Porter–Silber reaction, given by the glyoxal (II) but not by the α-ketol (I), served as a convenient means of determining the extent of the oxidation.[7] The reaction can be terminated immediately by addition of EDTA (disodium ethylenedinitrilotetraacetate) to bind the copper; this reagent does not interfere with the Porter–Silber reaction.

The rate of oxidation of 3α,21-dihydroxy-5β-pregnane-11,20-dione (I) with methanolic cupric acetate at room temperature under conditions in which the ratio of copper to steroid varied from 1:2 to 1:100 is shown in Fig. 1. The catalytic nature of the process is illustrated by the fact that even with a ratio of 1:20 there is rapid and apparently complete conversion of the α-ketol to the glyoxal. When the copper to steroid ratio

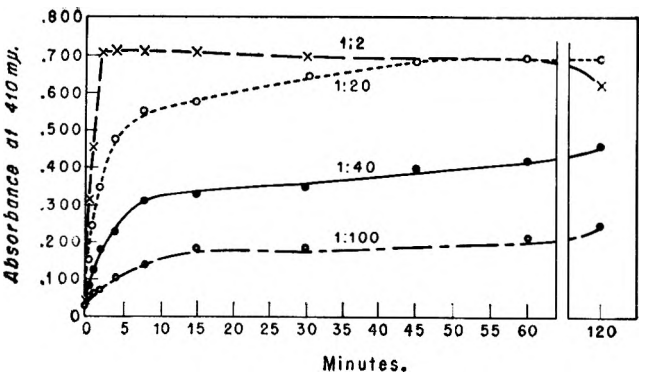

Fig. 1.—Rates of oxidation of 3α,21-dihydroxy-5β-pregnane-11,20-dione (I) with methanolic cupric acetate as indicated by increase in color produced in the Porter–Silber reaction. Molar ratios of copper to steroid were 1:2, 1:20, 1:40, and 1:100; steroid concentration was 0.00091 *M*.

was 1:40 or less, oxidation proceeded slowly and was incomplete after two hours. The presence of water lowers the rate of oxidation. With a copper to steroid ratio of 1:8 and a reaction time of one hour, absorbance readings in the Porter–Silber reaction for solutions containing 0, 5, 12.5, and 25% of water in methanol were 0.650, 0.655, 0.540, and 0.300, respectively.

Preparative scale experiments with a number of α-ketols were performed using copper to steroid ratios varying from 1:8 to 1:2 and oxidation times ranging from fifteen minutes to one hour. Oxidation rates were raised substantially by passing air into or over the surface of the reaction mixtures.

The optimal yield of glyoxal (II) from 3α,21-dihydroxy-5β-pregnane-11,20-dione (I) was obtained with a copper to steroid ratio of 1:8 and a reaction time of fifteen minutes. More prolonged reaction was attended by lower yields because of rearrangement of the glyoxal to a 20-epimeric mixture of methyl 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oates.[8]

Almost immediately after mixing methanolic solutions of 3α,21-dihydroxy-5β-pregnane-11,20-dione (I) and cupric acetate, the originally blue-green solution became amethyst in color, then the solution became turbid, and the color changed from amethyst to yellow to green. The original clear blue-green color was restored in about ten minutes. In several experiments in which smaller amounts of copper acetate were used it was possible to regenerate repeatedly the blue-green from the amethyst color merely by swirling the flask or by bubbling air into the solution for a few seconds.

(1) Abridgement of thesis submitted by M. L. Lewbart to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biochemistry, June, 1961.

(2) This investigation was carried out during the tenure of a Fellowship from the Division of General Medical Sciences, U. S. Public Health Service.

(3) M. L. Lewbart and V. R. Mattox, *Nature*, **183**, 820 (1959).

(4) R. H. Silber and C. C. Porter, "Methods of Biochemical Analysis," Vol. 4, Interscience Publishers, New York, N. Y., 1957, pp. 139–169.

(5) J. P. Conbere, U. S. Patent 2,773,077 (1956).

(6) J. Weijlard, U. S. Patent 2,773,078 (1956).

(7) M. L. Lewbart and V. R. Mattox, *Anal. Chem.*, **33**, 559 (1961).

(8) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

Initially, the glyoxal (II) was recovered from the reaction mixture by addition of an excess of aqueous EDTA, concentration of the solution under reduced pressure to remove the methanol, and extraction with methylene chloride. When the methylene chloride solution was washed with water and taken almost to dryness, the residue was no longer completely soluble in methanol and a crystalline polymer[9] was obtained in low yield. When the residue was treated with benzene, the polymer was obtained in almost quantitative yield. In one experiment one-half of a methylene chloride extract of glyoxal was washed with both dilute sodium bicarbonate and water and the other half was washed with water alone. When the solvent was removed and the residues were dissolved in benzene, that fraction washed with water gave a heavy deposit of polymer in approximately one minute. The product from the bicarbonate-washed fraction deposited polymer to the same extent after about eighteen hours. These findings suggest that polymerization may be promoted by the small amounts of acetic or steroidal acid which are present.

Polymerization of the glyoxal (II) was avoided in the following manner. The oxidation mixture was diluted with water and extracted with ethyl acetate. After being washed with dilute sodium bicarbonate solution and water, the wet organic phase was taken to dryness. Crystallization from aqueous acetone gave the glyoxal hydrate in 94% yield.

A small amount of 3α-hydroxy-11-oxo-5β-etianic acid[10] (V) was obtained from the aqueous bicarbonate solution. This result indicates that during the oxidation, a small amount of steroid underwent cleavage between C-20 and C-21.

Successive treatment of both the glyoxal (II) and the polymer with dry methanolic hydrogen chloride followed by acetylation afforded the known acetoxy dimethyl acetal[11] (IV) in yields of 80 and 60%, respectively. The glyoxal (II) was convertible into a quinoxaline (III) by the method of Leanza, *et al.*[12]

nan-20-one (XIV) than with the 11-dehydro analog (I); the reaction time had to be extended to forty-five minutes. The corresponding glyoxals were obtained in 76 and 89% yield.

The rate of cupric acetate oxidation of 3α,21-dihydroxy-5β-pregn-16-ene-11,20-dione (IX) was slower than that of other α-ketols and a reaction time of one hour was employed. The glyoxal (X) was obtained in 82% yield. Of all the glyoxals studied this one showed the greatest tendency to undergo polymerization. However, if the product from the oxidation reaction was processed rapidly and crystallized immediately from aqueous acetone, the amount of methanol-insoluble material in the final product could be reduced to less than 1%.

Treatment of the Δ^{16}-steroidal glyoxal (X) with methanolic hydrogen chloride followed by neutralization of the acid with potassium carbonate and acetylation of the product with acetic anhydride–pyridine gave the acetoxy dimethoxy derivative (XII) in 86% yield. In earlier experiments when the methanolic hydrogen chloride was neutralized by addition of an excess of potassium carbonate, the yield of XII was only 40%. By neutralization with an equivalent amount of alkali the yield was more than doubled. A possible explanation for these results stems from the work of Fukushima and Gallagher[13] who found that Δ^{16}-20-keto steroids undergo a 1,4-attack by methanolic alkali to give saturated 16α-methoxy derivatives.

The quinoxaline of X could not be obtained from its precursor by the method of Leanza, *et al.*[14] Presumably addition of sodium bisulfite to the Δ^{16}-steroidal glyoxal (X) occurs. The quinoxaline (XI) was obtained by refluxing an alcoholic solution of the glyoxal and *o*-phenylenediamine.

Treatment of cortisone (XVII) for one hour at room temperature with 0.5 molar equivalent of cupric acetate resulted in essentially complete oxidation to the corresponding 21-aldehyde (XVIII). In the work of Con-

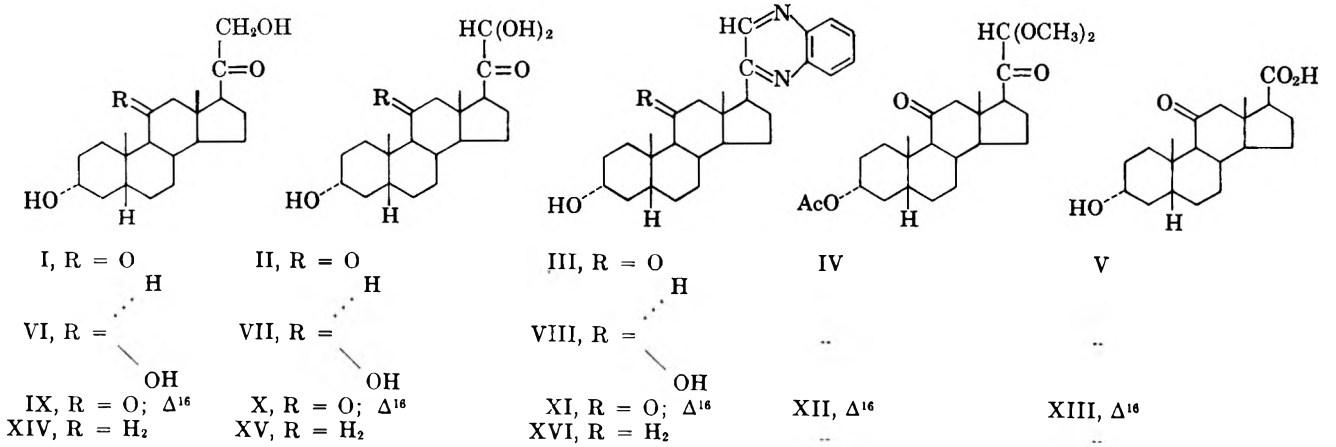

Figure 2

The sequence of color changes and the rate of oxidation occurred more slowly with 3α,11β,21-trihydroxy-5β-pregnan-20-one (VI) and 3α,21-dihydroxy-5β-pregnane[5] and Weijlard,[6] the copper to cortisone ratio was 1:30 and the reaction was carried out at 50–55° for fourteen hours in methanol which contained a small amount of water and acetic acid. Whereas they found that "any additional amount of catalyst (cupric ace-

(9) The tendency for this type of compound to polymerize is well known. H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1949).

(10) J. von Euw, A. Lardon, and T. Reichstein, *ibid.*, **27**, 1287 (1944).

(11) V. R. Mattox, *J. Am. Chem. Soc.*, **74**, 4340 (1952).

(12) This procedure involves the initial formation of an aldehyde–bisulfite addition compound, followed by treatment with *o*-phenylenediamine.[14]

(13) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

(14) W. J. Leanza, J. P. Conbere, E. F. Rogers, and K. Pfister, 3rd, *ibid.*, **76**, 1691 (1954).

tate) above about 3% will not increase the rate of reaction or the yield obtained," it is apparent from the present study that, under the specified conditions, larger amounts of cupric acetate bring about a greater rate of oxidation.

The glyoxal from cortisone was characterized as a hydrate (XVIII) and a quinoxaline (XIX) which had properties in good agreement with those reported.[14] When the glyoxal was crystallized from aqueous methanol, it separated as a colorless substance which had a melting point different from that of the hydrate. Ele-

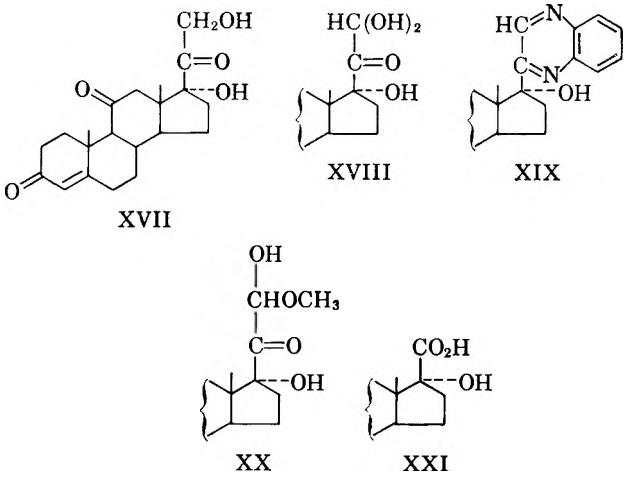

Figure 3

mental and Zeisel analyses showed that the glyoxal was associated with one molecule of methanol. This product is formulated as a hemiacetal (XX) rather than as a free glyoxal with methanol of crystallization. Recrystallization of the hemiacetal from aqueous acetone yielded the glyoxal hydrate (XVIII). Crystallization of the glyoxal from aqueous ethanol gave a compound different from the one obtained by crystallization from methanol. The infrared spectra in Nujol of the two hemiacetals and the glyoxal were different. After evaporation of benzene solutions of the hemiacetals and the glyoxal hydrate the residues had identical spectra in chloroform. The glyoxal hydrate is sparingly soluble in chloroform, but the hemiacetals dissolve readily. Solutions of this glyoxal and others described in the paper are colorless in methanol and aqueous methanol. Solutions of the glyoxals in chloroform are yellow and have maxima[15] at about 450 mμ with molecular extinction coefficients of less than 40. These properties suggest that the mole of solvent in the hydrates and alcoholates is combined with the aldehyde group at C-21.

Steps used in the preparation of several α-ketolic steroids are indicated in Fig. 4. Three of these compounds (C, E, and N) are metabolites of adrenocortical hormones. In reports dealing with their isolation,[16-18] identification has been made largely by comparison of infrared spectra with reference compounds supplied by other workers in the field. To the authors' knowledge,

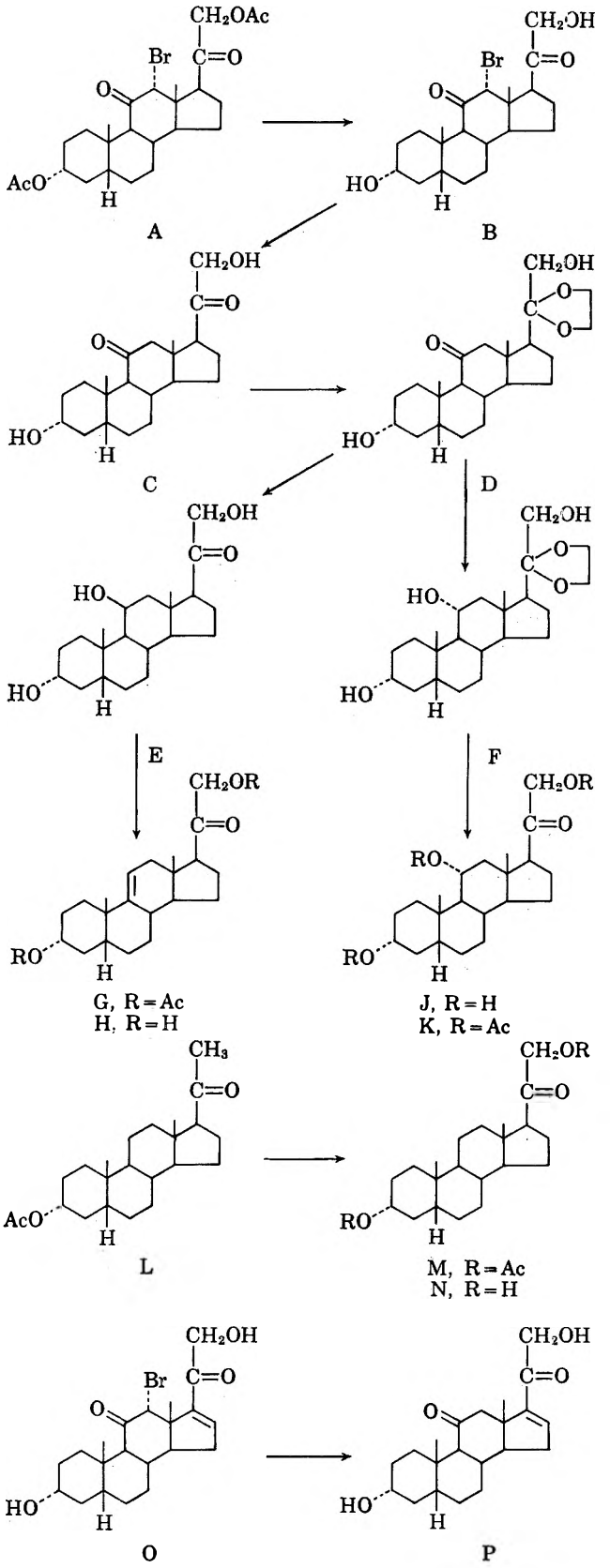

Figure 4

the physical constants and analyses for these substances have not been reported.

The presence of an α-ketolic group was deduced from the method of preparation and was verified by the rapid reduction of tetrazolium blue by the compounds in question. Several of the substances have been converted to the corresponding glyoxals. The double bond

(15) This spectral constant is typical of that for steroidal glyoxals.

(16) L. L. Engel, P. Carter, and L. L. Fielding, *J. Biol. Chem.*, **213**, 99 (1955).

(17) E. M. Richardson, J. C. Touchstone, and F. C. Dohan, *J. Clin. Invest.*, **34**, 285 (1955).

(18) W. R. Eberlein and A. M. Bongiovanni, *J. Biol. Chem.*, **223**, 85 (1956).

in G and H is assigned $\Delta^{9(11)}$, rather than Δ^{11}, because dehydration of 11β-hydroxy steroids with boron trifluoride gives $\Delta^{9(11)}$ derivatives.[19]

Experimental

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured in methanol at a concentration of about 1% and at a temperature of 24 ± 2° unless otherwise designated. Analyses were by J. F. Alicino, Metuchen, N. J.

3α,21-Dihydroxy-12α-bromo-5β-pregnane-11,20-dione (B).—To 153.6 g. (0.3 mole) of 3α,21-diacetoxy-12α-bromo-5β-pregnane-11,20-dione[20] in 800 ml. of chloroform and 2800 ml. of methanol was added 200 ml. of water and 338 ml. of concentrated hydrochloric acid. After 22 hr. at room temperature, 400 g. of sodium acetate trihydrate in 1 l. of water was added and most of the organic phase was evaporated under reduced pressure. The aqueous residue was extracted three times with a total of 2 l. of methylene chloride. The organic layer was washed with dilute sodium hydroxide and water, dried, and concentrated to dryness. Recrystallization from 1100 ml. of hot acetone gave 105 g. (m.p. 152.5–155.5°) of bromodiol (B) as a 1:1 solvate. The mother liquor yielded an additional 23.5 g. (m.p. 151–153°) of product. A sample, which had been recrystallized from acetone and air dried, lost 11.35% in 2 hr. at 100° and 0.1 mm.; calcd. for loss of 1 mole of acetone, 11.95%; m.p. 163–165°; $[\alpha]_D$ −1 ± 2° (chloroform).

Anal. Calcd. for $C_{21}H_{31}O_4Br$: C, 59.01; H, 7.31. Found: C, 59.34; H, 7.59.

3α,21-Dihydroxy-5β-pregnane-11,20-dione (C).—To an agitated solution of 29.2 g. (60 mmoles) of 3α,21-dihydroxy-12α-bromo-5β-pregnane-11,20-dione (containing 1 mole of acetone) in 500 ml. of glacial acetic acid was added 40 g. of powdered zinc in portions over a period of 1 hr. The temperature was maintained at 40–45° during the addition of zinc and for a subsequent 30-min. period. The reaction mixture was filtered into 2 l. of water and the zinc was washed with 50 ml. of acetic acid. The product was recovered by extraction with methylene chloride (1250 ml. in three portions). After successive washings with 300 ml. of water, 400 ml. of *N* sodium hydroxide, and 300 ml. of water, the organic phase was dried and concentrated to dryness. Three crops of cubes were obtained from methanol (14.9 g., m.p. 215–217°; 4.3 g., m.p. 213–215°; 1.0 g., m.p. 209–211°). A sample for analysis was recrystallized from methanol; m.p. 215–216°; $[\alpha]_D$ + 129 ± 2°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.51; H, 8.97.

3α,21-Dihydroxy-5β-pregnane-11,20-dione 20-Ethylene Ketal (D).—A suspension of 10.5 g. (30 mmoles) of 3α,21-dihydroxy-5β-pregnane-11,20-dione in 300 ml. of benzene and 15 ml. of ethylene glycol was dried by refluxing for 10 min. in an apparatus fitted with a water separator.[21] To the dried mixture was added 300 mg. of *p*-toluenesulfonic acid and refluxing was resumed for 3 hr. The reaction mixture was cooled, washed with dilute sodium bicarbonate and water, and concentrated to dryness. Crystallization from acetone afforded three crops of needles (6.7 g., m.p. 188.5–190.5°; 2.2 g., m.p. 187–189°; 0.4 g., m.p. 183–186°). A sample for analysis was recrystallized from methanol; m.p. 191.5–193.5°; $[\alpha]_D$ + 67 ± 2°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.33; H, 9.09.

3α,11β,21-Trihydroxy-5β-pregnan-20-one (E).—To 7.84 g. (20 mmoles) of 3α,21-dihydroxy-5β-pregnane-11,20-dione 20-ethylene ketal in 250 ml. of methanol was added 15.2 g. (400 mmoles) of sodium borohydride in 75 ml. of water. After 36 hr. at room temperature, excess reducing agent was decomposed with acetic acid. The reaction mixture was added to 400 ml. of water and extracted with methylene chloride, which, after being washed with water, was dried, and concentrated to dryness. The 11β-hydroxy-20-ketal, which could not be obtained in crystalline form, was dissolved in a mixture of 250 ml. of methanol and 25 ml. of 8% (v./v.) sulfuric acid in water and the solution was refluxed for 50 min. The reaction mixture was diluted with 450 ml. of water and extracted with methylene chloride. Addition of 15 ml. of acetone and 30 ml. of ether to the residue from the methylene chloride extract brought about crystallization (5.15 g., m.p. 145–146.5°; 0.72 g., m.p. 144.5–146°). The sample for analysis was recrystallized from acetone–ether; m.p. 145.5–147°; $[\alpha]_D$ +133 ± 2°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.98; H, 9.98.

3α,11α,21-Trihydroxy-5β-pregnan-20-one 20-Ethylene Ketal (F).—To 3.92 g. (10 mmoles) of 3,21-dihydroxy-5β-pregnane 11,20-dione 20-ethylene ketal in 400 ml. of *n*-propyl alcohol was added in one portion 40 g. of metallic sodium.[22] The mixture was allowed to reflux spontaneously for 1 hr. The precipitated sodium propoxide was dissolved by addition of 150 ml. of methanol and the unchanged sodium was decomposed by slow addition of 250 ml. of water. After evaporation of most of the organic solvents the aqueous residue was extracted with three 100-ml. portions of ethyl acetate. The extract was washed twice with water, dried, and concentrated. Crystals separated slowly (3.4 g., m.p. 200–201°; 0.24 g., m.p. 195.5–197.5°). Recrystallization from ethyl acetate gave the analytical sample; m.p. 200–201°; $[\alpha]_D$ +33± 1°.

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.02; H, 9.70. Found: C, 70.77; H, 9.30.

3α,21-Diacetoxy-5β-pregn-9(11)-en-20-one (G).—To 700 mg. (2 mmoles) of 3α,11β,21-trihydroxy-5β-pregnan-20-one was added 2 ml. each of pyridine and acetic anhydride. After 10 hr. at room temperature the product was recovered in the usual manner. Since the resulting 3α,21-diacetoxy-11β-hydroxy-5β-pregnan-20-one could not be crystallized, it was dissolved in 50 ml. of glacial acetic acid and treated with 2 ml. of boron fluoride etherate for 20 hr. at room temperature. The product, recovered by dilution of the reaction mixture with water and extraction with methylene chloride, crystallized as needles and rosettes from ether (489 mg., m.p. 108–112°; 119 mg., m.p. 106–108°; 100 mg., m.p. 105–106.5°). On recrystallization from ether, prisms were obtained (673 mg.); m.p. 124–127°; $[\alpha]_D$ +134 ± 3°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 72.08; H, 8.71. Found: C, 72.19; H, 8.81.

3α,21-Dihydroxy-5β-pregn-9(11)-en-20-one (H).—To 416 mg. (1 mmole) of 3α,21-diacetoxy-5β-pregn-9(11)-en-20-one in 25 ml. of methanol and 4 ml. of water was added 2 ml. of concentrated hydrochloric acid. After 20 hr. at room temperature, 2.5 g. of sodium acetate trihydrate in 10 ml. of water was added and the mixture was concentrated to turbidity. The aqueous residue was extracted with methylene chloride and the organic phase, after being washed with dilute sodium bicarbonate and water, was concentrated to dryness. Crystallization from ether gave needles (168 mg., m.p. 145.5–146.5°; 82 mg., m.p. 144–145°); $[\alpha]_D$ +121 ± 2°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.88; H, 9.76.

3α,11α,21-Trihydroxy-5β-pregnan-20-one (J).—A solution of 3α,11α,21-trihydroxy-5β-pregnan-20-one 20-ethylene ketal (3.4 g.) in methanol (100 ml.) and 8% (v./v.) sulfuric acid (10 ml.) was refluxed for 1 hr. The product, recovered by addition of the reaction mixture to 500 ml. of water and extraction with methylene chloride, crystallized from ethyl acetate as needles (2.5 g., m.p. 180.5–182.5°; 0.46 g., m.p. 180–181°; 0.05 g., m.p. 179–180°). A sample for analysis was recrystallized from acetone and dried for 3 hr. at 100° and 1–2 mm.; m.p. 180–181.5°; $[\alpha]_D$ +103 ± 2°.

Anal. Calcd. for $C_{21}H_{34}O_4 \cdot CH_3COCH_3$: C, 70.55; H, 9.87. Found: C, 70.98; H, 9.54.

3α,11α,21-Triacetoxy-5β-pregnan-20-one (K).—Acetylation of 3α,11α,21-trihydroxy-5β-pregnan-20-one (240 mg.) was carried out in 1 ml. each of pyridine and acetic anhydride for 11 hr. at room temperature. The product crystallized from acetone–petroleum ether (301 mg., 92.1%; m.p. 187–189°). Recrystallization from acetone–petroleum ether did not raise the melting point; $[\alpha]_D$ +88 ± 2°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46; CH_3CO, 27.01. Found: C, 67.81; H, 8.35; CH_3CO, 28.44.

3α,21-Dihydroxy-5β-pregnan-20-one (N).—A solution of 10.8

(19) H. Heyman and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

(20) The physical constants and analytical data (G. A. Fleisher, unpublished findings) are given. Constants: m.p. 162.5–163°; $[\alpha]_D$ +32 ± 2° (chloroform). *Anal.* Calcd. for $C_{25}H_{39}O_6Br$: C, 58.71; H, 6.90; Br, 15.63. Found: C, 58.93; H, 6.86; Br, 15.82.

(21) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(22) H. L. Herzog, M. A. Jevnik, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 269 (1953).

g. (30 mmoles) of 3α-acetoxy-5β-pregnan-20-one[23] (m.p. 101–102°) in 400 ml. of glacial acetic acid and 10 ml. of acetic anhydride was maintained at 70–80° while being agitated with a magnetic stirring bar. To this solution was added 14.7 g. (33 mmoles) of lead tetraacetate[24] in portions over a 2-hr. period. After an additional 16 hr. at 70–80°, at which time a test with starch–iodide paper was negative, the reaction mixture was added to ice, diluted with 1500 ml. of water, and extracted three times with a total volume of 450 ml. of methylene chloride. The organic phase was washed with dilute sodium hydroxide and water, dried, and concentrated to dryness. Since only a small amount of poor quality diacetate (M) could be crystallized from the residue, it was hydrolyzed directly by treatment with a mixture of 350 ml. of methanol, 35 ml. of water, and 42 ml. of concentrated hydrochloric acid for 24 hr. at room temperature. After addition of 50 g. of sodium acetate trihydrate in 250 ml. of water, most of the methanol was removed under reduced pressure. The aqueous residue was extracted with 250 ml. of petroleum ether and, since the residue from the organic phase gave only a faint test with alkaline blue tetrazolium, it was discarded. The aqueous layer was extracted with methylene chloride and, after successive washings with dilute sodium hydroxide and water, the solvent was evaporated. The crude diolone (N) crystallized from benzene with 0.5 mole of solvent of crystallization (6.0 g., m.p. 138–143°; 1.8 g., m.p. 128–133°). Repeated crystallizations from ethyl acetate, aqueous methanol, and ether furnished 4.2 g. (42%, m.p. 153–154°) of pure 3α,21-dihydroxy-5β-pregnan-20-one. A sample for analysis was recrystallized from acetone; m.p. 152.5–153.5°; $[\alpha]_D$ +113 ± 2°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.44; H, 10.25. Found: C, 75.72; H, 10.15.

3α,21-Diacetoxy-5β-pregnan-20-one (M).—To 334 mg. (1 mmole) of 3α,21-dihydroxy-5β-pregnan-20-one was added 1 ml. each of pyridine and acetic anhydride. After 10 hr. at room temperature the product was recovered. Crystallization from ether–petroleum ether gave 309 mg. (74%, m.p. 94–96°) of needles. A sample, recrystallized from ether and dried at 65° and 0.1 mm., melted at 97–98°; $[\alpha]_D$ +148 ± 2°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.73; H, 9.15. Found: C, 71.51; H, 9.28.

3α,21-Dihydroxy-5β-pregn-16-ene-11,20-dione (P).—A stirred solution of 4.5 g. of 3α,21-dihydroxy-12α-bromo-5β-pregn-16-ene-11,20-dione[25] (O) in 150 ml. of methanol was treated under nitrogen with excess chromous chloride, prepared by percolating 15.9 g. of $CrCl_3 \cdot 6H_2O$ in 100 ml. of methanol and 1 ml. of concentrated hydrochloric acid through a 1 × 13 cm. column of amalgamated zinc.[26] The addition of chromous chloride took 30 min. After an additional 15-min. period the reaction mixture was added to 1 l. of water and the solution was extracted with methylene chloride. The extract was washed with dilute sodium hydroxide and water, dried, and concentrated to dryness. Crystallization from ethyl acetate gave needles (2.67 g., m.p. 181.5–182.5°; 0.12 g., m.p. 178.5–180°). The sample for analysis was prepared by recrystallization from acetone; m.p. 183–185°; $[\alpha]_D$ +88 ± 2°; λ_{max}^{MeOH} 238 mμ, ε 8400.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73. Found: C, 72.59; H, 8.69.

3α,21,21-Trihydroxy-5β-pregnane-11,20-dione (II) and 3α-Hydroxy-11-oxo-5β-etianic Acid (V).—To 3.48 g. (10 mmoles) of 3α,21-dihydroxy-5β-pregnane-11,20-dione in 100 ml. of methanol was added 50 ml. of 0.025 *M* (1.25 mmoles) methanolic cupric acetate. After 20 sec. the color changed from blue to amethyst. Air was bubbled into the solution rapidly to hasten the oxidation. A sequence of further color changes ensued, but after approximately 10 min. the reaction mixture was blue once more. After 15 min. at room temperature the solution was added to 1 l. of water and the mixture was extracted twice with 200 ml. of ethyl acetate. The extract was washed with dilute sodium bicarbonate and water, filtered, and concentrated to dryness.

The combined aqueous washes were acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract yielded a crystalline product (86 mg., 2.5%, m.p. 291–293° dec.). Mixture melting point with authentic **3α-hydroxy-11-oxo-5β-etianic acid**[10] (V) (m.p. 292–294° dec.) showed no depression. The acetylation products of both authentic (m.p. 217.5–219.5°) and copper acetate-derived (m.p. 218–220°) acids showed no depression of melting point on admixture.

The residue from the neutral fraction gave crystals from aqueous acetone (3.14 g., m.p. 154–155°; 0.27 g., m.p. 153–155°) in a yield of 94%. The sample for analysis was recrystallized from acetone and dried at room temperature to constant weight under reduced pressure over anhydrous calcium chloride; m.p. 153.5–155°; $[\alpha]_D$ +109 ± 1°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.28; H, 8.78. Found: C, 69.32; H, 9.18.

A sample of the glyoxal hydrate was dried for 18 hr. at 1–2 mm. and 125° in order to remove water of hydration; $\lambda_{max}^{CHCl_3}$ 450 mμ, ε 23.[15]

Formation of Polymer from 3α,21,21-Trihydroxy-5β-pregnane-11,20-dione.—In another preparation of II from 3.48 g. of I the reaction mixture was extracted with methylene chloride; the extract was washed with water and taken to dryness. When the residue was dissolved in benzene, a fine, white solid separated slowly. By repeated filtration of the white precipitate and concentration of the yellow mother liquor, a total of 3.39 g. (m.p. 200.5–201.5°) of product was obtained. The compound was poorly soluble in benzene, methylene chloride, acetone, methanol, and ethyl acetate. It gave a positive Porter–Silber reaction and, on successive treatment with dry methanolic hydrogen chloride and pyridine–acetic anhydride in the manner described later, afforded **3α-acetoxy-21,21-dimethoxy-5β-pregnane-11,20-dione**[11] (IV) in 60% yield.

3α-Acetoxy-21,21-dimethoxy-5β-pregnane-11,20-dione (IV).—3α,21-Dihydroxy-5β-pregnane-11,20-dione (3.48 g., 10 mmoles) was oxidized to the glyoxal in the manner described earlier. The amorphous yellow product was dissolved in 130 ml. of methanol and 30 ml. of 1.35 *N* hydrogen chloride in dry methanol was added. The colorless solution was refluxed for 2 hr. and, following addition of potassium carbonate (10 g. in 25 ml. of water), it was concentrated to remove the organic solvent. The aqueous residue was extracted with methylene chloride. The organic layer was washed with water, filtered through anhydrous sodium sulfate, and concentrated to dryness. The residue was treated with 10 ml. each of pyridine and acetic anhydride for 10 hr. at room temperature. The product (IV) crystallized from ether–petroleum ether to give 2.78 g. (64.0%) of rosettes, m.p. 104.5–105°; $[\alpha]_D$ −132 ± 2° (chloroform); reported[11] m.p. 106–107°; $[\alpha]_D$ +131 ± 2° (chloroform). The mother liquor gave successive crops (0.37 g., m.p. 101–102°; 0.31 g., m.p. 91–92°) of crystals. The infrared spectra of the purified product and of authentic dimethyl acetal (IV) were identical.

2-(3α-Hydroxy-11-oxo-5β-androstan-17β-yl)quinoxaline (III).—To a solution of 364 mg. (1 mmole) of 3α,21,21-trihydroxy-5β-pregnane-11,20-dione in 2 ml. of methanol was added 160 mg. of sodium bisulfite in 10 ml. of water. The mixture was heated on a steam bath for 5 min., the methanol was removed, and the residue in 10 ml. of water was treated with 160 mg. of *o*-phenylenediamine in 5 ml. of hot water for 30 min. on a steam bath. The product was crystallized from methanol–ether to give yellow needles (270 mg., 65%, m.p. 181.5–182.5°). Additional crops of product brought the total yield to 91%. The analytical sample had m.p. 180.5–181.5°; $[\alpha]_D$ +111 ± 1°; λ_{max1}^{MeOH} 237 mμ, ε 31,000; λ_{max2}^{MeOH} 319 mμ, ε 8000.

Anal. Calcd. for $C_{27}H_{34}O_2N_2$: C, 77.60; H, 8.13; N, 6.70. Found: C, 77.52; H, 8.04; N, 6.84.

3α,11β,21,21-Tetrahydroxy-5β-pregnan-20-one (VII).—To a solution of 350 mg. (1 mmole) of 3α,11β,21-trihydroxy-5β-pregnan-20-one in 25 ml. of methanol was added 25 ml. of 0.005 *M* (0.125 mmole) methanolic cupric acetate. Air was bubbled into the solution for 45 min. and, following the addition of 50 mg. of EDTA (disodium ethylenedinitrilotetraacetate) in 3 ml. of water, the methanol was removed. The residue was diluted with water and extracted with methylene chloride. The yellow extract, after being washed with dilute sodium bicarbonate and water, was concentrated to dryness. Yellow crystals were obtained from aqueous acetic acid (240 mg., m.p. 154.4–155.5°; 25 mg., m.p. 152–154.5°). The sample for analysis was dried to constant weight at room temperature and 1–2 mm. over anhydrous calcium chloride; m.p. 154.5–155.5°; $[\alpha]_D$ +120 ± 2°.

Anal. Calcd. for $C_{21}H_{32}O_4 \cdot 1.5\ H_2O$: C, 67.19; H, 9.39. Found: C, 66.91, 67.27; H, 10.02, 9.38.

A portion of the analytical sample, dried for 2 hr. at 5–10 μ

(23) Prepared by acetylation of 3α-hydroxy-5β-pregnan-20-one (Canada Packers, Ltd., Toronto, Canada) with pyridine and acetic anhydride.

(24) F. Sondheimer, G. Rosenkranz, O. Mancera, and C. Djerassi, *J. Am. Chem. Soc.*, **75**, 2601 (1953).

(25) F. C. Colton, W. R. Nes, D. A. Van Dorp, H. L. Mason, and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

(26) W. F. McGuckin and H. L. Mason, *J. Am. Chem. Soc.*, **77**, 1822 (1955).

mercury and 100° lost 7.22%; calcd. for loss of 1.5 moles of water, 7.20%.

2-(3α,11β-Dihydroxy-5β-androstan-17β-yl)quinoxaline (VIII).—Conversion of 183 mg. (0.5 mmole) of 3α,11β,21,21-tetrahydroxy-5β-pregnan-20-one to its quinoxaline derivative was accomplished by the procedure used for the preparation of III from II. The crude product crystallized from acetone to give 189 mg. of yellow needles, m.p. 118–127°. A sample for analysis was crystallized from acetone and dried to constant weight under reduced pressure at room temperature.

Anal. Calcd. for $C_{27}H_{36}O_2N_2 \cdot CH_3COCH_3$: C, 75.27; H, 8.84; N, 5.86. Found: C, 75.37; H, 8.74; N, 6.42.

Another sample, which had been recrystallized from acetone and dried to constant weight under reduced pressure at room temperature, was dried for a further 46 hr. at 1–2 mm. and 100°. The weight loss was 11.25%; calcd. for loss of 1 mole of acetone, 12.15%; m.p. 127–129° $[\alpha]_D$ +127 ± 1°; λ_{max1}^{MeOH} 237 mμ, ε 28,800; λ_{max2}^{MeOH} 319 mμ, ε 8000.

Anal. Calcd. for $C_{27}H_{36}O_2N_2$: C, 77.10; H, 8.56; N, 6.67. Found: C, 76.51; H, 8.85; N, 6.47.

3α,21,21-Trihydroxy-5β-pregn-16-ene-11,20-dione (X) and 3α-Hydroxy-11-oxo-5β-eti-16-enic Acid (XIII).—To 1.73 g. (5 mmoles) of 3α,21-dihydroxy-5β-pregn-16-ene-11,20-dione in 125 ml. of methanol was added an equal volume of 0.005 *M* methanolic cupric acetate. After 1 hr., during which time the solution was aerated, EDTA (250 mg.) in water (10 ml.) was added and the methanol was evaporated. The aqueous residue was diluted with 50 ml. of water and extracted with methylene chloride. The organic layer was washed with dilute sodium bicarbonate and water and concentrated to dryness.

The acidic fraction recovered from the aqueous washings was recrystallized from acetone to give 25 mg. of needles, m.p. 267.5–268.5° dec. Product, recrystallized from ethyl acetate while solution was hot, gave prisms (m.p. 276–278° dec.; λ_{max}^{MeOH} 218 mμ, ε 7600) which did not depress melting point of the acid obtained by treatment of 3α,21-dihydroxy-5β-pregn-16-ene-11,20-dione with periodic acid. The infrared spectra of the two samples of XIII in Nujol were identical. Crystals separated from cold ethyl acetate as long needles; in Nujol the infrared spectrum of the long needles was markedly different from that of the prisms. Neither the prisms nor the needles was solvated.

Treatment of 200 mg. of 3α,21-dihydroxy-5β-pregn-16-ene-11,-20-dione in 10 ml. of methanol with 400 mg. of H_2IO_6 in 2 ml. of water at room temperature for 5 hr. followed by separation of the organic acid and crystallization gave 54 mg. of **3α-hydroxy-11-oxo-5β-eti-16-enic acid**, m.p. 276–279°. The product crystallized from hot ethyl acetate as prisms, m.p. 276–278°.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.41; H, 8.51.

The neutral fraction from the cupric acetate oxidation was dissolved in 25 ml. of 80% aqueous acetone and water was added to the point of turbidity. After removal of a small amount of insoluble material, the solution was concentrated until crystals began to form. The yield of air-dried product was 1.48 g. (82%). The compound exhibited unusual melting behavior. When placed on the stage at or above 170°, it melted immediately. After being subjected to initial temperatures below 160° for a brief period, the crystals melted only partially even when the temperature was raised to over 250°. The sample for analysis was crystallized from aqueous acetone and dried to constant weight at room temperature and 1–2 mm. over anhydrous calcium chloride; $[\alpha]_D$ +63 ± 2°; λ_{max}^{MeOH} 242 mμ, ε 8500.

Anal. Calcd. for $C_{21}H_{30}O_5 \cdot H_2O$: C, 66.29; H, 8.46. Found: C, 65.79; H, 8.53.

3α-Acetoxy-21,21-dimethoxy-5β-pregn-16-ene-11,20-dione (XII).—To a solution of 362 mg. (1 mmole) of 3α,21,21-trihydroxy-5β-pregn-16-ene-11,20-dione (X) in 25 ml. of methanol was added 5 ml. of 1.35 *N* hydrogen chloride in dry methanol. After 15 hr. at room temperature the reaction mixture was neutralized by the slow addition of 4.5 ml. of 5% sodium carbonate plus 100 ml. of water, and extracted with methylene chloride. The extract was washed with water and concentrated to dryness. The residue was treated with 1 ml. each of pyridine and acetic anhydride for 5 hr. at room temperature. The acetylated product was crystallized from ether–petroleum ether (352 mg., m.p. 149–151°; 20 mg., m.p. 147–149°). After being stored several weeks at room temperature the originally colorless compound had become yellow and its melting point had decreased by approximately 10°. Recrystallization from aqueous methanol gave the analytical sample; m.p. 153.5–155°; $[\alpha]_D$ +75 ± 2°; λ_{max}^{MeOH} 245 mμ, ε 8650.

Anal. Calcd. for $C_{25}H_{36}O_6$: CH_3O, 14.37. Found: CH_3O, 14.75.

2-(3α-Hydroxy-11-oxo-5β-androst-16-en-17β-yl)quinoxaline (XI).—To 181 mg. (0.5 mmole) of 3α,21,21-trihydroxy-5β-pregn-16-ene-11,20-dione in 5 ml. of absolute ethanol was added 80 mg. of *o*-phenylenediamine. After being refluxed for 1 hr., the solvent was evaporated and the residue crystallized from acetone (134 mg., 65%). Two crystal forms were present; one melted at 202–203°, and the other at 225–227°. When the temperature of a sample on the stage was raised above 228° and then cooled, all of the resulting crystals melted at 226.5–227.5°; $[\alpha]_D$ +129 ± 1°; λ_{max1}^{MeOH} 213 mμ, ε 21,900; λ_{max2}^{MeOH} 260 mμ, ε 23,400; λ_{max3}^{MeOH} 338 mμ, ε 9600.

Anal. Calcd. for $C_{27}H_{32}O_2N_2$: C, 77.86; H, 7.75; N, 6.73. Found: C, 77.46; H, 7.88; N, 6.94.

3α,21,21-Trihydroxy-5β-pregnan-20-one (XV).—3α,21-Dihydroxy-5β-pregnan-20-one (334 mg., 1 mmole) was converted to its glyoxal by the procedure used for the preparation of VII from VI. Crystallization from aqueous acetone gave a light yellow product (310 mg., 89%, m.p. 128–130°). A sample for analysis was crystallized from aqueous acetic acid and dried to constant weight under reduced pressure over anhydrous calcium chloride; m.p. 128.5–130°; $[\alpha]_D$ +99 ± 2°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.08; H, 9.89.

2-(3α-Hydroxy-5β-androstan-17β-yl)quinoxaline (XVI).—Conversion of 3α,21,21-trihydroxy-5β-pregnan-20-one (175 mg., 0.5 mmole) to its quinoxaline derivative was effected by the procedure used for the preparation of III from II. Crystallization from acetone gave yellow needles (112 mg., m.p. 198–201°; 22 mg., m.p. 195–200°). The analytical sample had m.p. 205–205.5°; $[\alpha]_D$ +140 ± 2°; λ_{max1}^{MeOH} 238 mμ, ε 31,300; λ_{max2}^{MeOH} 319 mμ, ε 8200.

Anal. Calcd. for $C_{27}H_{36}ON_2$: C, 80.15; H, 8.97; N, 6.92. Found: C, 79.86; H, 8.88; N, 6.88.

17,21-Dihydroxy-21-methoxypregn-4-ene-3,11,20-trione (XX) and 17-Hydroxy-3,11-dioxo-4-etienic Acid (XXI).—To a solution of 3.60 g. (10 mmoles) of cortisone[27] in 250 ml. of methanol was added 250 ml. of 0.01 *M* methanolic cupric acetate. Air was bubbled into the solution for 1 hr. After addition of 500 mg. of EDTA in 50 ml. of water, the methanol was evaporated. The aqueous residue was extracted with methylene chloride and, after being washed with dilute sodium bicarbonate and water, the yellow solution was concentrated to dryness.

The acidic fraction yielded 16 mg. of needles (m.p. 251–258° dec.) from acetone. A mixture melting point with an authentic sample of 17-hydroxy-3,11-dioxo-4-etienic acid showed no depression.

Crystallization of the neutral fraction from aqueous methanol gave 2.93 g. (75%) of hemiacetal (XX), m.p. 125–126° (on melting point stage at 120°), and 0.52 g., m.p. 123–126°. A sample for analysis was recrystallized from aqueous methanol and dried for 14 hr. at room temperature and 0.1 mm. over phosphorus pentoxide; m.p. 113–115° (on melting point stage at 100°); $[\alpha]_D$ +179 ± 2°; λ_{max}^{MeOH} 238 mμ, ε 15,900.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.66; H, 7.74; CH_3O, 7.94. Found: C, 67.50; H, 7.77; CH_3O, 7.44.

17,21,21-Trihydroxypregn-4-ene-3,11,20-trione (XVIII).—The hemiacetal (XX) was recrystallized from aqueous acetone to yield the hydrate (XVIII) which was dried for 14 hr. at room temperature and 0.1 mm. over phosphorus pentoxide; m.p. 140–145° (on stage at 130°); $[\alpha]_D$ +182 ± 2°; λ_{max}^{MeOH} 238 mμ, ε 15,800; reported[14] m.p. 170–190°; $[\alpha]_D$ +182° (*c* 2, methanol); λ_{max}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 418 (which corresponds to ε 15,700).

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.01; H, 7.49. Found: C, 67.02; H, 7.65.

2-(17-Hydroxy-3,11-dioxopregn-4-en-17β-yl)quinoxaline (XIX).—Conversion of 17,21-dihydroxy-21-methoxypregn-4-ene-3,11,-20-trione (200 mg.) to its quinoxalyl derivative was effected in the usual manner.[14] The crude product (203 mg., 92%, m.p. 231–234°) gave needles (173 mg., m.p. 243–244.5°) from methanol. A sample, recrystallized from methanol and air dried, lost 7.06% when dried for 3 hr. at 100° and 1–2 mm. over phosphorus pentoxide; calcd. for loss of 1 mole of methanol, 6.92%; m.p. 245–246°; λ_{max1}^{MeOH} 237 mμ, ε 47,500; λ_{max2}^{MeOH} 319 mμ, ε 8150. The reported constants are m.p. 242–243°; λ_{max1}^{MeOH} 238 mμ, $E_{1\,cm}^{1\%}$ 1045 (which corresponds to ε 44,900); λ_{max2}^{MeOH} 319 mμ, $E_{1\,cm}^{1\%}$ 185 (which corresponds to ε 7950).

(27) The cortisone was kindly donated by Merck and Co., Rahway, N. J.

Syntheses of Amide Derivatives of DL-β-Carboxy-γ-aminobutyric Acid

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Amides of DL-β-carboxy-γ-aminobutyric acid have been synthesized, starting with itaconic anhydride. This was opened by the appropriate amine to yield 2-methylene-N-alkylsuccinamic acids, to the double bond of which one mole of benzylamine was added. Hydrogenolysis of the resulting benzylamino derivatives gave the required amides of the free amino acid. The structure of the 2-methylene-N-alkylsuccinamic acids is established.

DL-β-Carboxy-γ-aminobutyric acid (aminomethylsuccinic acid, α-carboxymethyl-β-alanine) (I) was pre-

$$H_2N-CH_2-\underset{\displaystyle COOH}{\underset{|}{CH}}-CH_2COOH$$

I

pared by addition of benzylamine to the double bond of itaconic acid and subsequent debenzylation.[1] It is a β-amino acid which, due to its special structure, may be a potential antagonist to aspartic acid, glutamic acid, γ-aminobutyric acid, or β-alanine, all of which have great importance in many biological processes.

It seemed interesting to synthesize amide (peptide) derivatives of this amino acid. Itaconic anhydride was used as starting material. This on reaction with amines led to the formation of the corresponding amides. Only a few aromatic itaconamides are known[2-4] and their structure (position of the amide group) has not been identified. They were prepared either by reaction of amines with itaconic anhydride or by opening of the corresponding itaconimides with alkali. The derivatives obtained by the former method had higher melting points and our derivatives were similar to them in regards to solubility and melting points.

The following evidence proves that the opening of itaconic anhydride with amines results in the formation of 2-methylene-N-alkylsuccinamic acids (I).

$$CH_2=\underset{\displaystyle CH_2CO}{\underset{|}{\overset{|}{C}}}\overset{\displaystyle O}{\diagdown\!\diagup}\overset{|}{CO} + RNH_2 \longrightarrow CH_2=\underset{\displaystyle CH_2CONHR}{\underset{|}{C}}COOH$$

I

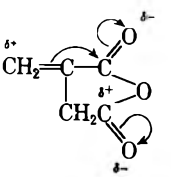
Reaction of methanol with the anhydride leads to the formation of only one monomethyl ester,[5] m.p. 70°. The structure of this ester has been proved by Hancock and Linstead[6] and shown to be 4-methyl 2-methylene succinate (II).

$$CH_2=\underset{\displaystyle CH_2COOCH_3}{\underset{|}{C}}COOH$$

II

We found additional evidence from the fact that reaction of the ester with benzylamine in dioxane led to elimination of methanol and formation of N-benzyl-4-carboxy-2-pyrrolidone,[1,7] showing that the methyl ester occupied the γ-position with respect to the methylene group. The same pyrrolidone derivative was obtained on reaction of monobenzyl ester[8] (obtained similarly on reaction of benzyl alcohol with itaconic anhydride) with benzylamine, showing that opening of the anhydride leads to the exclusive formation of 4-alkyl esters of 2-methylene succinic acid. It may be mentioned that reaction of dimethyl itaconate with one mole benzylamine led to the formation of N-benzyl-4-carbomethoxy-2-pyrrolidone,[9] and with two moles of benzylamine the second methyl ester group was replaced by benzylamine to form the corresponding amide.

It is expected that opening of the anhydride with amines will lead similarly to the preferential formation of 2-methylene-N-alkylsuccinamic acids. In itaconic anhydride the two carbonyl groups are attached to an unsaturated and saturated carbon atom, respectively, thus making a decisive difference in their reaction with nucleophilic reagents. The exclusive formation of the ester or amide derivatives in a γ-position with respect to the methylene group, may be due to conjugation of C=C bond of the anhydride to the nearby C=O group, which leads to lowering of the partial positive charge of the carbon atom of the carbonyl group, whereas the remote carbonyl group is not affected.



Thus attack by a nucleophilic reagent will occur at the γ-carbonyl group with formation of γ-derivatives. Steric effects of the methylene group also may favor the preferential formation of the γ-derivatives.

Indeed, the amides obtained added benzylamine to their double bonds, giving 3-carboxy-4-benzylamino butyramides (III), and without formation of pyrrolidone derivatives, which should have been formed if the carboxyl group, which is in a γ-position with respect to the methylene group, was free.

$$CH_2=\underset{\displaystyle CH_2CONHR}{\underset{|}{C}}COOH + C_6H_5CH_2NH_2 \longrightarrow C_6H_5CH_2NH-\underset{\displaystyle CH_2CONHR}{\underset{|}{CH}}-CH_2COOH$$

III

It is known[7,10-12] that itaconic acid very readily gives pyrrolidone derivatives on reaction with amines and,

(1) A. Zilkha, E. S. Rachman, and J. Rivlin, *J. Org. Chem.*, **26**, 376 (1961).
(2) G. Piutti, *Gaz. chim. ital.*, **40**, I, 538 (1910).
(3) R. Anschütz and F. Reuter, *Ann.*, **254**, 129 (1889).
(4) N. Bland and J. F. Thorpe, *J. Chem. Soc.*, 1496 (1912).
(5) R. Anschütz and J. Drugman, *Ber.*, **30**, 2649 (1897).
(6) J. E. H. Hancock and R. P. Linstead, *J. Chem. Soc.*, 3490 (1953).
(7) P. L. Paytash, E. Sparrow, and J. C. Gathe, *J. Am. Chem. Soc.*, **72**, 1415 (1950).
(8) R. Anschütz, *Ann.*, **461**, 190 (1928).
(9) Y. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).
(10) P. L. Paytash, M. J. Thomson, and M. E. Fykes, *J. Am. Chem. Soc.*, **74**, 4549 (1952).
(11) P. L. Paytash, M. J. Thomson, and E. B. Clarke, *ibid.*, **76**, 3500 (1954).
(12) M. Lipp, F. Dallacker, and H. Rey, *Ber.*, **91**, 2242 (1958).

TABLE I

PREPARATION OF 2-METHYLENE-N-ALKYLSUCCINAMIC ACIDS

Substance,[h] N-alkyl-2-methylene-succinamic acid	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Butyl	50[a]	115	$C_9H_{15}NO_3$	58.4	58.3	8.1	7.9	7.6	7.5
Isobutyl	73	130	$C_9H_{15}NO_3$	58.4	58.3	8.1	8.1	7.6	7.4
n-Hexyl	55[a]	125	$C_{11}H_{19}NO_3$	62.0	62.4	8.9	8.8	6.6	6.7
Cyclohexyl	50[a]	153	$C_{11}H_{17}NO_3$	62.6	62.5	8.1	7.9	6.6	6.3
Benzyl	90	149	$C_{12}H_{13}NO_3$	65.8	65.7	5.9	5.9	6.4	6.3
Phenyl[b]	88	166	$C_{11}H_{11}NO_3$	64.4	63.8	5.4	5.4	6.8	6.8
4-Methoxyphenyl[c]	95	176	$C_{12}H_{13}NO_4$	61.3	62.1	5.5	5.7	6.0	6.3
2-Methoxyphenyl[d]	75	129	$C_{12}H_{13}NO_4$	61.3	60.5	5.5	5.6	6.0	5.8
4-Ethoxyphenyl[e]	95	184	$C_{13}H_{15}NO_4$	62.7	62.7	6.0	6.4	5.6	5.7
Carbethoxymethyl[f,g]	66[a]	102	$C_9H_{13}NO_5$	50.2	50.3	6.1	6.4	6.5	6.5

[a] The rather low yield was due to difficulties in crystallizing the product. [b] M.p. previously reported, 151.5°,[3] 162°.[4] [c] M.p. previously reported,[2] 167°. [d] Same m.p as previously reported.[2] [e] M.p. previously reported,[2] 166°. [f] Calcd. % of ethoxyl: 20.9. Found: 21.0. [g] Recrystallized from ethyl acetate. [h] Substances were recrystallized from water or ethanol if not indicated otherwise.

TABLE II

PREPARATION OF DL-3-CARBOXY-4-BENZYLAMINO-N-ALKYLBUTYRAMIDES

Substance,[c] 3-carboxy-4-benzylamino-N-alkyl-butyramide	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Butyl	60	184	$C_{16}H_{24}N_2O_3$	65.8	66.0	8.2	8.2	9.6	9.4
Isobutyl	55	182	$C_{16}H_{24}N_2O_3$	65.8	65.6	8.2	8.4	9.6	9.6
n-Hexyl	80	185	$C_{18}H_{28}N_2O_3$	67.5	67.9	8.8	8.7	8.8	8.9
Cyclohexyl	87	202	$C_{18}H_{26}N_2O_3$	67.9	67.7	8.2	8.1	8.8	8.5
Benzyl	75	188	$C_{19}H_{22}N_2O_3$	69.9	70.2	6.8	6.8	8.6	8.7
Phenyl	90	200	$C_{18}H_{20}N_2O_3$	69.2	70.1	6.4	6.0	9.0	8.7
4-Methoxyphenyl	10[a]	161	$C_{19}H_{22}N_2O_4$	66.7	66.6	6.4	6.2	8.2	8.1
2-Methoxyphenyl	35	145	$C_{19}H_{22}N_2O_4$	66.7	66.7	6.4	6.5	8.2	8.1
4-Ethoxyphenyl	10[a]	175	$C_{20}H_{24}N_2O_4$	67.4	68.4	6.7	6.7	7.9	7.7
Carbethoxymethyl[b]	70	194	$C_{16}H_{22}N_2O_6$	59.6	59.5	6.8	7.0	8.7	8.5

[a] Yield of substance that crystallized directly from the reaction mixture. From the filtrate it was not possible to isolate another crop. [b] Calcd. % of ethoxyl: 14.0. Found: 14.3. [c] Substances were recrystallized from alcohol or water.

only under very careful conditions, have we previously found[1] that it is possible to add benzylamine to the double bond without causing cyclization (pyrrolidone formation). It may be mentioned that 2-methylene-N-phenylsuccinamic acid did not cyclize to the corresponding pyrrolidone derivative even on heating in dioxane solution for several hours.

Several aliphatic and aromatic amides of itaconic acid were obtained in good yield (Table I) by reaction of itaconic anhydride with amines in chloroform solution; with ethyl glycinate the derivative crystallized with difficulty. 2-Methylenesuccinamic acid was obtained on reaction of gaseous ammonia with itaconic anhydride in chloroform.

Addition of one mole of benzylamine to the double bond of the 2-methylenesuccinamic acids led to the formation of 3-carboxy-4-benzylamino-N-alkylbutyramides (Table II). These gave a positive reaction with ninhydrin on paper chromatograms and were reduced, in the presence of palladium chloride on charcoal (30%), to the corresponding debenzylated amino acids (Table III), contrary to N-benzyl-4-carboxy-2-pyrrolidone; which being an N-benzylamide did not give these reactions. With 2 - methylene - N - carbethoxymethylsuccinamic acid, smooth addition of benzylamine to the double bond occurred without attack of the ester group; showing that addition to the double bond is preferable to amidation.[13]

The double bond of the 2-methylenesuccinamic acids is reactive and other amines besides benzylamine add to the double bond.

The dipeptide ester, DL-ethyl-3-carboxy-4-aminobutyryl glycinate, was similarly obtained. We tried to obtain the free dipeptide by preferential saponification of the ester group with dilute alkali,[14] but the peptide bond also was disrupted leading to the formation of the free amino acids.

It was of interest to prepare the N,N-dibenzyl derivative of 3-carboxy-4-aminobutyric acid. The N,N-dibenzyl group can act as a protecting group for the synthesis of peptides of this amino acid (it can be removed by hydrogenolysis). It has no secondary hydrogen available on the nitrogen for lactam formation and, in this respect, offers advantage over the N-benzyl group where the secondary amino group can easily cyclize to a γ-lactam, in cases where the 1-carboxyl group of the amino acid is free. 3-Carboxy-4-dibenzylaminobutyric acid was obtained by heating itaconic acid with dibenzylamine in dioxane.

Experimental

Melting points were determined in a Fisher-Johns apparatus. The ascending method of paper chromatography (80% phenol) was used.

(13) A. Zilkha and M. D. Bachi, *J. Org. Chem.*, **24**, 1096 (1959).

TABLE III

PREPARATION OF DL-3-CARBOXY-4-AMINO-N-ALKYLBUTYRAMIDES

Substance,[d] 3-carboxy-4-Amino-N-alkyl-butyramide	M.p., °C.	R_f	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Butyl[a]	220	0.92	$C_9H_{18}N_2O_3$	53.5	53.2	8.9	9.1	13.9	14.1
Isobutyl[a]	232	0.90	$C_9H_{18}N_2O_3$	53.5	52.9	8.9	9.0	13.9	13.9
n-Hexyl[a]	234	0.94	$C_{11}H_{22}N_2O_3$	57.4	56.9	9.6	9.3	12.2	12.1
Cyclohexyl[a]	231	0.94	$C_{11}H_{20}N_2O_3$	57.9	58.6	8.8	9.0	12.3	12.4
Carbethoxymethyl[b,c]	202	0.94	$C_9H_{16}N_2O_5$	46.6	46.2	6.9	7.0	12.1	12.3

[a] Obtained in approximately quantitative yield. [b] Recrystallized from water–acetone. [c] Obtained in 80% yield. [d] Substances were recrystallized from water if not indicated otherwise.

Itaconic anhydride was prepared in 92% yield by heating itaconic acid with acetyl chloride,[15] m.p. 65°.

Preparation of 2-Methylene-N-alkylsuccinamic Acids.—To an ice-cooled solution of 0.1 mole of itaconic anhydride in 60 ml. of dry chloroform, 0.1 mole of amine was added dropwise with mechanical stirring during 15 min. The reaction mixture was stirred for 2 hr. at room temperature, and the product was filtered and washed with chloroform. Another crop (5–20% yield) was obtained on evaporation of the filtrate.

With amino acid esters, the reaction mixture was stirred for another hour at 40°. The chloroform was evaporated *in vacuo;* the residue was dissolved in a small volume of ethyl acetate and left to crystallize in a refrigerator.

The products gave a positive reaction for double bonds with aqueous permanganate solution and a negative reaction with ninhydrin.

2-Methylenesuccinamic Acid.—Excess dry gaseous ammonia was passed into an ice-cooled solution of itaconic anhydride in chloroform. The ammonium salt which precipitated was filtered, dissolved in water, and heated for a few minutes to expell excess ammonia. The solution was then passed through a column packed with cation exchange resin (nuclear sulfonic acid type resin, Amberlite IR-120) and evaporated *in vacuo*. The product which crystallized was obtained in 40% yield. It was recrystallized from ethanol, m.p. 152°.

Anal. Calcd. for $C_5H_7NO_3$: C, 46.5; H, 5.4; N, 10.8. Found: C, 46.9; H, 5.5; N, 10.8.

Preparation of DL-3-Carboxy-4-benzylamino-N-alkylbutyramides.—2-Methylene-N-alkylsuccinamic acid (0.1 mole) was suspended in 70 ml. of dry dioxane and heated under reflux and mechanical stirring until it dissolved. Benzylamine (0.1 mole) was then added and the reaction mixture heated in an oil bath at 120° for 2–3 hr. The reaction product generally started to precipitate within 15–30 min. The reaction mixture was cooled and the product was filtered and washed with acetone. An additional crop was obtained on evaporation of the filtrate and recrystallization of the residue from alcohol, acetone, or water.

The pure products gave negative permanganate and ninhydrin reactions.

Preparation of DL-3-Carboxy-4-amino-N-alkylbutyramides.—DL-3-Carboxy-4-benzylamino-N-alkylbutyramide (0.02 mole) was suspended in 120 ml. of absolute ethanol and 0.4 g. of catalyst (palladium chloride on charcoal, 30%, was added). The hydrogenolysis was carried out in a Parr low pressure hydrogenation apparatus for about 16 hr. at 50–60°. The product generally precipitated on the catalyst from which it was extracted with boiling water. The free amino acids generally crystallized out on cooling.

DL-3-Carboxy-4-dibenzylaminobutyric Acid.—Itaconic acid (13 g., 0.1 mole) was dissolved in 50 ml. of dry dioxane, dibenzylamine (19.7 g., 0.1 mole) was added, and the reaction mixture was heated for 4 hr. at 120°. The dioxane was evaporated *in vacuo;* the residue was dissolved in a small volume of ethanol and left to crystallize in a refrigerator; yield, 19 g. (58%); m.p. 148°, on recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.4; N, 4.3. Found: C, 70.3; H, 6.6; N, 4.1.

N-Benzyl-4-carboxy-2-pyrrolidone.—To a solution of 2.9 g. (0.02 mole) of monomethyl ester of itaconic acid, m.p. 70°, in 20 ml. of dioxane was added 2.1 g. (0.02 mole) of benzylamine. The solution was heated in an oil bath at 110–120° for 2 hr. The solvent was removed *in vacuo* and the pyrrolidone crystallized from water, m.p. and m.m.p.,[1] 144°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.9; N, 6.4. Found: C, 66.1; H, 6.1; N, 6.6.

On using 2 moles of benzylamine, the benzylamine salt of the pyrrolidone was obtained; m.p. and m.m.p.,[1] 111°.

Benzylamide Derivative of N-Benzyl-4-carboxy-2-pyrrolidone.—To a solution of 5.2 g. (0.033 mole) of dimethyl itaconate in 20 ml. of dioxane was added 7.1 g. (0.066 mole) of benzylamine. The solution was heated in an oil bath at 110–120° for 2 hr. The solvent was removed *in vacuo*, and the product crystallized from water; yield, 3 g. (30%); m.p. 104°. It contained no methoxyl groups.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: N, 9.1. Found: N, 9.2.

(14) Y. Liwschitz and A. Zilkha, *J. Am. Chem. Soc.*, **76**, 3698 (1954); *J. Chem. Soc.*, 4394 (1954).

(15) A. Anschütz and W. Petri, *Ber.*, **13**, 1539 (1880).

Epoxide Studies. I. The Ring Opening of *cis*- and *trans*-N,N-Diethylphenylglycidamide

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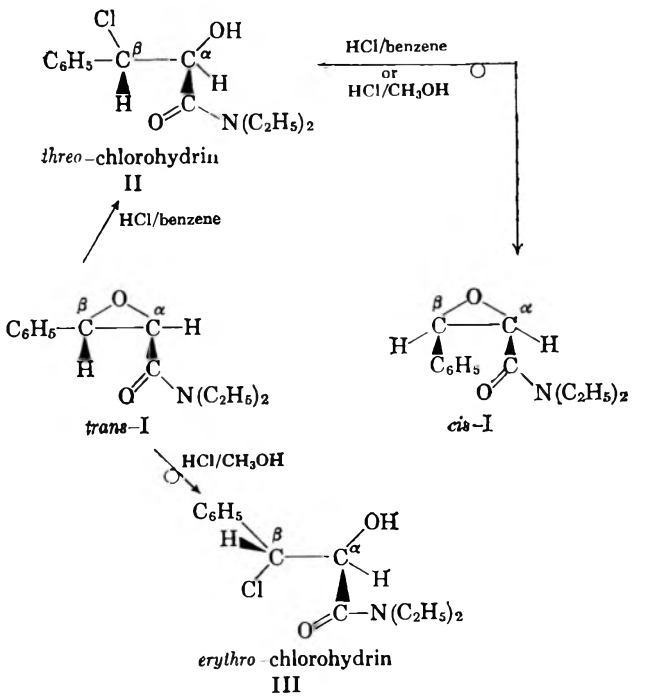
Treatment of *trans*-N,N-diethyl-3-phenylglycidamide (*trans*-I) with hydrogen chloride in benzene gave the *threo*-chlorohydrin II with retention of configuration whereas with hydrogen chloride in methanol, the *erythro*-chlorohydrin III was formed. *cis*-Glycidamide (*cis*-I) with either of these reagents afforded only II. In the presence of base, II gave mixtures of *cis*–*trans*-I and III gave only *trans*-I. The stereochemistry and mechanisms of these transformations are reported.

The opening of an epoxide ring by nucleophilic reagents has been regarded generally as a bimolecular nucleophilic displacement (S_N2) on carbon proceeding with inversion of configuration.[1] For example, the reaction of *cis*- and *trans*-stilbene oxides with hydrogen

(1) (a) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737–799 (1959); (b) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 1, pp. 27.

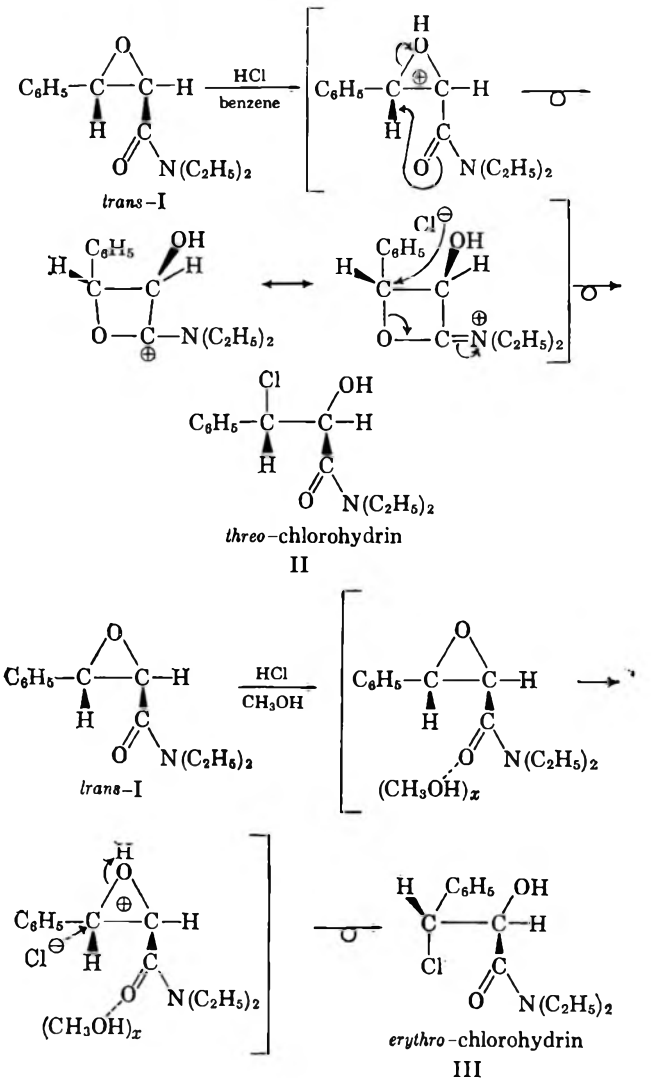
halides to form halohydrins[2] and the acid-catalyzed hydrolysis of *trans*-N,N-diethyl-3-phenylglycidamide to *erythro*-diol[3] both proceed with inversion of configuration. Certain epoxides, however, open with retention of configuration. The acid hydrolysis of *trans*-α-methylstilbene oxide to the *threo*-diol,[4] the conversion of *cis*- and *trans*-dypnone oxides to the *erythro*- and *threo*-chlorohydrins,[5] respectively, with hydrogen chloride in acetic acid or in ethanol, and the formation of the *threo*-diol from *trans*-3-phenylglycidic acid in dilute acid[6] proceed with retention of configuration.

This paper describes the stereochemistry of the ring opening of *cis*- and *trans*-N,N-diethyl-3-phenylglycidamides by hydrogen chloride in nonpolar (benzene) and polar (methanol) solvents. *trans*-N,N-Diethyl-3-phenylglycidamide (*trans*-I) with hydrogen chloride in benzene gave the *threo*-chlorohydrin II whereas with hydrogen chloride in methanol, the *erythro*-chlorohydrin III was formed. *cis*-N,N-Diethyl-3-phenylglycidamide (*cis*-I) with either of these reagents afforded only the *threo*-chlorohydrin II.[7] The *erythro* configuration for chlorohydrin III (m.p. 119–120°) was established by its conversion[3,8] to *trans*-I with base (98% yield).



The chlorohydrin II (m.p. 87–88°) obtained from *trans*-I was assigned the *threo* configuration since it was identical with the ring-opening product from *cis*-I and its infrared spectrum was identical with that of the *erythro* isomer III.

The observed retention of configuration in the formation of *threo*-chlorohydrin II from *trans*-I in benzene could be explained on the basis of participation of the neighboring amido group.[5,9] The net result would involve two inversions at the β-carbon atom or retention of configuration. In methanol, participation of the amido group is inhibited by hydrogen bonding (solvation) of the carbonyl group with the solvent. Consequently, the chlorohydrin III is formed with inversion of configuration. The clean inversion of configuration in the formation of the *threo*-chlorohydrin II from *cis*-I in benzene could be interpreted as the result of steric interaction. The effects attributable to the participation of the neighboring amido group could be eliminated or greatly reduced when phenyl and amido groups are *cis*.[10]



It is noteworthy that in the presence of base which brings about complete conversion of *erythro*-chlorohydrin III to *trans*-I, the *threo*-chlorohydrin II yields a mixture containing *cis*–*trans*-I in 60 and 40%, respectively.[11] Since *cis*-I does not undergo epimerization under the experimental conditions, the observed differences in intramolecular SN2 reactions of the diastereoisomeric chlorohydrins II and III are undoubtedly due to steric effects. With the aid of Newman projections, the formation of *trans*-I from *erythro*-chlorohydrin III would involve the more favored conformer in the transition state in which the two bulky groups (phenyl and diethylamido) are *trans* to each other. On the other hand, ring closure of *threo*-chloro-

(2) (a) D. Reulos, *Compt. rend.*, **216**, 774 (1943); (b) D. Reulos and C. Collin, *ibid.*, **218**, 795 (1944).

(3) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963).

(4) J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).

(5) H. H. Wasserman and N. E. Aubrey, *ibid.*, **78**, 1726 (1956).

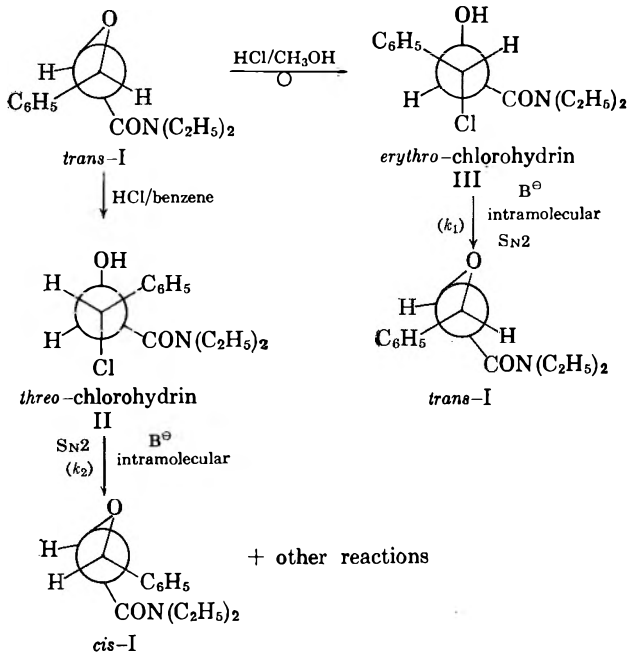
(6) J. Böeseken, *Rec. trav. chim.*, **41**, 199 (1922).

(7) The chlorohydrins are assigned the α-hydroxy-β-chloro structures; see ref. 3.

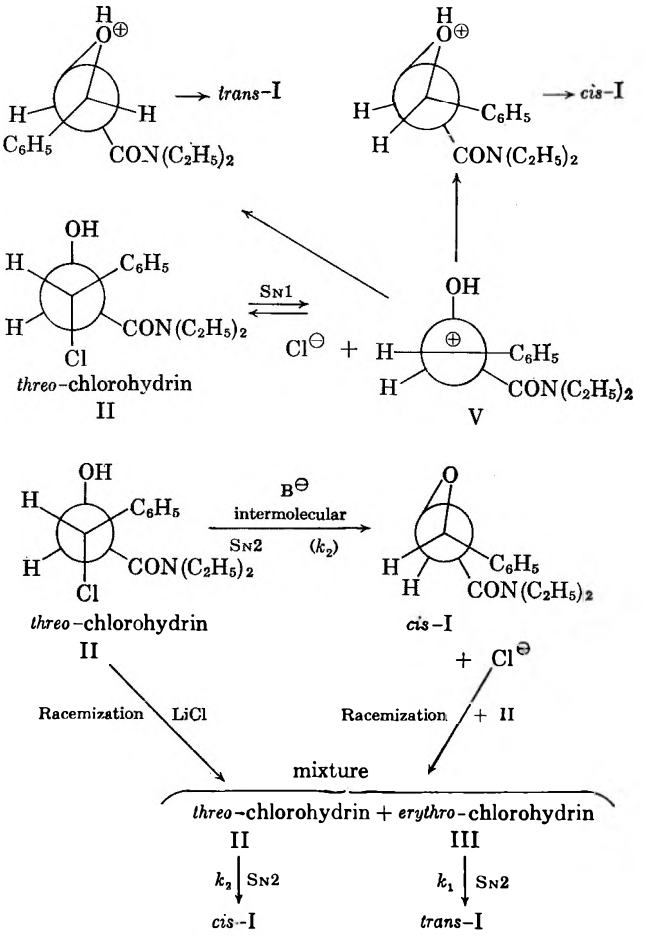
(8) (a) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939); (b) H. J. Lucas and C. W. Gould, Jr., *ibid.*, **63**, 2541 (1941); (c) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632 (1953).

(9) S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943).

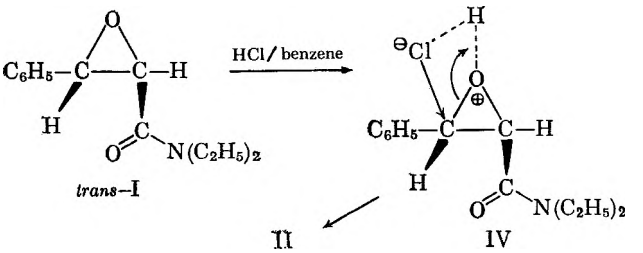
hydrin II to *cis*-I involves the eclipsing of two bulky groups. Because of this unfavorable conformation in the transition state for *threo*-chlorohydrin II, other reactions take place which lead to *trans*-I.



As a result of the relatively greater steric strain in the ring closure of the *threo*-chlorohydrin II, the rate of the intramolecular SN2 displacement of II to *cis*-I is undoubtedly slower than that of III to *trans*-I ($k_2 < k_1$). Racemization of II to form a mixture of the diastereoisomeric chlorohydrin II and III could, therefore, take place by chloride ion liberated from the ring closure. Consequently II would give a mixture of *cis*–*trans*-I. As a test of this mechanism, the reaction of the *threo*-chlorohydrin II with base was repeated, in the presence of lithium chloride. Since the rate of racemization is proportional to the concentration of the halide ion,[12] the ratio of *trans*-I–*cis*-I should be increased.[13] Indeed, from this experiment, we obtained a higher ratio of *trans*-I–*cis*-I (75:25)[14] as compared with the ratio of 40:60 in the absence of the lithium chloride.



(10) A less attractive interpretation for the observed retention of configuration for *trans*-I in benzene could be depicted as an internal displacement mechanism (SNi) [see W. A. Cowdry, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937), and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953)]. The ion pair IV would cleave so that chloride ion would attack the β-carbon atom from the same side as that undergoing C–O fission to give II. The observed inversion of configuration



in methanol could then be due to the shielding of the solvated ion pair and thereby facilitating the SN2 displacement at the β-position. A bimolecular nucleophilic displacement with inversion would, therefore, be favored. However, the previous interpretation appears untenable since the corresponding *cis*-I in both types of solvent gave only chlorohydrin II with inversion of configuration.

(11) The yields were calculated from n.m.r. spectrum. The reliability of n.m.r. spectra in quantitative determination of *cis*–*trans*-epoxy amides is demonstrated in a previous paper; see ref. 3.

(12) B. Holmberg, *J. prakt. Chem.*, (2) **88**, 553 (1913).

(13) For the racemization of alkyl halides by halide ion see E. D. Hughes, F. Jalinsberger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935).

Experimental

***threo*-N,N-Diethyl-3-chloro-2-hydroxy-3-phenylpropioamide (*threo*-Chlorohydrin II from *trans*-I).**—To a solution of 2.0 g. (0.075 mole) of dried (hydrogen sulfate) hydrogen chloride in 95 g. of benzene (dried over sodium) was added 4.24 g. (0.019 mole) of *trans*-N,N-diethyl-3-phenylglycidamide.[3] The solution was stirred at 25° for 1 hr. The solution was evaporated to dryness at room temperature under reduced pressure. The crude product was recrystallized from heptane–benzene to give 4.76 g. (97% yield) of colorless solid, m.p. 87–88°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.20; H, 7.12; N, 5.47; Cl, 13.89; mol. wt., 255. Found: C, 61.14; H, 7.02; N, 5.44; Cl, 14.23; mol. wt.,[15] 259.

***erythro*-N,N-Diethyl-3-chloro-2-hydroxy-3-phenylpropioamide (*erythro*-Chlorohydrin III from *trans*-I).**—To a stirred solution at 2° containing 31 g. of 22% by weight of hydrogen chloride (0.187 mole) in methanol was added dropwise a solution of 8.18 g. (0.0373 mole) of *trans*-N,N-diethyl-3-phenylglycidamide in 20 ml. of methanol. The solution was allowed to stand at room temperature for 1 hr. Removal of the solvent under vacuum left a light yellow viscous oil. The oil was taken up in chloroform, washed with dilute sodium bicarbonate solution, then with water, and dried over magnesium sulfate. The crude material after recrystallization from hexane gave 8.96 g. (94% yield) of colorless plates, m.p. 119–120°.

(14) A less favorable mechanism for the formation of *cis*–*trans*-I mixture from *threo*-chlorohydrin II would be as depicted. Although benzyl chloride will readily undergo SN1 reactions because of the resonance stabilization of the benzyl carbonium ion V, this reaction would be depressed by the presence of a common ion salt such as lithium chloride. Consequently, a decrease in the ratio of *trans*-I–*cis*-I should be observed. See L. C. Bateman, E. D. Hughes, and C. K. Ingold, *ibid.*, 1017 (1940).

(15) Molecular weight has determined by vapor pressure osmometer using benzene as the solvent.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.20; H, 7.12; N, 5.47; Cl, 13.89; mol. wt., 255. Found: C, 61.34; H, 7.27; N, 5.47; Cl, 14.02; mol. wt.,[15] 242.

Preparation of *threo*-Chlorohydrin II from *cis*-I.—By following the same procedure as described for *trans*-I, *cis*-I gave 84% yield of *threo*-chlorohydrin II, m.p. 87–88°, from hydrogen chloride in benzene solution and 76% yield of II, m.p. 87–88°, from hydrogen chloride in methanol. A mixture melting point of these chlorohydrins with that from *trans*-I gave no depression and their infrared spectra were identical. Their elemental analyses and molecular weights were in agreement with those calculated for the desired product.

Treatment of *erythro*-Chlorohydrin III with Base.—A solution of 0.20 g. (0.0037 mole) of sodium methoxide in 10 ml. of methanol was added over a period of 10 min. to a solution of 0.94 g. (0.0037 mole) of *erythro*-chlorohydrin III in 11 ml. of 95% ethanol at 0°. After standing at room temperature for 20 min., the solvent was evaporated *in vacuo* at room temperature. The solid was stirred with water and taken up in ether. The ether solution was washed with water and dried over magnesium sulfate. Removal of ether afforded 0.84 g. of a colorless solid which was chromatographed on alumina. Elution with chloroform–benzene gave 0.80 g. (98% yield) of *trans*-I, m.p. 87–88°. The infrared and n.m.r. spectra were identical with that of *trans*-I.[3]

Treatment of *threo*-Chlorohydrin II with Base.—The same procedure as described for *erythro*-chlorohydrin III with base was followed. There was obtained 0.74 g. (91% yield) of viscous oil which solidified slowly on standing. The n.m.r. spectrum[3] indicated this product to consist solely of 60% *cis*-I and 40% of *trans*-I.[11]

Treatment of *threo*-Chlorohydrin II with Base in the Presence of Lithium Chloride.—A solution of 0.1150 g. (0.00212 mole) of sodium methoxide in 5 ml. of 95% ethanol was added to a solution of 0.5411 g. (0.00212 mole) of *threo*-chlorohydrin II and 0.1217 g. (0.00287 mole) of lithium chloride in 20 ml. of 95% ethanol. The solution was allowed to stand at room temperature for 16 hr. After the work-up as described in the previous experiments, there remained 0.3953 g. (85% yield) of solid. The n.m.r. spectrum[3] showed this material to contain only 25% of *cis*-I and 75% of *trans*-I.[11]

Epimerization Study of *cis*-I with Base.—When the *cis*-I was treated with sodium methoxide in ethanol solution at room temperature, the n.m.r. spectrum and melting point of the product were identical with the starting *cis*-I.

Nitriles and Amidines of Optically Active Acylamino Acids and Peptides

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Nitriles of acylated amino acids and peptides were made by treatment of the corresponding amides with pyridine and phosphorus oxychloride. The optical activity was retained. The amidines were made by conversion of the nitriles to iminoethers, which then were converted to amidines. In this way acetyl-L-phenylalanine nitrile, α-acetyl-ε-tosyllysine nitrile, N-benzoyl-L-phenylalanylserine nitrile, N-benzoyl-L-phenylalanyl-O-benzylserine nitrile, N-acetyl-L-phenylalanineamidine, the corresponding N-benzylamidine, α-acetyl-ε-tosyllysineamidine, and the corresponding N-benzylamidine were prepared. The conversion of the dipeptide nitriles to their amidines was largely unsuccessful because of an intramolecular decomposition which gave N-benzoylserineamidine from N-benzoylphenylalanylserine nitrile.

To understand the fundamental mechanism of action of certain enzymes, Woolley, *et al.*,[1] proposed that polypeptides of two new and unusual amino acids should be synthesized. One of these amino acids, which may be given the trivial name of acetylphenylalanohistidine (Fig. 1), was expected, when polymerized, to exhibit the specific enzymic activity of chymotrypsin, and the other, acetyllysohistidine, was expected to have the specific activity of trypsin. The synthesis of these compounds, according to either of the two routes previously explored,[1] would require the preparation of amidines and N-benzylamidines of acetylated α-amino acids. The purpose of the present paper is to describe the synthesis of such amidines in optically active condition. Such optical activity was necessary for the purpose in hand. In addition, a third route leading toward phenylalanohistidine has been explored. It would begin with the amidine of the dipeptide, benzoylphenylalanylserine, which would then be caused to cyclize to a 4-aminoimidazole according to the method of imidazole ring formation developed by Shaw and Woolley.[2] The peptide should thus yield an imidazole which, by removal of the 4-amino group and completion of the histidine side chain, should give the desired phenylalanohistidine derivative. The formation of dipeptide amidines was, therefore, investigated.

A convenient route to amidines starts with nitriles which are converted to imino ethers (imino esters) with alcohol and hydrogen chloride. The imino ethers are then treated with ammonia or other amines to yield the amidines. Racemic α-aminonitriles and their acyl derivatives have been known for a long time since they are intermediates in the Strecker synthesis of amino acids from aldehydes and ammonium cyanide. Because optically active amidines were needed for the present work, a route which could be expected to yield optically active compounds was sought. The dehydration of optically active amides to optically active nitriles was attempted. The usual methods for this reaction (phosphorus oxychloride, phosphorus pentoxide, toluenesulfonyl chloride) failed when applied to acetylphenylalanine amide or α-acetyl-ε-tosyllysine amide. However, the method of Delaby, *et al.*,[3] in which an amide is treated briefly in the cold with pyridine and phosphorus oxychloride, succeeded both for the amino acid derivatives as well as for the peptide derivatives.

The conversion of the nitriles to amidines proved to be difficult, but was accomplished finally when adequate methods for the separation of the final products were developed and when the lability to acid of the acetyl group attached to the α-amino group was appreciated. Thus, in the formation of the imino ethers it was necessary to avoid large excesses of hydrogen chloride. Similarly, in order to escape deacetylation, strong acids

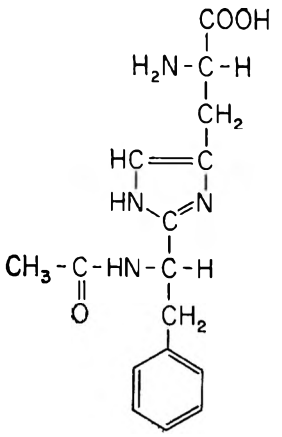
(1) D. W. Woolley, J. W. B. Hershey, and I. H. Koehelik, *Proc. Natl. Acad. Sci. U. S.*, **48**, 709 (1962).

(2) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **181**, 89 (1949).

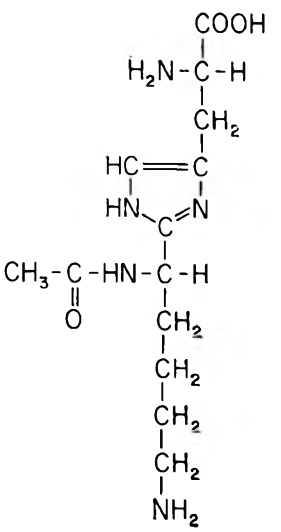
(3) R. Delaby, G. Tsatsas, and X. Lusinchi, *Bull. soc. chim. France*, 409 (1958).

were not used during the isolation of the amidines. No effort was made to isolate the imino ethers, but, instead, they were converted directly to the amidines. These were obtained pure only by means of countercurrent distribution. The conventional methods of isolation failed, probably because of the difficulty with which these amidine hydrochlorides crystallized.

A curious rearrangement prevented the realization of the dipeptide amidines. When N-benzoylphenylalanylserine nitrile was subjected to the reactions for formation of the imino ether and amidine, a mixture was obtained. The only product which was isolated in pure condition was benzoylserine amidine. The phenylalanine residue had been extruded. It was thought that protection of the hydroxyl group of the serine residue might prevent this surprising reaction, but when N-benzoylphenylalanyl-O-benzylserine nitrile was treated similarly, the same type of rearrangement occurred. A fraction was obtained which yielded on hydrolysis only O-benzylserine and no phenylalanine. It was not possible to separate the desired dipeptide amidine from either reaction in analytically pure condition, although in both cases a separate fraction was obtained by countercurrent distribution, which on hydrolysis gave the expected two amino acids. The yields, however, were too small to justify pursuit of this route to the phenylalanohistidine compounds.



Acetylphenylalanohistidine



Acetyllysohistidine

Figure 1

Experimental

Methods.—All melting points were determined in capillary tubes. All evaporations were conducted under reduced pressure below 40°. All compounds were recrystallized to constant melting point. Countercurrent distributions were carried out in the apparatus of Craig. Paper electrophoresis was done at room temperature with paper strips 54 cm. long in 0.1 *M* pyridine acetate at pH 5.0 and with 800 v. across the length of the paper. When "dry" pyridine was required, it was distilled from sodium shortly before use. Chloroform was dried over calcium chloride.

N-Acetyl-L-phenylalanine Nitrile, or L-2-Acetamido-3-phenylpropionitrile.—A solution of 20.6 g. (100 mmoles) of N-acetyl-L-phenylalanine amide in 320 ml. of dry pyridine was cooled to −5°, stirred vigorously, and treated dropwise with 10 ml. (100 mmoles) of freshly distilled phosphorus oxychloride. The addition required 10 min. The mixture was held at 0° for an additional 10 min. and was then quickly concentrated below 40° to a sirup (less than 80 g.). Benzene (700 ml.) and water (200 ml.) were added, followed by enough concentrated hydrochloric acid to give a pH of 2–3 in the aqueous phase. The aqueous phase was separated and extracted twice more with benzene. The combined extracts were washed with 20 ml. of water which contained enough sodium bicarbonate to give a final pH of 7, dried with magnesium sulfate, and freed of solvent under reduced pressure. The residue was then recrystallized from hot benzene (50 ml.) by addition of hexane (125 ml.). The yield was 9.5 g.; m.p. 106–108°, unchanged by further crystallization; $[\alpha]^{21}D$ −10.2° (*c* 2.5, ethanol).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.0; H, 6.6; N, 15.1.

Although N-acetyl-L-phenylalanine amide has been described as being prepared *via* the ester, it was found advantageous to make it from acetylphenylalanine by the mixed anhydride method with triethylamine, ethyl chloroformate, and aqueous ammonia.

N-Acetyl-L-phenylalanineamidine Hydrochloride.—Acetyl-L-phenylalanine nitrile (5.64 g., 30 mmoles) dissolved in 30 ml. of dry chloroform was cooled to 4° and treated with 5.4 ml. of absolute ethanol which was 6.6 *M* with respect to dry hydrogen chloride (20% excess hydrogen chloride). The solution was held at 4° overnight and then at 25° for 2 hr. At this point the imino ether hydrochloride had separated either as an oil or as crystals. The solvents were removed under reduced pressure at 25° and the residue was dissolved in 10 ml. of absolute ethanol at 0°. A saturated solution of dry ammonia in absolute ethanol (20 ml.) was added and the mixture was held in a tightly stoppered flask for 4 days at 25°. The solvents were removed under reduced pressure and the residue was dissolved in the system methanol–chloroform–water, 2:2:1; the top layer was adjusted to pH 3 with hydrochloric acid; and a countercurrent distribution was performed. The positions of the peaks were located by measurement of absorption at 260 mμ. Unchanged nitrile (1.11 g.) was found in tubes 0 to 30 after 160 transfers and could be recovered. The desired amidine exhibited its peak in tube 130. The contents of the tubes which contained the amidine were combined and a small amount of ammonium chloride was removed by evaporation of the solvents and extraction of the residue with absolute ethanol, in which the amidine hydrochloride was very soluble. The yield was 2.2–3.3 g.

The crystallization of this amidine hydrochloride was extremely difficult. Usually it was obtained an as amorphous solid, but it could be crystallized by rubbing with chloroform. It was rather hygroscopic. It gave no ninhydrin test when it was pure but, if any deacetylated amidine was present, it gave a positive test with ninhydrin.

The pure amidine hydrochloride showed only slight optical activity, $[\alpha]^{26}D$ +2.7° (*c* 3.0, ethanol). The low optical activity was not the result of racemization of the optical center because hydrolysis for 24 hr. with refluxing 6 *N* hydrochloric acid yielded L-phenylalanine with the correct rotation. The amidine was unusually difficult to hydrolyze completely with acid. Conditions which caused complete liberation of phenylalanine from acetylphenylalanine amide (6 *N* hydrochloric acid, 20 hr. at 100°) still left detectable amounts of the deacetylated amidine (*i.e.*, phenylalanineamidine).

If the holding of the imino ether reaction at 25° for 2 hr. was omitted, the yield was considerably reduced, but, if the conditions were made more vigorous than those given before, some deacetylation occurred at the imino ether stage. The hydrochloride was so hygroscopic that its melting point (82°) was not a useful criterion of purity. The compound did not form a water-insoluble picrate or flavianate.

Anal. Calcd. for $C_{11}H_{16}ClN_3O$: C, 54.7; H, 6.6; N, 17.4. Found: C, 54.0; H, 6.6; N, 17.4.

In order to obtain analytical values for carbon approaching the theoretical, it was necessary to burn the compound slowly. With the usual conditions for burning, values for C were always low (52 to 53% C).

Acetylphenylalanine-N-benzylamidine Hydrochloride.—The imino ether hydrochloride was prepared from acetyl-L-phenylalanine nitrile (1.88 g., 10 mmoles) exactly as described for the preceding experiment, but, instead of an alcoholic solution of ammonia, a solution of 1.25 ml. (11.5 mmoles) of benzylamine in 5 ml. of absolute ethanol was used. It was important to avoid the use of a larger excess of benzylamine. The subsequent operations were then the same as for the unbenzylated amidine except that the countercurrent system was chloroform–methanol–water, 2:1:1. In the countercurrent separation, the benzylamidine showed a peak in tube 74 of 97 transfers. The benzylamidine

hydrochloride was difficult to crystallize, but, by careful addition of ether to a dry, alcoholic solution, crystals which melted at 165° could sometimes be obtained. It did, however, form a picrate which was slightly soluble in water and well crystallized. When recrystallized the picrate melted at 135–137°. The yield of hydrochloride was 1.2 g.

Anal. Calcd. for $C_{18}H_{22}ClN_3O$: C, 65.1; H, 6.6; N, 12.7. Found: C, 64.2; H, 6.8; N, 12.6.

Calcd. for picrate, $C_{24}H_{24}N_6O_8$: C, 55.0; H, 4.6; N, 16.0. Found: C, 54.7; H, 4.7; N, 15.9.

It was found quite impossible to isolate either the benzylated or unbenzylated amidine without the use of countercurrent distribution.

Hydrolysis for 24 hr. in refluxing 6 *N* hydrochloric acid yielded phenylalanine and benzylamine as revealed by paper electrophoresis. If the hydrolysis was for less than 24 hr., a third spot always appeared on the papers. This was due to phenylalanine-benzylamidine which moved 12 cm. at pH 5.0 when histidine moved 13.8 cm. and benzylamine 17.5 cm.

Phenylalanine-N-benzylamidine Dihydrochloride.—When a solution of 1 g. of acetylphenylalanine-N-benzylamidine hydrochloride in 100 ml. of 0.05 *N* hydrochloric acid was concentrated under reduced pressure at 40° to a sirup and this residue was triturated with absolute ethanol (10 ml.), a crystalline solid remained undissolved. This was recrystallized from water by addition of ethanol to give L-phenylalanine-N-benzylamidine dihydrochloride (111 mg.), m.p. 215°.

Anal. Calcd. for $C_{16}H_{21}Cl_2N_3$: C, 58.9; H, 6.4. Found: C, 59.1; H, 6.6.

Hydrolysis of this compound, and electrophoresis of the hydrolysate gave benzylamine and phenylalanine. The intact amidine formed a purple color with ninhydrin and moved 12 cm. at pH 5.0 when histidine alongside moved 13.8 cm.

α-Acetyl-ε-tosyl-L-lysine—ε-Tosyl-L-lysine (25 g., 83 mmoles) was acetylated with 9.2 ml. (98 mmoles) of acetic anhydride by the usual Schotten–Baumann procedure for the acylation of amino acids. The product was recrystallized from water; 27.4 g., m.p. 145–146°; $[\alpha]^{23}D$ +6.1° (*c* 3.0, ethanol).

Anal. Calcd. for $C_{15}H_{22}N_2O_5S$: C, 52.6; H, 6.5; N, 8.2. Found: C, 52.5; H, 6.4; N, 8.2.

α-Acetyl-ε-tosyl-DL-lysine Amide.—A solution of α-acetyl-ε-tosyl-L-lysine (21.1 g., 61.7 mmoles) and triethylamine (17.3 ml., 123.4 mmoles) in 500 ml. of dry tetrahydrofuran was cooled to −10°. Ethyl chloroformate (6.5 ml., 67.9 mmoles) was added dropwise during 5 min. with vigorous mechanical stirring. The solution was stirred an additional 10 min. and then 13 ml. of aqueous concentrated ammonium hydroxide was added all at once. The cooling bath was removed and the contents stirred 30 min. Water (200 ml.) was added and the solution was concentrated to about 150 ml. and stored overnight at 4°. The white precipitate was filtered off and recrystallized from water; 18.7 g., m.p. 167–168°.

Anal. Calcd. for $C_{15}H_{23}N_3O_4S$: C, 52.7; H, 6.8; N, 12.3. Found: C, 52.5; H, 6.8; N, 12.2.

The lysine underwent racemization during the formation of the amide. This was demonstrated by hydrolysis (refluxing 6 *N* hydrochloric acid for 3 hr.) to ε-tosyllysine, which was isolated. It was found to have no rotation, whereas material similarly isolated from the hydrolysis of α-acetyl-ε-tosyllysine (the starting material of the synthesis) had $[\alpha]^{22}D$ +13.1° (*c* 3.0, 2 *N* hydrochloric acid) (lit.[4] $[\alpha]^{22}D$ +13.6°).

Attempts to synthesize the amide by treatment of the corresponding ester with alcoholic ammonia were unsuccessful.

α-Acetyl-ε-tosyl-DL-lysine Nitrile.—α-Acetyl-ε-tosyl-DL-lysine amide (10.0 g., 29.3 mmoles) in 200 ml. of dry pyridine was treated dropwise with phosphorus oxychloride (2.69 ml., 29.3 mmoles) at −5° and worked up as in the case of acetylphenylalanine nitrile, except that ethyl acetate instead of benzene was used for partitioning. The crude product, 7.5 g., was finally purified by countercurrent distribution (60 transfers) in the system ethanol 460–ethyl acetate 675–hexane 225–water 440. The nitrile peak was in tube 32. A small amount of amide with a peak in tube 8 was thus removed. The nitrile could not be crystallized. Infrared spectroscopy showed an absorption peak for nitriles at 2235 $cm.^{-1}$.

Anal. Calcd. for $C_{15}H_{21}N_3O_3S$: C, 55.7; H, 6.6; N, 13.0. Found: C, 55.4; H, 6.7; N, 12.5.

(4) R. Roeske, F. H. C. Stewart, R. J. Stedman, and V. du Vigneaud, *J. Am. Chem. Soc.*, **78**, 5883 (1956).

α-Acetyl-ε-tosyl-DL-lysineamidine Hydrochloride.—α-Acetyl-ε-tosyl-DL-lysine nitrile (7.0 g., 21.5 mmoles) was dissolved in 1.5 ml. of ethanol (25 mmoles) and 50 ml. of dry chloroform. Dry hydrogen chloride was bubbled through the solution for 20 min. at 0°. The flask was tightly stoppered and placed at 4° overnight. The solvents were removed under reduced pressure and the residue was dissolved in cold ethanol saturated with ammonia (150 ml.). The solution was held at room temperature in a tightly stoppered flask for 3 days. The solvents were removed under reduced pressure and the residue was dissolved in the solvent system chloroform–methanol–0.1 *N* hydrochloric acid, 3:2:2, acidified to about pH 1 and separated by countercurrent distribution (100 transfers). The amidine hydrochloride was in tubes 80 to 95, whereas unchanged nitrile was maximal in tube 15 and a small amount of amide was maximal in tube 45. The amidine fraction was brought to pH 5 with ammonium hydroxide, evaporated, and the residue freed of ammonium chloride by fractional precipitation with ether from absolute ethanol. By careful addition of more ether, crystals of the amidine hydrochloride were obtained; m.p. 171–172°.

Anal. Calcd. for $C_{15}H_{25}ClN_4O_3S$: C, 47.8; H, 6.6; N, 14.9. Found: C, 47.3; H, 6.6; N, 14.5.

The amidine picrate was prepared and crystallized from water; m.p. 172–174°.

Anal. Calcd. for $C_{21}H_{27}N_7O_{10}S$: N, 17.2. Found: N, 17.2.

α-Acetyl-ε-tosyl-DL-lysine-N-benzylamidine Acetate.—The α-acetyl-ε-tosyl-DL-lysine nitrile (6.37 g., 19.7 mmoles) was converted to the imino ether hydrochloride, as in the preceeding example, and was caused to react with benzylamine (3.26 ml., 30 mmoles) in absolute ethanol for 3 days at room temperature. Evaporation of the solvents and countercurrent distribution (96 transfers) in 1-butanol–water–acetic acid, 15:18:2, gave the benzylamidine as the acetate with a peak in tube 84. Evaporation of the solvents gave the oily salt which was purified further by precipitation from alcohol with ether, but which was never crystallized.

Anal. Calcd. for $C_{22}H_{30}N_4O_3S \cdot C_2H_4O_2$: C, 58.7; H, 7.0; N, 11.4. Found: C, 58.4; H, 6.5; N, 11.3.

N-Benzoyl-L-phenylalanylserine Ethyl Ester.—DL-Serine ethyl ester hydrochloride (1.7 g., 10 mmoles) was suspended in 20 ml. of methylene chloride and treated with 1.41 ml. of triethylamine. The suspension was stirred for 5 min., filtered, and the filtrate was treated with a solution of 2.1 g. (10 mmoles) of dicyclohexylcarbodiimide in 10 ml. of methylene chloride, and immediately thereafter with 2.7 g. of benzoyl-L-phenylalanine in 10 ml. of the same solvent. The mixture was held at room temperature overnight, treated with 0.3 ml. of acetic acid for 1 hr., and filtered. The filtrate was extracted with aqueous *N* hydrochloric acid and then with sodium bicarbonate, and the solvent was evaporated. A small amount of dicyclohexylurea was removed by solution of the dipeptide ester in ethyl acetate and filtration. The ester was then crystallized from ethyl acetate–benzene to yield 1.2 g. of the pure compound. It was not determined whether both diastereoisomers were present or whether resolution of the serine residue had occurred during the recrystallization. The use envisioned for the dipeptide did not require optically active serine. This use was the conversion to 2-(α-benzamido-β-phenylethyl)-4-amino-5-hydroxymethylimidazole in which the asymmetric center of the serine would disappear. The dipeptide ester melted at 142–143°.

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.6; H, 6.3; N, 7.4.

N-Benzoyl-L-phenylalanylserine Amide. (A) From the Ester.—N-Benzoyl-L-phenylalanylserine ethyl ester (1.2 g.) was dissolved in 50 ml. of absolute ethanol and the solution was saturated with dry ammonia. After 4 days at room temperature, the reaction mixture was concentrated under reduced pressure to dryness and the residue was recrystallized from ethyl acetate by addition of benzene. The yield was 1.0 g.; m.p. 176°, unchanged by further recrystallization.

Anal. Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.2; H, 5.9; N, 11.8. Found: C, 64.6; H, 5.9; N, 11.5.

(B) From Serine Amide.—A suspension of 3.13 g. (20 mmoles) of DL-serine amide hydrochloride in 25 ml. of methylene chloride was stirred and treated with 2.82 ml. (20 mmoles) of triethylamine. Immediately thereafter, the resulting suspension was treated with a solution of 4.2 g. (20 mmoles) of dicyclohexylcarbodiimide in 20 ml. of methylene chloride, and then with 5.4 g. (20 mmoles) of N-benzoyl-L-phenylalanine in 30 ml. of the same solvent. The mixture was stirred at room temperature

overnight and then worked up as described before for the corresponding ester. The resulting dipeptide amide was recrystallized as described in A and was found to melt at 176°.

N-Benzoyl-L-phenylalanyl-O-benzylserine Ethyl Ester.—DL-O-Benzylserine (9.75 g., 50 mmoles) was converted to its ethyl ester hydrochloride by treatment first with refluxing absolute ethanol containing 2 equivalents of dry hydrogen chloride and then by repeated treatment with refluxing absolute ethanol in the customary fashion for esterifications. The ester hydrochloride was dried thoroughly *in vacuo* and then was dissolved in methylene chloride (50 ml.). Condensation was then carried out with benzoyl-L-phenylalanine (13.5 g., 50 mmoles) by addition of triethylamine (7.05 ml., 50 mmoles) and dicyclohexylcarbodiimide (10.3 g., 50 mmoles) exactly as was described in the preceding examples. The product was recrystallized from ethyl acetate–benzene; m.p. 120–121°.

Anal. Calcd. for $C_{28}H_{30}N_2O_6$: C, 70.9; H, 6.3; N, 5.9. Found: C, 70.9; H, 6.4; N, 5.7.

N-Benzoyl-L-phenylalanyl-O-benzylserine.—The ethyl ester of the preceding section (21.6 g.) was dissolved in 200 ml. of ethanol and treated with 60 ml. of *N* sodium hydroxide for 2 hr. Acidification with hydrochloric acid, evaporation of the ethanol, and partition between benzene and water at pH 8 gave the sodium salt of the desired acid in the aqueous phase. Acidification yielded an oil which was crystallized from benzene to give 17.6 g., m.p. 162–163°.

Anal. Calcd. for $C_{26}H_{26}N_2O_5$: C, 70.0; H, 5.8; N, 6.3. Found: C, 69.8; H, 5.7; N, 6.1.

N-Benzoyl-L-phenylalanyl-O-benzylserine Amide.—In contrast to the behavior of benzoylphenylalanylserine ethyl ester, the corresponding O-benzylserine ester failed to yield the amide when treated either with alcoholic ammonia at room temperature, or with liquid ammonia in a bomb at room temperature. Unchanged ester was always recovered. Consequently, the desired amide was prepared from the dipeptide acid by way of the mixed anhydride.

Benzoyl-L-phenylalanyl-O-benzylserine (17.6 g., 40 mmoles) in 100 ml. of tetrahydrofuran and 5.61 ml. (40 mmoles) of triethylamine was stirred and cooled to −5° and treated dropwise with 4.3 ml. (45 mmoles) of ethyl chloroformate. Ten minutes after the end of the addition, concentrated aqueous ammonia (11 ml.) was added quickly in one portion. The mixture was stirred for 30 min., diluted with 250 ml. of water, and concentrated under reduced pressure to 75 ml. The solution was then extracted four times with ethyl acetate at pH 7.0 and the combined extracts were evaporated. The residue was recrystallized from benzene to yield 8.8 g., m.p. 157–160°.

Anal. Calcd. for $C_{26}H_{27}N_3O_4$: C, 70.1; H, 6.1; N, 9.4. Found: C, 70.2; H, 6.0; N, 9.3.

N-Benzoyl-L-phenylalanyl-O-acetylserine Nitrile.—Benzoyl-L-phenylalanylserine amide (2.24 g., 6.3 mmoles) was dissolved in 15 ml. of dry pyridine, and the solution was cooled to −5°, stirred, and treated first with 0.5 ml. (7.0 mmoles) of acetyl chloride and then with 0.64 ml. (6.3 mmoles) of phosphorus oxychloride. The reaction mixture was worked up in the way described for acetylphenylalanine nitrile and the product was recrystallized from benzene; 400 mg.; m.p. 169–170°.

Anal. Calcd. for $C_{21}H_{21}N_3O_4$: C, 66.5; H, 5.6; N, 11.1. Found: C, 66.1; H, 5.7; N, 10.8.

N-Benzoyl-L-phenylalanyl-O-benzylserine Nitrile.—Treatment of benzoylphenylalanyl-O-benzylserine amide with pyridine and phosphorus oxychloride in the manner described for acetylphenylalanine amide gave the desired nitrile which was crystallized from benzene. The yield was 2.8 g. from 8.3 g. of amide, m.p. 142–144°.

Anal. Calcd. for $C_{26}H_{25}N_3O_3$: N, 9.8. Found: N, 9.6.

Formation of Benzoylserineamidine in the Attempted Conversion of Benzoylphenylalanylserine Nitrile to the Dipeptide Amidine.—Benzoylphenylalanylserine nitrile (1.87 g.) was converted to the imino ether in chloroform solution (15 ml.) by addition of 0.71 ml. of 8.4 *M* ethanolic hydrogen chloride in the manner described for the corresponding reaction with acetylphenylalanine nitrile. The reaction product was then treated at room temperature for 4 days with ethanolic ammonia. The product of this reaction was then separated countercurrently through 96 transfers in the solvent system composed of chloroform–methanol–water, 2:1:1. Peaks detectable by ultraviolet absorption at 260 mμ were found in the starting tubes (unchanged nitrile), in tube 50, and in the final tubes. The peak in tube 50 probably contained the desired dipeptide amidine hydrochloride, because it yielded serine and phenylalanine when hydrolyzed, but an analytically pure compound was not obtained from it. The material in tubes 81–99 was redistributed through 68 transfers in the solvent system, chloroform–methanol–water, 2:2:1. The peak of ultraviolet absorption was in tube 53. The material recovered from this peak by evaporation of the solvents was a glassy substance (200 mg.) which proved to be benzoylserineamidine hydrochloride. When hydrolyzed and chromatographed on paper, it gave serine as the only amino acid.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_2$: C, 49.3; H, 5.7; N, 17.2. Found: C, 49.8; H, 5.7; N, 17.1.

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Ultraviolet Spectra and Polarographic Reduction Potentials of Some Cinnamic Acids[1]

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The effect of *para* and *ortho* substitutents on the ultraviolet spectra and half-wave reduction potentials of *trans*-cinnamic acid is interpreted in terms of their electronic and, in the case of *ortho*-substitution, steric effects. Only qualitative relations exist between the spectroscopic and polarographic data.

The effect of substituents on the dissociation constants[2a] of *trans*-cinnamic acid and the rates of hydrolysis of its ethyl esters[2b] have been discussed. However, no detailed study has been published concerning the effect of the substituents on the ultraviolet spectra or polarographic reduction potentials of these acids. (Such limited data as are available on the ultraviolet spectra of simple derivatives is indicated in the footnotes to Table I[3]).

A series of *trans*-cinnamic acids was prepared (see Table II) by standard methods and their ultraviolet spectra determined in 95% ethanol. These acids showed two regions of high intensity absorption (Table I), at 215–230 mμ and 270–320 mμ. The first region usually possessed two maxima of about equal intensity and the wave lengths and intensities varied little with

(1) Contribution number 130 from the Instituto de Química de la Universidad Nacional Autonoma de México.

(2) (a) *Cf.* M. Charton and H. Meislich, *J. Am. Chem. Soc.*, **80**, 5940 (1959); (b) B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958).

(3) *Cf.* A. Mangini and F. Montanari, *Boll. sci. fac. chim. ind., Bolcgna* **12**, 166 (1954).

TABLE I

ULTRAVIOLET ABSORPTION AND HALF-WAVE REDUCTION POTENTIALS OF *trans*-CINNAMIC ACIDS[a]

	λ_{max}^1	λ_{max}^2	$-E_{1/2}$ v.	i_d/cm.$^{2/3}t^{1/6}$
Cinnamic acid	216 (17,700)	273 (21,000)[b]	2.05[g]	2.01[g]
	222 (15,600)			
p-Methyl	209 (10,600)	283 (21,400)[c]	2.05	2.00
	222 (14,250)			
o-Methyl	210 (17,300)	277 (17,000)[d]	1.59	0.95
	222 (15,400)		2.07	1.08
p-Methoxy	226 (10,000)	297 (21,700)	2.04	2.10
		306 (22,150)		
m-Methoxy	216 (20,300)	275 (17,500)	2.00	1.86
		314* (5,400)		
o-Methoxy	214 (16,500)	274 (18,500)	1.65	0.88
	224 (16,800)	320 (10,800)	2.06	0.94
p-Hydroxy	223 (14,450)	286 (19,000)	1.55	0.65
			2.05	1.20
m-Hydroxy	215 (13,000)	276 (16,900)	1.60	0.85
	234 (10,750)	314* (4,600)	2.05	1.22
o-Hydroxy	224 (9,100)	273 (12,200)	2.04	0.60
		320 (7,800)	2.15	0.38
p-Nitro	211 (12,100)	282 (18,900)[e]	0.85	0.35
			1.01	0.75
			2.25	0.92
m-Nitro	216 (10,200)	260 (27,600)[e]	0.87	0.35
			1.15	0.87
			2.15	1.03
o-Nitro	211 (20,450)	302 (18,400)[e]	0.85	0.26
			1.00	0.80
			2.15	0.97
p-Chloro	216 (16,700)	275 (22,800)	1.90	2.36
	228* (9,900)			
o-Chloro	210 (18,400)	265 (14,900)[d]	1.89	0.41
		317* (1,700)	1.95	1.90
p-Bromo	220 (11,900)	281 (21,300)[f]	2.01	2.31
o-Bromo	212 (17,500)	273 (15,350)[d]	1.85	1.04
	220 (17,250)		2.07	0.70
p-Iodo	224 (18,600)	287 (28,000)	1.67	1.60

[a] Wave lengths in mμ, molar extinction coefficients in parentheses. Asterisk denotes inflection. Spectroscopic data refer to 95% ethanol solution. $E_{1/2}$ values against the saturated calomel electrode for 0.175 *M* tetra-*n*-butylammonium iodide in 75% dioxane–water, i_d/cm.$^{2/3}t^{1/6}$ in microamp./mmole mg.$^{2/3}$ sec.$^{1/2}$. [b] Ref. 18 gives 220 (17,500), 267 (20,200). [c] R. Andrisano and A. Tundo, *Atti Accad. naz. Lincei*, [8] **13**, 158 (1952), give 219 (15,500), 279 (21,500) for water. [d] Ref. 3 gives *o*-methyl, 208 (18,200), 270 (16,600); *o*-chloro, 212 (19,500), 222* (17,000), 265.5 (17,000), 306* (2,400); and *o*-bromo, 212 (20,500), 218* (19,000), 266 (17,000), 300* (3,200), 318* (1800). [e] P. Grammaticakis, *Compt. rend.*, **239**, 883 (1954), gives *p*, 295 (20,000); *m*, 263 (25,000), 305* (1,250); and *o*, 248 (12,500), 290* (40,000) (data taken from curves). [f] R. Andrisano and G. Pappalardo, *Gazz. chim. ital.*, **85**, 391 (1955), give 212 (14,800), 218 (16,000), 272 (24,500). [g] Ref. 5 gives $E_{1/2}$ 2.04 v., i_d/cm.$^{2/3}$ $t^{1/6}$ 1.99 microamp./mmole mg.$^{2/3}$ sec.$^{1/6}$.

TABLE II

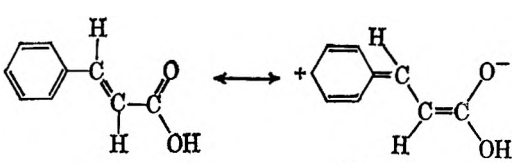
MELTING POINTS OF *trans*-CINNAMIC ACIDS

	M.p., °C.	Lit. m.p., °C.
Cinnamic acid	132	133[a]
o-Methyl	174	174–175[b]
p-Methyl	198	198–199[b]
o-Methoxy	183	185–186[c]
m-Methoxy	120	117[d]
p-Methoxy	170	172[e]
o-Hydroxy	205	207–208[f]
m-Hydroxy	191	191[g]
p-Hydroxy	210	207[e]
o-Nitro	240	240[h]
m-Nitro	200–201	198[e]
p-Nitro	284–285	290–291[i]
o-Chloro	213	212[j]
p-Chloro	245	240–242[j]
o-Bromo	215–216	212–212.5[k]
p-Bromo	257–260	246–248[k]
p-Iodo	254	255[l]

[a] W. M. Radionow, *J. Am. Chem. Soc.*, **51**, 847 (1929). [b] R. Stoermer, F. Grimm, and E. Laage *Ber.*, **50**, 980 (1917). [c] R. Stoermer and C. Friemel. *ibid.*, **44**, 1843 (1911). [d] H. Bauer and P. Vogel, *J. prakt. Chem.*, **88**, 329 (1863). [e] P. N. Kurien, K. C. Pandya, and V. R. Surange, *J. Indian Chem. Soc.*, **11**, 823 (1934). [f] R. Fittig and A. Ebert, *Ann.*, **226**, 351 (1884). [g] W. Borsche and F. Streitberger, *Ber.* **37**, 4128 (1907). [h] R. Stoermer, *ibid.*, **45**, 3100 (1912). [i] G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa, and A. Vecchi, *J. Am. Chem. Soc.*, **76**, 4391 (1954). [j] K. C. Pandya and R. B. Pandya, *Proc. Indian Acad. Sci.*, **14A**, 112 (1941). [k] M. M. Katon, E. P. Matkuina, and F. S. Florinsky, *Zh. Obschch. Khim.*, **21**, 1843 (1951). [l] R. L. Datta and N. R. Chatterjee, *J. Am. Chem. Soc.*, **41**, 295 (1919).

substitution. These maxima can be attributed to electronic transitions in the benzene ring iteslf (E-bands) and substitution has little effect on such bands.[4a] However, the second band or group of maxima varied in both wave length and intensity on substitution and must arise from electronic transitions throughout the whole conjugate system (a K-band).[4a]

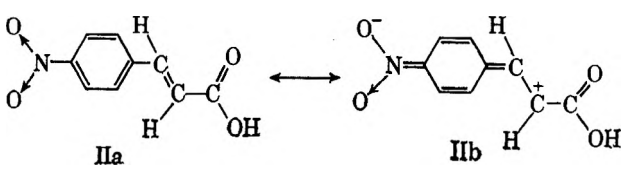
The order of bathochromic displacements for *para* substitution was: Cl (+ 2) < Br (+8) ~ NO_2 (+ 9) ~ Me (+10) < OH (+13) ~ I (+14) < MeO (+24). The changes in intensity were generally small, the *para* iodo compound alone showing a small decrease and the *p*-methoxy derivative giving a double maximum. The effect of a *para* substituent can only be electronic, and a substituent with a positive resonance effect, which by slightly lowering the energy level of the ground state and further lowering the energy level of the excited state, will reduce the energy of the transition to the excited state (Ia to Ib), resulting in an increase in the wave length of maximal absorption. Hydroxy and methoxy group (+R effects, although −I effects) produced the expected large shifts. The order of displacements of the halogen atoms (Cl < Br < I) is



Ia Ib

that of the increasing resonance effect of these atoms.[4a,b] The origin of the wave-length displacement for a *p*-nitro (−R and −I effects) is probably different in that the transition involved is IIa to IIb.

The resonance effect cannot operate throughout the whole molecule for a *meta* substituent and the displace-

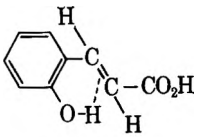


IIa IIb

(4)(a) O. H. Wheeler and P. H. Gore, *J. Org. Chem.*, **26**, 3298 (1961); (b) P. H. Gore and O. H. Wheeler, *ibid.*, **26**, 3295 (1961). A referee has pointed out that cinnamic acid is largely dissociated in water [K_a = 4.4 × 10^{-5}, H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, Inc., New York, N. Y., 1955, Chap. 14] and a 2 × 10^{-5} *M* solution (for optical density 0.4) is 72% as its anion in pure water. However, the K_a in 95% ethanol will be much smaller [K_a in 40% acetone–water is 2.6 × 10^{-6}; R. D. Kleene, F. H. Westheimer, and G. W. Wheland, *J. Am. Chem. Soc.*, **63**, 791 (1941)] and a value of 10^{-7} would correspond to 8% anion in 2 × 10^{-5} *M* solution. Traces of base would result in anion formation, and may account for the numerous maxima previously observed[3] for *o*-chloro- and *o*-bromocinnamic acid (see footnote, Table I). In the present work the spectra of cinnamic acid in 95% ethanol containing a drop of 2 *N* hydrochloric acid was the same as in 95% ethanol, and it was assumed that all the substituted cinnamic acids were in the form of their undissociated acids.

ments observed were accordingly very small (MeO +2, OH +3, and NO_2 −13 mμ, with decrease in intensity in the last two cases and splitting of maximum in the first). Hypsochromic shift in the *m*-nitro compound may result from an increase in the energy level of the excited state of the benzene ring thereby increasing the energy of transition, although a transition between the nitro group and the aromatic ring may also be involved. Similar electronic effects for *meta* and *para* substitution have been observed in other conjugate aromatic systems.[4]

Substituents in an *ortho* position can exert both an electronic and steric effect. The wave-length displacements were much smaller than for the *para* isomers (OH and Br 0, MeO +1, Me + 4, and Cl −8) and the intensities much less due to the opposing steric effect of the bulky *ortho* substituents. The hydroxy, methoxy, and nitro compounds showed a second maximum at much higher wave length. In the case of the hydroxy compound, this is most probably due to hydrogen bonding,[4] which could take place between the hydroxy group and the π-electrons of the side-chain double bond (III).



III

The hydrocinnamic acids (Table III) showed the same E-band (at 220 mμ), but only low absorption at *ca.* 280 mμ.

TABLE III

PHYSICAL CONSTANTS OF HYDROCINNAMIC ACIDS

	λ_{max}[a]	λ_{max}[a]	M.p., °C.	Lit. m.p., °C.
o-Methoxy	224 (11,050)	277 (3,100)		
		284* (2,750)	82	81[b]
m-Methoxy	218 (7,500)	273 (2,100)	50–52	56[c]
		279 (1,900)		
p-Methoxy	218 (7,250)	272 (2,000)	103	104–105[d]
		278 (1,900)		

[a] Wave lengths in mμ, molar extinction coefficients in parentheses. Asterisk denotes inflection. [b] R. Pschorr and H. Einbech, *Ber.*, **38**, 2074 (1905). [c] K. H. Slotta and H. Heller, *ibid.*, **63**, 3029 (1930). [d] G. Barger and G. S. Walpole, *J. Chem. Soc.*, **95**, 1723 (1909).

The polarographic half-wave reduction potentials of the cinnamic acids were measured (see Table I) in 75% dioxane–water using 0.175 *M* tetra-*n*-butylammonium iodide as supporting electrolyte and 0.05 *M* tetra-*n*-butylammonium hydroxide to eliminate the carboxylic acid hydrogen wave.[5] It has been shown[6] that the reduction involves two electrons, giving β-phenylpropionic acid. All the cinnamic acids gave a reduction wave of $E_{1/2}$ about 2.0 v. and this must arise from reduction of the side-chain double bond. However, many of the substituted cinnamic acids, particularly those with nitro and iodo groups, showed other reduction waves at lower potentials, and these must arise from reduction of these substituents. *Para* Methyl, methoxy, and hydroxy substituents produced no change in the $E_{1/2}$ values, with little difference in the diffusion current constants (i_d/cm.$^{2/3}$ $t^{1/6}$) in the first two cases.

A *para* chloro substituent caused reduction at a less negative potential (−0.15 v.). The reduction potentials are a measure of the energy barrier to addition of electronic charge to the double bond,[7] and the −I effect of chlorine, by decreasing the electronic charge on the double bond (Ib), will facilitate reduction. A further decrease in reduction potential might be expected for the *p*-bromo compound, but the bromo group will be reduced at about −2.0 v. and the single reduction wave must involve this process, together with that of the side-chain double bond. The first wave of the *p*-iodo acid corresponds to reduction of the iodo group[7] and the second to that of the cinnamic acid formed by this reduction. Aromatic nitro compounds often reduce in alkaline medium in two stages affording the hydroxylamine and aniline.[8] The nitrocinnamic acids all showed three reduction waves, corresponding to the reduction of the nitro group and the subsequent reduction of the hydroxylamino or amino acids so formed. The increase in potential of the last wave of *p*-nitro cinnamic acid as compared with cinnamic acid itself (+0.20 v.) is consistent with the +I effect of an amino group, transmitted to the side-chain double bond and this effect is less in the case of the *meta* and *ortho* compounds.

o-Methyl-, methoxy-, chloro-, and bromocinnamic acids all gave two reduction waves, in contrast to their *para* isomers, and the $E_{1/2}$ value of the second wave was always more negative. The diffusion current constants were, moreover, much smaller, suggesting that reduction occurs by a different process. The origin of these effects must be in steric inhibition of resonance with the side chain by the bulky *ortho* substituents reducing the effectiveness of the resonance effect and making reduction more difficult.[8] The $E_{1/2}$ of the third wave of *o*-nitrocinnamic acid was similarly less negative (NH_2 has −I effect), although the $E_{1/2}$ values of the first two waves, attributed to reduction of the nitro group itself, remained unchanged. The *o*-hydroxy acid was apparently anomolous (two waves, the second at a very negative potential), but such effects have been noted in hydrogen-bonded compounds.[9]

No quantitative relation existed between the wave lengths or frequencies of the maxima of the conjugate absorption band and the half-wave reduction potentials, although certain parallelisms have been noted in simpler carbonyl compounds.[10] No relation is to be expected since the processes taking place are quite different. The wave length of maximal absorption depends on the energy difference between the ground and excited states and polar effects by increasing the energy levels of the ground and excited states to different extents cause displacements to longer wave length. However, the polarographic reduction potentials depend on the electron density at the reduced site, and substituents only produce differences (which may be in

(5) S. Wawzonek, S. C. Wang, and P. Lyons, *J. Org. Chem.*, **15**, 543 (1950).

(6) G. Semerano and A. Chisini, *Gazz. chim. ital.*, **66**, 510 (1936).

(7) E. Gergely and T. Iredale, *J. Chem. Soc.*, 3226 (1953).

(8) (a) M. Fields, C. Valle, and M. Kane, *J. Am. Chem. Soc.*, **71**, 421 (1949); (b) S. F. Dennis, A. S. Powell, and M. J. Astle, *ibid.*, **71**, 1484 (1949); (c) C. Frevost, P. Souchay, and C. Malen, *Bull. soc. chim. France*, 78 (1953).

(9) L. Holleck, H. Marsen, and H. J. Exner, *Z. Naturforsch.*, **9b**, 90 (1954).

(10) (a) A. Winkel and G. Proske, *Ber.*, **69**, 1917 (1936); (b) N. J. Leonard, H. A. Laitinen, and E. H. Mattus, *J. Am. Chem. Soc.*, **75**, 3300 (1953).

either direction) when their effects are transmitted to the reducible group.

Experimental

Cinnamic Acids.—*trans*-Cinnamic acid was an Eastman Kodak White Label sample. *p*-Nitrocinnamic acid was prepared by nitration of cinnamic acid and purified *via* its ethyl ester.[11] *p*-Iodocinnamic acid was prepared by iodination of cinnamic acid with iodine in acetic acid in the presence of nitric acid[12] and purified by chromatography on magnesol and elution with acetone.

o- and *p*-methyl-, chloro-, and bromo-, *m*-nitro-, and *p*-hydroxy- and *p*-methoxy-, as well as *p*-iodocinnamic acids were prepared by reaction of the appropriate benzaldehyde with malonic acid in 95% ethanol in the presence of piperidine.[13]

o- and *m*-hydroxy- and methoxy- and *o*-nitrocinnamic acids were prepared similarly in pyridine solution with piperidine.[14]

o- and *m*-methoxybenzaldehydes were prepared by methylation of the hydroxybenzaldehyde with methyl sulfate and sodium hydroxide.[15] *o*- and *p*-chloro- and bromobenzaldehydes were prepared by Etard oxidation of the corresponding toluenes,[16] and *o*-nitrobenzaldehyde was prepared by oxidation of *o*-nitrotoluene in acetic acid and anhydride followed by hydrolysis of the so-formed diacetate.[17]

The hydrocinnamic acids were prepared by hydrogenation of the cinnamic acids in acetic acid using a platinum oxide catalyst.

The corrected melting points were determined on a Köfler block and are recorded in Tables II and III.

Absorption Spectra.—The absorption spectra were determined in purified 95% ethanol using a Beckman DK2 spectrometer and 1-cm. cells at concentrations such that the optical density was 0.8–0.2 (see Table I).

Polarographic Reductions.—The polarographic determinations were made in 0.175 *M* tetra-*n*-butylammonium iodide–0.05 *M* tetra-*n*-butylammonium hydroxide in 75% dioxane–water (D^{25}_{25} 1.037, dioxane purified by refluxing with sodium) using standard conditions[5] and employing a Sargent Model XI polarograph. The half-wave reduction potentials were measured against a saturated calomel electrode (Table I). The capillary had a drop time of 3.6 sec. and mercury flow of 1.51 mg./sec.

Acknowledgment.—This study was supported in part by grants from the Rockefeller Foundation, New York, New York.

(11) W. Davey and J. R. Guilt, *J. Chem. Soc.*, 204 (1950).
(12) R. L. Datta and N. R. Chatterjee, *J. Am. Chem. Soc.*, **41**, 295 (1919).
(13) A. I. Vogel, "Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1948, p. 682.
(14) J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syn.*, **31**, 35 (1951).
(15) *Cf.* D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 37.
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Action of Trifluoroacetic Anhydride on N-Substituted Amic Acids[1,2]

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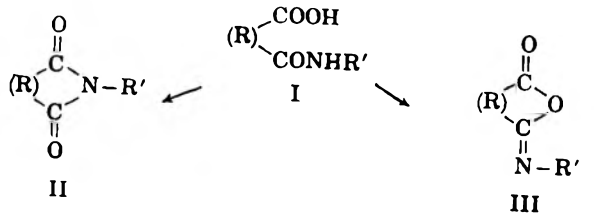
The action of trifluoroacetic anhydride on various N-aryl amic acids was investigated to determine whether dehydration by this reagent always forms isoimides. N-Substituted maleamic and phthalamic acids were dehydrated to isoimides, and the method appears to be general for the synthesis of N-aryl maleisoimides and phthalisoimides. Several products were obtained from saturated amic acids depending on the number of carbon atoms separating the amide and carboxyl groups, but in no instance was a saturated isoimide formed. Although the α- and β-N-methylcamphoramic acids were not dehydrated by trifluoroacetic anhydride, the reported dehydrations by acetyl chloride and phosphorus oxychloride to isoimides, the only report of saturated isoimides, have been confirmed. Maleisoimdes have been found to react with piperidine by ring opening to form diamides rather than by addition to the carbon–carbon double bond, and this reaction has been used to confirm the structure of N-1-naphthylmaleisoimide. The intensities of the two characteristic infrared bands of cyclic isoimides have been shown to be useful in distinguishing isoimides from imides.

The dehydration of N-substituted amic acids (I) is known to produce imides (II) or isoimides (III), depending on the conditions employed for the dehydration and on the nature of the amic acid. The literature



on imides is quite extensive, and a variety of reagents has been used in the synthesis of imides. The reagents most commonly employed to effect dehydration of amic acids to imides are phosphorus pentoxide,[3,4] acetic anhydride plus fused sodium acetate,[5] acetyl chloride,[6,7] and thionyl chloride.[3,8,9] Simple heating of the amic acid or direct fusion of a mixture of the anhydride and amine without isolation of the intermediate amic acid are also very common methods. Various other dehydrating agents have been employed less extensively: in the preparation of phthaloylamino acids, for example, numerous techniques have been developed for dehydration under relatively mild conditions to avoid decomposition or racemization of the amino acid.[9-11]

The reagents reported to dehydrate amic acids to isoimides are fewer in number and, judging from the literature, several would appear not to be general in their action. These reagents, in chronological order of

(1) Support of this work by a Frederick Gardner Cottrell grant from the Research Corporation is gratefully acknowledged.
(2) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 111-Q of the abstracts.
(3) A. E. Kretov and N. E. Kul'chitskaya, *Zh. Obshch. Knim.*, **26**, 208 (1956); *Chem. Abstr.*, **50**, 13771 (1956).
(4) A. Piutti, *Atti reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] **18**, II, 312 (1909); *Chem. Abstr.*, **4**, 2451 (1910).
(5) N. E. Searle, U.S. Patent 2,444,536 (1948); *Chem. Abstr.*, **42**, 7340 (1948).
(6) E. Giustiniani, *Gazz. chim. ital.*, **28**, II, 189 (1898).
(7) K. von Auwers, *Ann.*, **309**, 316 (1899).
(8) W. H. Warren and R. A. Briggs, *Ber.*, **64**, 26 (1931).
(9) F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).
(10) A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).
(11) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *ibid.*, **19**, 1786 (1954).

their reported use in the synthesis of isoimides, are acetyl chloride,[12] phosphorus oxychloride,[12] trifluoroacetic anhydride,[13] trifluoroacetic anhydride plus triethylamine,[14] other halogenated aliphatic acid anhydrides plus triethylamine,[14] ethyl chloroformate plus triethylamine,[14] N,N′-dicyclohexylcarbodiimide,[14] and acetic anhydride plus sodium acetate.[15,16] Of these, however, acetyl chloride, phosphorus oxychloride, ethyl chloroformate plus triethylamine, and acetic anhydride plus sodium acetate also have been used to form imides; trifluoroacetic anhydride alone has been reported to effect the dehydration of only one amic acid to the corresponding isoimide, and acetic anhydride plus sodium acetate formed isoimides only in certain instances.[15]

Isoimides constitute a potentially interesting class of compounds on which there has been relatively little investigation until recently and which appear to be reaction intermediates in several reactions. There is evidence to suggest that one path in the formation of imides by dehydration of amic acids may proceed *via* isoimides.[14,17] Isoimides have been postulated as intermediates in the reaction of phthaloyl chloride with ammonia to form *o*-cyanobenzoic acid,[18] in the synthesis of β-cyano esters from N-unsubstituted amic acids,[19] in the reaction of amides with carboxylic anhydrides to form nitriles or imides,[20] in the interconversion of nitriles and carboxylic acids,[21] in the reaction of ketimines with carboxylic acids,[22] in the reaction of imidoyl chlorides with salts of carboxylic acids,[23] and in the reaction of the N-methyl-5-phenylisoxazolium cation with acetate.[24] In some of these reactions the product isolated was the imide, assumed to have resulted by isomerization of an initially formed isoimide.

We have been interested in a general study of the chemistry of isoimides and, as part of this investigation, we have studied the formation of isoimides by the dehydration of amic acids. The results obtained employing trifluoroacetic anhydride as the dehydrating agent are reported in this paper.

N-Substituted Maleamic and Phthalamic Acids.—With only one exception, trifluoroacetic anhydride in dioxane was found to dehydrate N-arylmaleamic and N-arylphthalamic acids to N-arylmaleisoimides[25] and N-arylphthalisoimides, respectively, with yields generally in the range of 70–90% (*cf.* Tables I and II). The method was essentially that employed by Tsou, *et al.*,[13] in which a slight excess of trifluoroacetic anhydride is added to a solution or suspension of the amic acid in dioxane at room temperature. Since the hydrolysis of maleisoimides is catalyzed by acids,[15] Cotter, *et al.*,[14] have proposed that, in those instances in which trifluoroacetic anhydride has been found to be ineffective, the initially formed isoimide is subsequently hydrolyzed, presumably during the work-up procedure, catalyzed by the trifluoroacetic acid formed as a by-product. In an experiment designed to test this hypothesis, they treated maleanilic acid with trifluoroacetic anhydride in the presence of sufficient triethylamine to neutralize the liberated trifluoroacetic acid and obtained the maleisoimide in 50% yield.

This interpretation would appear to account satisfactorily for the failure to obtain maleisoimides from the action of trifluoroacetic anhydride on certain maleamic acids. Nevertheless, in our studies dehydration in the absence of any added base was successful in all but one instance. The yield of N-phenylmaleisoimide was low (30%); this isoimide appeared to be somewhat less stable toward hydrolysis than the other aryl maleisoimides. Since N-(*m*-nitrophenyl)maleisoimide was found to hydrolyze very rapidly during the isolation, the reaction mixture was poured into 10% sodium bicarbonate solution to prevent hydrolysis. With N-(1-naphthyl)maleamic acid, however, even this modified procedure was not completely successful. An impure oil having infrared absorption bands at 5.60 and 5.99 μ (sh 5.85 μ) characteristic of cyclic isoimides was obtained, but it could not be purified, and the elemental analysis was unsatisfactory owing to hydrolysis to the amic acid. That the product was the isoimide was shown by the reaction with piperidine (following). The N-(1-naphthyl)maleamic acid was studied because Tsou, *et al.*, had tried trifluoroacetic anhydride on only three amic acids: N-(1-naphthyl)-, N-(5-hydroxy-1-naphthyl)-, and N-(4-hydroxy-1-naphthyl)maleamic acids. Only the last compound was dehydrated to an isoimide, the other two being recovered unchanged. Consequently, a better test of Cotter's hypothesis that the failure to obtain these isoimides results from hydrolysis of the initially formed isoimides is with one of these naphthyl derivatives. The method of Cotter, *et al.*, using triethylamine in the dehydration mixture was also employed; an oil identical in infrared spectrum to that obtained using trifluoroacetic anhydride alone was obtained, and elemental analysis was again unsatisfactory and indicated hydrolysis. These observations thus support the interpretation of Cotter, *et al.*, and demonstrate that hydrolysis of isoimides can be prevented by pouring the reaction mixture into bicarbonate as well as by having triethylamine present during the dehydration.

Saturated Amic Acids.—Since trifluoroacetic anhydride was found to be a general reagent for the formation of isoimides in the maleic and phthalic series the action of this anhydride on a homologous series of saturated amic acids was investigated since the only examples of a saturated isoimide ring are the camphorisoimides.[12] The results of treatment of N-arylmalonamic, -succinamic, -glutaramic, and -adipamic acids

(12) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **12**, 12 (1893); **13**, 93 (1894); **14**, 252 (1895).

(13) K. C. Tsou, R. J. Barrnett, and A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).

(14) (a) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961); (b) C. K. Sauers and R. J. Cotter, U.S. Patent 2,995,577 (1961); *Chem. Abstr.*, **56**, 5839 (1962).

(15) A. E. Kretov, N. E. Kul'chitskaya, and A. E. Mal'nev, *J. Gen. Chem. USSR*, **31**, 2415 (1961).

(16) T. L. Fletcher and H. L. Pan, *J. Org. Chem.*, **26**, 2037 (1961).

(17) W. R. Roderick, paper presented at the Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., 1961.

(18) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **11**, 84 (1892).

(19) C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).

(20) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

(21) W. G. Toland and L. L. Ferstandig, *J. Org. Chem.*, **23**, 1350 (1958).

(22) C. L. Stevens and M. E. Munk, *J. Am. Chem. Soc.*, **80**, 4065 (1959).

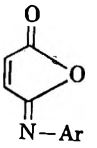
(23) F. Cramer and K. Baer, *Ber.*, **93**, 1231 (1960).

(24) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(25) We prefer to use the term *isoimide* as a class name, adding the usual prefix to indicate the parent acid: *e.g.*, *maleisoimide* rather than *isomaleimide*. This usage is consistent with the nomenclature of imides and amic acids and should lessen any confusion with acids the names of which include the prefix *iso* (*e.g.*, tetrahydroisophthalic acid). Isoimides are named systematically as imino derivatives of lactones: *e.g.*, 3-(4-methoxyphenylimino)phthalide and 5-(4-methoxyphenylimino)-2(5H)-furanone.

TABLE I

N-ARYLMALEISOIMIDES

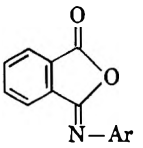


Ar	Molecular formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-Dimethylaminophenyl	$C_{12}H_{12}N_2O_2$	137	85	66.65	66.43	5.59	5.72	12.96	12.78
p-Methoxyphenyl	$C_{11}H_9NO_3$	71	75	65.02	63.81	4.46	4.26	6.89	6.85
p-Ethoxyphenyl	$C_{12}H_{11}NO_3$	71–74	75	66.35	66.08	5.10	5.11	6.45	6.40
p-Tolyl	$C_{11}H_9NO_2$	74	70	70.58	70.77	4.85	5.00	7.48	7.45
Phenyl	$C_{10}H_7NO_2$	60	30	69.36	...[a]	4.07	...	8.09	...
o-Nitrophenyl	$C_{10}H_6N_2O_4$	107–109	82	55.05	55.04	2.77	2.79	12.84	13.08
m-Nitrophenyl	$C_{10}H_6N_2O_4$	57	50	55.05	55.05	2.77	2.79	12.84	12.92
p-Nitrophenyl	$C_{10}H_6N_2O_4$	112–113	80	55.05	54.05	2.77	2.74	12.84	12.69

[a] Could not be purified; reported as a pure compound (ref. 14).

TABLE II

N-ARYLPHTHALISOIMIDES



Ar	Molecular formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-Dimethylaminophenyl	$C_{16}H_{14}N_2O_2$	170	55	72.16	71.93	5.30	5.59	10.52	10.58
o-Methoxyphenyl	$C_{15}H_{11}NO_3$	121	70	71.14	71.26	4.37	4.29	5.53	5.62
p-Methoxyphenyl	$C_{15}H_{11}NO_3$	134	80	71.14	70.60	4.37	4.34	5.53	5.66
o-Tolyl	$C_{15}H_{11}NO_2$	136	80	75.93	75.84	4.67	4.49	5.90	5.98
p-Tolyl	$C_{15}H_{11}NO_2$	123	80	75.93	76.07	4.67	4.41	5.90	5.85
Phenyl	$C_{14}H_9NO_2$	112[a]	80	75.32	...	4.06	...	6.28	...
o-Chlorophenyl	$C_{14}H_8NO_2Cl$	139	90	65.25	65.35	3.13	3.30	5.44	5.44
p-Chlorophenyl	$C_{14}H_8NO_2Cl$	160	89	65.25	65.64	3.13	3.23	5.44	5.39
o-Nitrophenyl	$C_{14}H_8N_2O_4$	162	60	62.69	62.22	3.01	3.16	10.45	10.41
m-Nitrophenyl	$C_{14}H_8N_2O_4$	138	50	62.69	62.56	3.01	3.03	10.45	10.60
p-Nitrophenyl	$C_{14}H_8N_2O_4$	172	91	62.69	62.49	3.01	3.07	10.45	10.58

[a] Lit. m.p. 116°.

TABLE III

PRODUCTS OBTAINED FROM THE ACTION OF TRIFLUOROACETIC ANHYDRIDE ON SATURATED AMIC ACIDS

Amic acid	Product	M.p., °C.	Yield, %
N-Phenylmalonamic	Polymer ?	*ca.* 210	77
N-Phenylsuccinamic	Succinic dianilide	231	60
N-(*p*-Methoxyphenyl)-succinamic	Amic acid recovered		
N-Phenylglutaramic	N-Phenylglutaramic anhydride	145	40
N-(*p*-Methoxyphenyl)-glutaramic	N-(*p*-Methoxyphenyl)-glutaramic anhydride	159	50
N-Phenyladipamic	N-Phenyladipamic anhydride	138	50

with trifluoroacetic anhydride under the same conditions employed for N-substituted maleamic and phthalamic acids are summarized in Table III.

Treatment of N-phenylmalonamic acid (malonanilic acid) with trifluoroacetic anhydride gave products which, although they could not be identified, appeared not to be the imide and which are definitely not the isoimide. The products were amorphous, without definite melting point, gave unsatisfactory analyses, and could not be purified. The action of thionyl chloride on malonanilic acid has been reported to give the imide,[8] but the properties of the product and difficulty in reproducing the reaction suggest a polymer.[26] Phosphorus pentachloride has been reported to convert malonanilic acid to a trichloroquinoline.[27] We have treated malonanilic acid with these two reagents and found the products to be very similar but not identical with those obtained with trifluoroacetic anhydride. The action of dehydrating agents on malonamic acids is, therefore, complex; all that can be concluded from the previous data is that imide or isoimide are not formed.

N-(*p*-Methoxyphenyl)succinamic acid was recovered unchanged from treatment with trifluoroacetic anhydride, but N-phenylsuccinamic acid was converted to succinic dianilide. N-Phenylglutaramic, N-(*p*-methoxyphenyl)glutaramic, and N-phenyladipamic acids were each dehydrated to the respective amic acid anhydrides (IV). The amic acid anhydride structures

$$2\mathrm{Ar{-}NH{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}(CH_2)_nCOOH} + (CF_3CO)_2O \longrightarrow [\mathrm{Ar{-}NH{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}(CH_2)_n\overset{\overset{\mathrm{O}}{\|}}{C}]_2O} + 2CF_3COOH$$

IV, n = 3 or 4

(26) F. E. King, *J. Chem. Soc.*, 1318 (1949).

(27) L. Rügheimer, *Ber.*, **17**, 736 (1884).

were assigned on the basis of the following chemical, spectral, and analytical evidence. The product from N-phenylglutaramic acid had three infrared absorption bands in the carbonyl region at 5.55, 5.75, and 6.05 μ, as well as an N–H band at 2.98 μ, indicating that the product was neither the isoimide or imide. The bands indicated an amide and an anhydride and were similar to those reported by Thamm for N-aryl succinamic anhydrides obtained from the action of ketenes on amic acids.[28] Elemental analyses supported the structural assignments, although the per cent carbon was low, probably the result of hydrolysis to amic acid. Chemical evidence included hydrolysis of these products to the amic acids and ammonolysis with aniline to give both the amic acids and dianilides.

With this failure to dehydrate saturated amic acids to isoimides using trifluoroacetic anhydride, the action of another fluorinated anhydride, heptafluorobutyric anhydride, was studied with the succinamic acids, since these seemed most likely to give rise to stable isoimides. Because of the different and unexpected products obtained, it was necessary to investigate the action of this reagent on each of the other types of amic acid as well. The products from the other amic acids, however, were in each case the same as those obtained using trifluoroacetic anhydride. With the two succinamic acids studied, an acyl exchange occurred rather than dehydration. Thus N-phenylsuccinamic acid gave heptafluorobutyranilide, and N-(*p*-methoxyphenyl)-succinamic acid gave *p*-methoxyheptafluorobutyranilide. Succinic anhydride, which should be the other product, was not isolated.

Because of the failure to obtain saturated isoimides from the amic acids discussed earlier as well as from several other saturated amic acids, the reported preparations of the N-methylcamphorisoimides[12] were repeated. Treatment of N-methyl-α-camphoramic acid with acetyl chloride gave N-methyl-α-camphorisoimide. Treatment of N-methyl-β-camphoramic acid with phosphorus oxychloride gave, in very low yield, a mixture of N-methylcamphorimide and a compound having carbonyl absorptions similar to those of the α-isoimide and hence, presumably, the β-isoimide. The assignment of the isoimide structure to the product from the α-amic acid was confirmed by determination of the intensities of the infrared absorption bands (following). The existence of these saturated isoimides is thus confirmed. Trifluoroacetic anhydride, however, did not dehydrate these amic acids.

Interpretation of Results.—From the data presented it can be seen that the action of trifluoroacetic anhydride on amic acids may result in the formation of isoimides or of several other products. The formation of the various products observed can be rationalized by the scheme shown in Fig. 1. It is likely that the N-aryl amic acid first reacts with trifluoroacetic anhydride to form a mixed anhydride.[29] The mixed anhydride can undergo intramolecular cyclization in three ways: elimination of trifluoroacetic acid with formation of imide; elimination of trifluoroacetic acid with formation of isoimide; or elimination of trifluoroacetanilide with formation of anhydride. Reaction of the mixed

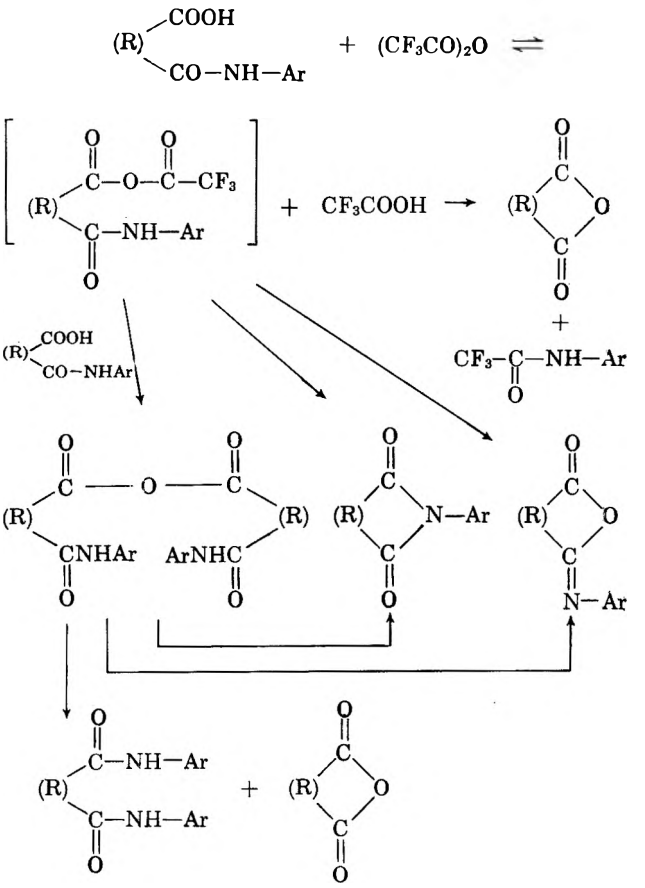


Fig. 1.—Possible scheme for the reaction of trifluoroacetic anhydride with amic acids.

anhydride with a second molecule of amic acid forms the amic acid anhydride, which may be isolated or may undergo a cyclization analogous to the third cyclization path of the mixed anhydride, forming diamide and anhydride. It is conceivable that the amic acid anhydride could also cyclize by elimination of amic acid and formation of imide or isoimide, analogous to the first two paths for the mixed anhydride.

Each of these intermediates and products has been obtained from amic acids in other studies. Evidence for the mixed anhydride as an intermediate in the dehydration of amic acids has been obtained,[17] and acetic succinamic anhydrides have been obtained by other means.[28] N-Aryl succinamic acid anhydrides have been reported as products from the action of diphenylketene on the amic acids.[28] Diamides have been obtained from the treatment of N-phenylmaleamic acid with phosphorus oxychloride,[30] from treatment of N-(*p*-ethoxyphenyl)maleamic acid with acetyl chloride,[31] and from thermal decomposition of *d,l-erythro*-dimethylsuccinanilic acetic anhydride.[28] Acyl exchange has been observed in the treatment of maleamic acids with excess acetic anhydride[3] and in the action of trifluoroacetic anhydride on peptides.[32]

In this scheme all amic acids are assumed to form the mixed anhydrides; subsequent behavior of the anhydride depends mainly on the structure of the amic acid. Formation of a cyclic product occurs when the most

(28) R. C. Thamm, Ph.D. dissertation, University of Illinois, 1957; *cf. Dissertation Abstr.*, **17**, 2428 (1957).

(29) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).

(30) W. A. van Dorp and P. M. Haarst, *Rec. trav. chim.*, **19**, 311 (1900).

(31) W. R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957).

(32) F. Weygand, R. Geiger, and U. Glöckler, *Ber.*, **89**, 1543 (1956); *cf.* K. D. Kopple and E. Bachli, *J. Org. Chem.*, **24**, 2053 (1959).

stable ring, a five-membered ring,[33] is formed; thus N-substituted phthalamic and maleamic acids form isoimides. The failure of succinamic acids to cyclize is not surprising even though they would form a five-membered ring, since studies have shown that succinic derivatives cyclize much less readily than maleic derivatives owing to the existence of the former in conformations unfavorable toward cyclization.[34] As predicted, succinic derivatives which are forced into favorable conformations by several α-substituents cyclize more readily.[34] Bicyclic amic acids in which the carboxyl (and, therefore, the mixed anhydride) and amide groups are held in a conformation favorable for cyclization should be dehydrated readily to cyclic products, and this is the case. For example, the reaction of 3,6-*endo*-methylene-1,2,3,6-tetrahydrophthalic anhydride with aniline gives the imide directly; when the amic acid is isolated, it cannot be recrystallized and spontaneously dehydrates to the imide.[35] The same factor is undoubtedly responsible for the relative ease of formation of camphorisoimides, since the carboxyl and amide groups of the camphoramic acids are fixed in a conformation suitable for cyclization. In the reaction of succinamic acids with heptafluorobutyric anhydride, cyclization of the mixed anhydride presumably does occur, except by path three to form succinic anhydride. With the mixed anhydrides from longer chain amic acids, cyclization does not occur readily and the mixed anhydride reacts with a second molecule of the amic acid to form the amic acid anhydride.

The action of fluorinated acid anhydrides on amic acids depends, therefore, on the number of carbon atoms separating the carboxyl and amide groups and, at least in the case of succinamic acids, on the nature of the N-substitutent and the nature of the dehydrating agent. The action of dehydrating agents on amic acids probably is also dependent upon other experimental conditions, such as temperature and reaction time, so that different products may be obtained from the action of a given dehydrating agent on an amic acid under different conditions.[17]

Reaction of Isoimides with Piperidine.—In the course of other attempts to prepare saturated isoimides by means other than the dehydration of amic acids, the reaction of piperidine with isoimides was studied. Various reagents, including piperidine, have been shown to add to N-arylmaleimides to form N-arylsuccinimides.[36] The addition of such reagents to the carbon–carbon double bond of a maleisoimide would give a succinisoimide. Of course, the isoimide ring should be more susceptible to nucleophilic attack than the imide ring, and ring cleavage may occur more readily than addition. Maleisoimides have been reported to react with amines by ring cleavage.[37]

Treatment of N-(*p*-methoxyphenyl)maleisoimide with piperidine at room temperature did not result in addition to give the desired α-piperidylsuccinisoimide. Instead, ring cleavage occurred forming the diamide, the piperidide of N-(*p*-methoxyphenyl)maleamic acid. Hence it would appear that saturated isoimides cannot be obtained by this route. This difference of maleimides and maleisoimides in their reactivity toward amines can be utilized to differentiate between these two structures. Thus with N-(1-naphthyl)maleisoimide, a viscous red oil which could not be purified or analyzed owing to its ready hydrolysis, the reaction with piperidine gave a product for which infrared, chemical, and analytical data indicated the piperidide of N-(1-naphthyl)maleamic acid. The formation of this product under such mild conditions is consistent with the isoimide structure, but not with the imide structure.

Infrared Absorption of Isoimides.—The N-arylmaleisoimides and N-arylphthalisoimides prepared in this study all exhibited two strong bands in the carbonyl region at 5.54 (C=O) and 5.88 μ (C=N), in agreement with the findings of other workers. While it is generally possible to distinguish isoimides from the corresponding imides, which also absorb in this region, in a few instances the bands of isoimides are at wave lengths quite different from the average wave lengths and hence they are not sufficient for assignment of the isoimide structure. It appeared that the intensities of the absorptions might be more characteristic of the structure than the wave lengths and would at least provide additional data to support the isoimide structure for certain members.

Accordingly, quantitative spectra of isoimides and the corresponding imides in dioxane solution were determined for the region 5.0–6.0 μ, and apparent molecular extinction coefficients were calculated from the maximum absorptions.[38] The results, presented in Table IV, show that it is possible to distinguish isoimides from imides by extinction coefficients. The value of the apparent molecular extinction coefficient of the longest wave-length band is of the order of 200–400 for isoimides and 850–1300 for imides. The difference is so large that it enables assignment of structure to an imide or isoimide in the absence of the infrared spectrum of the isomer.

The method was employed to confirm the assignment of the isoimide structure when it was in doubt. The mull spectrum of N-(*p*-dimethylaminophenyl)phthalisoimide, for example, has bands at 5.57 (sh), 5.67, and 5.95 μ and is more characteristic of an imide than of an isoimide. In dioxane solution there are only two bands, at 5.57 μ (ε 369) and 5.93 μ (ε 167); and, although the bands are at somewhat longer wave lengths than observed for other phthalisoimides, the intensities definitely are in the range for isoimides. N-Methyl-α-camphorisoimide was studied since there are no modern physical data to support this sole example of a saturated isoimide. This isoimide has absorptions at 5.63 μ (ε 314) and 5.85 μ (ε 471), whereas the imide has absorptions at 5.78 μ (ε 241) and 5.96 μ (ε 1233). Here the wave lengths differ quite widely from those of imides and isoimides in the maleic and phthalic series, but the apparent extinction coefficients fall in the appropriate

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

(34) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960).

(35) (a) M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *ibid.*, **66**, 404 (1944); (b) S. W. Fox and F. N. Minard, *ibid.*, **74**, 2085 (1952).

(36) A. Mustafa, W. Asker, S. Khattab, and S. M. A. D. Zayed, *J. Org. Chem.*, **26**, 787 (1961), and previous papers cited therein.

(37) C. K. Sauers and R. J. Cotter, U. S. Patents 3,023,240 (1962) [*Chem. Abstr.*, **57**, 11100 (1962)] and 3,041,376 (1962).

(38) While apparent molecular extinction coefficients lack the precision of integrated absorption intensities [D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952); L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1958, p. 271; T. L. Brown, *Chem. Rev.*, **58**, 581 (1958)], the use of the former in studies where the differences between different structures are large is justified by their ease of calculation.

TABLE IV

APPARENT MOLECULAR EXTINCTION COEFFICIENTS OF N-ARYL IMIDES AND ISOIMIDES IN DIOXANE

N-Substituent	Imides						Isoimides			
	λ, μ	ε	λ	ε	λ	ε	λ	ε	λ	ε
Phthalic series										
o-CH_3O—C_6H_4—	5.60	94	5.73	313	5.80	1240	5.53	372	5.85	415
p-CH_3O—C_6H_4—	5.60	70	5.72	189	5.80	1110	5.55	366	5.91	273
o-CH_3—C_6H_4—	5.60	99	5.73	226	5.81	1136	5.54	359	5.87	371
p-CH_3—C_6H_4—	5.61	83	5.74	255	5.82	1288	5.54	358	5.90	256
o-Cl—C_6H_4—	5.59	114	5.73	391	5.78	1146	5.52	329	5.85	509
p-Cl—C_6H_4—	5.60	89	5.74	395	5.81	974	5.54	340	5.88	383
Average	5.60	92	5.73	294	5.80	1149	5.54	354	5.88	367
Maleic series										
p-CH_3O—C_6H_4—					5.80	844	5.56	334	5.95	134
p-CH_3—C_6H_4—					5.79	847	5.55	358	5.93	205
p-$(CH_3)_2N$—C_6H_4—					5.82	852	5.58	617	5.65	304
Average					5.80	848	5.56	436	5.84	214

range and clearly support the assigned structures. For structural assignments where isomers absorb in the same region such that the range of wave lengths for one isomer overlaps the range for the other, as with imides and isoimides, the ranges of intensities of the absorptions may be widely separated and hence of considerable value in differentiating between isomeric structures.

Experimental[39]

Amic Acids.—The amic acids were prepared by reaction of equimolar amounts of the anhydride and of the amine at room temperature in solvents such as chloroform, ether, or benzene. The crude amic acids were dissolved in dilute sodium bicarbonate, and the resultant solutions were filtered and acidified. The amic acids were obtained in yields of 70–80% after purification and generally were used without recrystallization. Three new amic acids were prepared.

(a) **N-(*p*-Dimethylaminophenyl)phthalamic acid** was obtained in 53% yield as off-white crystals (from ethanol), m.p. 261–264°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.61; H, 5.63; N, 9.86. Found: C, 67.60; H, 5.50; N, 10.02.

(b) **N-(*p*-Dimethylaminophenyl)maleamic acid** was obtained in 83% yield as scarlet crystals (from ethanol), m.p. 212°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.55; H, 5.98; N, 11.96. Found: C, 61.18; H, 5.20; N, 11.68.

(c) **N-(*p*-Methoxyphenyl)succinamic acid**[40] was obtained in 81% yield as slightly pink crystals (from water), m.p. 162.5–163.0°.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.23; H, 5.94; N, 6.22.

Imides.—To support the assignment of isoimide structures, many of the corresponding imides were prepared for comparisons of infrared spectra. The imides were obtained by dehydration of the amic acid using acetic anhydride and sodium acetate or by direct heating. One new imide was prepared. **N-(*p*-Dimethylaminophenyl)maleimide** was obtained in 80% yield as reddish brown crystals (from acetone), m.p. 153–154°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.55; N, 12.96. Found: C, 66.42; H, 5.65; N, 12.75.

Maleisoimides and Phthalisoimides.—Since the procedures employed in the dehydration of N-substituted maleamic and phthalamic acids to isoimides were essentially the same for all compounds, only a general procedure is described.

To a solution or suspension of the amic acid in dry dioxane, 1.0 to 1.5 equivalents of trifluoroacetic anhydride was added. The solutions were allowed to stand at room temperature for 5 to 60 min.; the suspensions were stirred for 1 hr. at room temperature, during which time the amic acid went into solution. The solutions were poured into water to precipitate the products, which were collected within a few minutes and washed successively with water, 10% sodium bicarbonate, and water; in a few instances the precipitates were allowed to stand in 10% sodium bicarbonate for 30 min. The isoimides were crystallized from aqueous acetone. The yields, physical properties, and analyses of the isoimides prepared by this procedure are listed in Tables I and II.

The action of heptafluorobutyric anhydride was studied on N-(*p*-methoxyphenyl)maleamic acid and on N-(*p*-methoxyphenyl)-phthalamic acid using the same general procedure. The products, N-(*p*-methoxyphenyl)maleisoimide, obtained in 45% yield, m.p. 71°, and N-(*p*-methoxyphenyl)phthalisoimide, obtained in 65% yield, m.p. 134°, were identical in infrared spectra and melting points with the products obtained using trifluoroacetic anhydride.

Amic Acid Anhydrides.—Treatment of N-phenylglutaramic, N-(*p*-methoxyphenyl)glutaramic, and N-phenyladipamic acids with trifluoroacetic anhydride or heptafluorobutyric anhydride according to the general procedure described earlier yielded the amic acid anhydrides in each instance. To confirm the amic acid anhydride structures, each of the products was hydrolyzed to the original amic acid and treated with aniline or *p*-anisidine to form a mixture of the amic acid and the dianilide. Thus, from N-phenylglutaramic anhydride and aniline, both N-phenylglutaramic acid and glutaric dianilide were isolated and identified by melting points and infrared spectra.

(a) **N-Phenylglutaramic anhydride** was obtained in 40% yield as colorless crystals (from ethanol), m.p. 145°.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.52; H, 6.09; N, 6.88.

(b) **N-(*p*-Methoxyphenyl)glutaramic anhydride** was obtained in 50% yield as colorless crystals, m.p. 159°.

Anal. Calcd. for $C_{24}H_{28}N_2O_7$: C, 63.16; H, 6.14; N, 6.14. Found: C, 62.56; H, 5.95; N, 6.17.

(c) **N-Phenyladipamic anhydride** was obtained in 50% yield as colorless crystals, m.p. 135–138°.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.60; N, 6.60. Found: C, 66.58; H, 6.51; N, 6.60.

Products from Succinamic Acids.—N-(*p*-Methoxyphenyl)-succinamic acid was recovered unchanged from treatment with trifluoroacetic anhydride. Similar treatment of N-phenylsuccinamic acid gave succinic dianilide in 60% yield as colorless needles (from acetone), m.p. 230.5–231.0° (lit.[41] m.p. 230°).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.41; H, 6.03; N, 10.25.

Treatment of N-phenylsuccinamic acid with heptafluorobutyric anhydride gave heptafluorobutyranilide in 30% yield, m.p. 85° (lit.[42] m.p. 92°). Product was identical in infrared spectrum and melting point with the amide prepared directly from aniline and heptafluorobutyric anhydride, and a mixture showed no depression in melting point. From N-(*p*-methoxyphenyl)succinamic acid and heptafluorobutyric anhydride, *p*-methoxy-

(39) Melting points are not corrected. Analyses were performed by the Weiler and Strauss Microanalytical Laboratories, Oxford, England, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(40) This acid has been reported [A. Piutti, *Ber.*, **29**, 84 (1896)] without analytical data and as having a m.p. of 156–157°, with the imide, m.p. 162–163°. A sample of imide prepared from the amic acid had a m.p. of 161.0–162.5°.

(41) G. F. Morrell, *J. Chem. Soc.*, **105**, 1733 (1914).

(42) R. N. Hazeldine, *ibid.*, 2789 (1950).

heptafluorobutyranilide was obtained in 21% yield as colorless needles, m.p. 97°. The product was identical with the amide prepared directly from *p*-anisidine.

Products from N-Phenylmalonamic Acid.—Treatment of this amic acid with trifluoroacetic or heptafluorobutyric anhydrides gave a colorless powder in yields of 60–80% (calculated as dehydration product). The melting point varied with different preparations (210°, 186–190° dec.) and appeared to depend on the rate of heating. The infrared spectrum contained bands at 3.08 and 5.95 μ.

Anal. Calcd. for $C_9H_7NO_2$ (malonanilic acid–water): C, 67.07; H, 4.38; N, 8.69. Found: C, 66.63; H, 5.05; N, 8.49, corresponding to $C_9H_8NO_2$.

The products from thionyl chloride were colored, amorphous solids with broad melting range (205–220°). Attempted hydrolysis of an orange sample by boiling potassium hydroxide solution formed on acidification hydrogen sulfide and a green precipitate. The green solid had an infrared spectrum differing from that of the orange solid only in the sharpness of the carbonyl absorption.

Camphorisoimides and Related Compounds.—The literature procedures[12] were followed for the preparation of compounds in this series. N-Methyl-α-camphoramic acid was obtained by direct reaction of aqueous methylamine with suspended *d*-camphoric anhydride. N-Methylcamphorimide was prepared by heating the α-amic acid above its melting point and then distilling the melt. The yellow distillate did not solidify at room temperature; the infrared spectrum had four carbonyl bands indicating a mixture of camphoric anhydride (5.52, 5.65 μ) and the imide (5.80, 6.00 μ). One crystallization from ether and two from absolute ethanol gave needles, m.p. 38–40° (lit. m.p. 40–42°) having only the imide carbonyl bands. N-Methyl-β-camphoramic acid was obtained by dehydration of the α-amic acid to imide followed by hydrolysis of the crude imide. The β-amic acid was separated from α-amic acid, formed in smaller amounts, by fractional crystallization. The α-amic acid was dehydrated by heating with acetyl chloride followed by treatment with aqueous hydroxide to liberate the free isoimide; N-methyl-α-camphorisoimide was isolated in 16% yield as fine crystals (from ether), m.p. 132–133°. The β-amic acid was dehydrated with phosphorus oxychloride to a neutral product (9% yield) having four carbonyl bands indicating imide (5.80, 5.98 μ) and, presumably, β-isoimide (5.63, 5.90 μ).

Reaction of Isoimides with Piperidine.—The method was that of Mustafa, *et al.*[36] The products were not the amine adducts of the maleisoimides as shown by insolubility in acid and by infrared bands at 3.02 (N—H) and 5.97 μ (amide C=O) and absence of the original isoimide bands.

(a) **Piperidide of N-(*p*-methoxyphenyl)maleamic acid** was obtained in 40% yield as pale yellow crystals (from aqueous ethanol), m.p. 151.0–154.0°. The low yield resulted from the presence of amic acid in the sample of maleisoimide, indicated by the precipitation of the piperidinium salt of N-(*p*-methoxyphenyl)maleamic acid in 42% yield immediately on addition of piperidine; this salt was identified by comparison of its infrared spectrum with that of the salt prepared directly from the amic acid and piperidine.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.54; H, 6.96; N, 9.85.

(b) **Piperidide of N-(1-naphthyl)maleamic acid** was obtained in 86% yield as off-white needles (from acetone), m.p. 150.0–152.0°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54, N, 9.09. Found: C, 73.82; H, 6.38; N, 9.10.

(c) **α-Piperidyl-N-(1-naphthyl)succinimide.**—The piperidine adduct of N-(1-naphthyl)maleimide was prepared for comparison with the diamide obtained from the isoimide. The product was obtained in 74% yield as a semisolid which after several recrystallizations from 95% ethanol gave colorless crystals, m.p. 147–151°. The infrared spectrum had no N–H absorption and a sharp imide band at 5.86 μ, with shoulders at 5.66 and 5.95 μ.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.04; H, 6.77; N, 9.08.

Infrared Measurements.—Qualitative spectra were obtained in Nujol mulls on a Perkin-Elmer Infracord spectrophotometer, Model 137-B. Quantitative spectra were determined in purified dioxane[43] in an 0.0252-mm. cell on a Perkin-Elmer Model 21 spectrophotometer.

(43) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed.; D. C. Heath and Co., Boston, Mass., 1955, p. 285.

Novel Method for the Preparation of Acid Anhydrides by Means of Diphenylmercury and Tertiary Phosphine

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The reactions of phenylmercuric acetate with triethyl phosphite or tri-*n*-butylphosphine have been investigated. Further, a novel method for the preparation of acid anhydrides by means of diphenylmercury and tri-*n*-butylphosphine has been studied. The reactions of two moles of carboxylic acids with one mole each of diphenylmercury and of tri-*n*-butylphosphine gave the corresponding carboxylic acid anhydrides in high yields along with mercury, benzene, and tri-*n*-butylphosphine oxide. Similarly, pyrophosphates or sulfonic acid anhydride were prepared in high yields by the reactions of two moles of phosphoric monoesters or sulfonic acid with one mole each of diphenylmercury and of tri-*n*-butylphosphine. The mechanisms of these reactions are discussed.

It recently has been found that mercuric and mercurous carboxylates are reduced by means of triethyl phosphite or tertiary phosphines to give mercury and the corresponding acid anhydrides in good yields.[1]

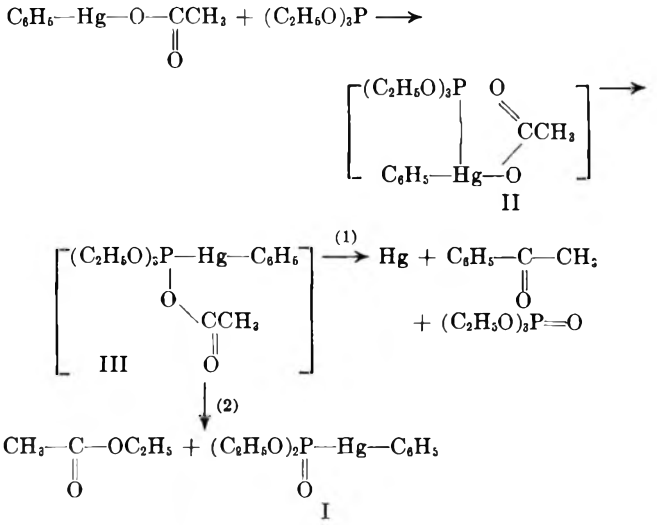
$$(RCO_2)_2Hg + R_3'P \longrightarrow Hg + (RCO)_2O + R_3'P{=}O$$
$$R' = C_2H_5O-,\ n\text{-}C_4H_9-,\ C_6H_5-$$

In the present study, the reduction of phenylmercuric acetate by the trivalent phosphorus compounds was tested first under the assumption that it would, when reduced, yield mercury and acetophenone. Indeed, an exothermic reaction was observed when the acetate reacted with triethyl phosphite at room temperature. Mercury and acetophenone, however, were not obtained, but ethyl acetate was produced in 74% yield along with a large amount of white crystals (I), m.p. 163–166°. These white crystals (I) were shown to be diethyl phenylmercuric phosphonate by means of elemental analysis and infrared absorption spectrum which has characteristic bands attributable to phosphorus–oxygen double bonds (1260 cm.$^{-1}$) and to a monosubstituted benzene ring (1600, 730 and 695 cm.$^{-1}$).

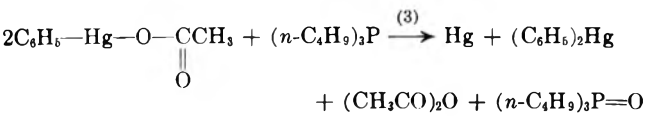
This reaction may proceed through an initial formation of adduct II of phenylmercuric acetate, and triethyl phosphite; this, subsequently, is transformed into III, conceivably by way of an internal nucleophilic displacement. The intermediate (III) thus formed has

(1) T. Mukaiyama, H. Nambu, and I. Kuwajima, *J. Org. Chem.*, **28**, 917 (1963).

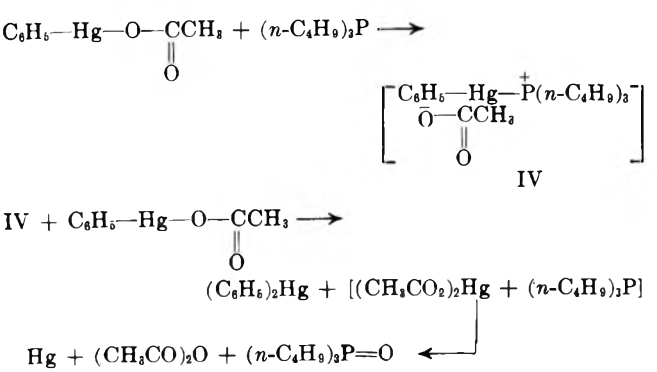
two possible pathways of decomposition, namely (1) the formation of mercury, acetophenone, and triethyl phosphate by electrophilic attack of an acetyl group on a phenyl group and (2) the formation of ethyl acetate and diethyl phenylmercuric phosphonate (I) by nucleophilic attack of an acetoxyl group on an ethyl group—*i.e.*, the Arbuzov type reaction—as described in the following scheme. Since the decomposition of III occurs more readily by the Arbuzov type reaction, the two products mentioned previously may result.



On the other hand, when tri-*n*-butylphosphine, which can not undergo the Arbuzov type reaction, was used in place of triethyl phosphite, mercury (46%), diphenylmercury (34%), acetic anhydride (31%), and tri-*n*-butylphosphine oxide (45%) were obtained, and tri-*n*-butylphosphine (40%) was recovered. However, when the reaction of two moles of phenylmercuric acetate with one mole of tri-*n*-butylphosphine was examined, mercury (80%), diphenylmercury (62%), acetic anhydride (49%), and tri-*n*-butylphosphine oxide (86%) were obtained, and tri-*n*-butylphosphine was not recovered.



This reaction can be explained in the following manner. The phosphonium acetate (IV), which may be derived from the reaction of phenylmercuric acetate with tri-*n*-butylphosphine, reacts further with phenylmercuric acetate to yield diphenylmercury and mercuric acetate. Of the two compounds thus formed, the latter is successively reduced by tri-*n*-butylphosphine to give mercury and acetic anhydride.



When equimolar amounts of phenylmercuric acetate and tri-*n*-butylphosphine reacted in the presence of an equimolar amount of carboxylic acid, the anhydride of the carboxylic acid was obtained along with mercury, acetic anhydride, tri-*n*-butylphosphine oxide, and benzene (see Table I).

TABLE I

THE REACTIONS OF PHENYLMERCURIC ACETATE AND TRI-*n*-BUTYLPHOSPHINE IN THE PRESENCE OF CARBOXYLIC ACIDS

	Yield, %				
Carboxylic acid	$(RCO)_2O$	$(CH_3CO)_2O$	Hg	$(n\text{-}C_4H_9)_3P{=}O$	C_6H_6
Acetic acid	82	82	92	90	86
Propionic acid	62	62	89	92	100

[a] These reactions were carried out at 60–65° for two hours without solvent.

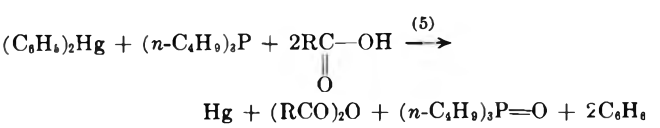
The reaction was extended further to the preparation of various carboxylic acid anhydrides in yields ranging from 74 to 87% by treating two moles of carboxylic acids with one mole each of diphenylmercury and of tri-*n*-butylphosphine (see Table II).

TABLE II

THE REACTIONS OF DIPHENYLMERCURY AND TRI-*n*-BUTYLPHOSPHINE IN THE PRESENCE OF CARBOXYLIC ACIDS

				Yield, %		
Carboxylic acid	Reaction solvent	Time, hr.	Temp., °C.	Anhydride	Hg	$(n\text{-}C_4H_9)_3P{=}O$
Acetic	Benzene	2.0	80	80	94	86
Propionic	Benzene	2.0	80	80	92	95
Butyric	Benzene	2.0	80	87	94	89
Benzoic	Dioxane	4.0	100	74	85	87
Phthalic	[a]			78	71	92

[a] In the case of phthalic acid, a white precipitate, m.p. 142–143°, was obtained by refluxing the benzene solution for 2 hr. Its mercury and phosphorus content could not be analyzed by the methods of A. Koten and R. Adams, *J. Am. Chem. Soc.*, **46**, 2764 (1924), and D. F. Boltz and M. G. Mellon, *Anal. Chem.*, **19**, 873 (1947). But, when it was pyrolyzed at 180°, mercury, phthalic anhydride, and tri-*n*-butylphosphine oxide were obtained. Assuming the precipitate to be a 1:1:1 adduct of the three starting materials, the yields were calculated.



These two types of reactions (4 and 5) are regarded as proceeding through an initial formation of phenylmercuric carboxylates which result by the reaction of diphenylmercury with carboxylic acids.[2] The subsequent reduction of phenylmercuric carboxylates by tri-*n*-butylphosphine yields the corresponding acid anhydrides, mercury, tri-*n*-butylphosphine oxide, and diphenylmercury. Diphenylmercury thus reproduced reacts again through the same process.

(2) M. M. Koton, *J. Gen. Chem. USSR* (Eng. Transl.), **9**, 912 (1939); *Chem. Abstr.*, **34**, 3928 (1940).

TABLE III

THE REACTIONS OF DIPHENYLMERCURY, TRI-*n*-BUTYLPHOSPHINE, AND THE MONOESTERS OF PHOSPHORIC ACID OR *p*-TOLUENESULFONIC ACID

Acid	Anhydride	Yield, %	Hg, %	$(n\text{-}C_4H_9)_3P{=}O$, %
$C_6H_5O{-}P(OH)_2$ (=O)	$C_6H_5O{-}P(OH){-}O{-}P(OH){-}OC_6H_5$ (=O)	86[a]	85	78
$p\text{-}ClC_6H_4O{-}P(OH)_2$ (=O)	$p\text{-}ClC_6H_4O{-}P(OH){-}O{-}P(OH){-}OC_6H_4{-}p\text{-}Cl$ (=O)	92[b]	89	83
$p\text{-}NO_2C_6H_4O{-}P(OH)_2$ (=O)	$p\text{-}NO_2C_6H_4O{-}P(OH){-}O{-}P(OH){-}OC_6H_4{-}p\text{-}NO_2$ (=O)	95[c]	95	83
$p\text{-}CH_3C_6H_4SO_3H$	$p\text{-}CH_3C_6H_4SO_2{-}O{-}SO_2C_6H_4{-}p\text{-}CH_3$	76	93	88

[a] R_f 0.74 (*n*-PrOH:NH_3:H_2O = 6:3:1). [b] R_f 0.79 (*n*-PrOH:NH_3:H_2O = 6:3:1). [c] R_f 0.90 (5% Na_2HPO_4:*i*-AmOH = 2:1), C. E Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

TABLE IV

THE REACTIONS OE DIPHENYLMERCURY, TRI-*n*-BUTYLPHOSPHINE, AND CARBOXYLIC ACIDS IN THE PRESENCE OF ALCOHOLS OR AMINES

				Yield, %		
Acid	ROH or RNH_2	Solvent	Time, hr.	Hg	$(n\text{-}C_4H_9)_3P{=}O$	Esters or amides
Acetic	$C_6H_5CH_2OH$	Dioxane	10	88	83	$CH_3CO_2CH_2C_6H_5$ 83
Propionic	$C_6H_5CH_2OH$	Dioxane	10	85	70	$C_2H_5CO_2CH_2C_6H_5$ 75
Butyric	$C_6H_5CH_2OH$	Benzene	10	88	82	$C_3H_7CO_2CH_2C_6H_5$ 79
Benzoic	C_2H_5OH	Benzene	10	85	80	$C_6H_5CO_2C_2H_5$ 76
Acetic	$C_6H_5NH_2$	Benzene	5.0	89	87	$CH_3CONHC_6H_5$ 80
Benzoic	$C_6H_5NH_2$	Benzene	5.0	92	85	$C_6H_5CONHC_6H_5$ 83

$$(C_6H_5)_2Hg + RC(=O){-}OH \longrightarrow C_6H_5{-}Hg{-}O{-}C(=O)R + C_6H_6$$

$$2C_6H_5{-}Hg{-}O{-}C(=O)R + (n\text{-}C_4H_9)_3P \longrightarrow$$

$$Hg + (C_6H_5)_2Hg + (RCO)_2O + (n\text{-}C_4H_9)_3P{=}O$$

Further, it was established that the reaction of monoesters of phosphoric acid or of *p*-toluenesulfonic acid with tri-*n*-butylphosphine and diphenylmercury gave *sym*-diesters of pyrophosphate or *p*-toluenesulfonic acid anhydride in high yields.

$$(C_6H_5)_2Hg + (n\text{-}C_4H_9)_3P + 2RO{-}P(OH)_2(=O) \longrightarrow$$

$$Hg + RO{-}P(OH){-}O{-}P(OH){-}OR + (n\text{-}C_4H_9)_3P{=}O + 2C_6H_6$$

$$(C_6H_5)_2Hg + (n\text{-}C_4H_9)_3P + 2p\text{-}CH_3{-}C_6H_4{-}SO_3H \longrightarrow$$

$$Hg + (p\text{-}CH_3{-}C_6H_4{-}SO_2)_2O + (n\text{-}C_4H_9)_3P{=}O + 2C_6H_6$$

When a solution of equimolar amounts of diphenylmercury, tri-*n*-butylphosphine, benzoic acid, and ethanol was refluxed for eight hours, ethyl benzoate was obtained in 76% yield along with mercury (85%) and tri-*n*-butylphosphine oxide (80%).

$$(C_6H_5)_2Hg + (n\text{-}C_4H_9)_3P + C_6H_5C(=O){-}OH + C_2H_5OH \longrightarrow$$

$$Hg + C_6H_5C(=O){-}OC_2H_5 + (n\text{-}C_4H_9)_3P{=}O + 2C_6H_6$$

Similarly, various carboxylic esters were produced in good yields by the reactions of diphenylmercury and tri-*n*-butylphosphine.

When aniline was used in place of alcohol in the preceding experiment, the corresponding anilides were obtained in good yields (see Table IV).

Furthermore, it became apparent that the reaction proceeds more readily when di-*p*-anisylmercury is used in place of diphenylmercury. These reactions are examined further.

Experimental

Materials.—Phenylmercuric acetate (m.p. 147–148°) and diphenylmercury (m.p. 121°) were prepared by the methods of Seide, *et. al.*,[3] and Blicke and Smith.[4]

Reaction of Phenylmercuric Acetate with Triethyl Phosphite.—When triethyl phosphite (3.4 g., 0.02 mole) was added all at once to phenylmercuric acetate (6.7 g., 0.02 mole) with vigorous shaking at room temperature, the reaction soon started with liberation of heat. After the reaction mixture was heated at 100° for 4 hr. with occasional shaking, the solid which was deposited was filtered. The filtrate was distilled, giving ethyl acetate, 1.3 g. (74%), b.p. 74–76°, and triethyl phosphate, 0.2 g. (5.5%), b.p. 90–92° (10 mm). Then the solid was dissolved in anhydrous dioxane and a trace of mercury was filtered off. The filtrate was evaporated *in vacuo* and a white crystal was obtained. It was washed with a small volume of anhydrous dioxane and dried *in vacuo*, yielding 5.2 g. (62%), m.p. 163–166°.

Anal. Calcd. for $C_{10}H_{15}O_3PHg$: P, 7.44; Hg, 48.1. Found: P, 7.21; Hg, 48.4.

Reaction of Phenylmercuric Acetate with Tri-*n*-Butylphosphine.—A solution of phenylmercuric acetate (6.7 g., 0.02 mole) and tri-*n*-butylphosphine (2.0 g., 0.01 mole) in 30 ml. of anhydrous benzene was refluxed for half an hour. Then the liberated mercury (1.65 g., 82%) was filtered off and the filtrate was concentrated. By the addition of petroleum ether to the residue, diphenylmercury, 2.2 g. (62%), m.p. and m.m.p. 115–117°, was obtained. After it was filtered off, the filtrate was concen-

(3) O. A. Seide, S. M. Scherlin, and G. J. Bras, *J. prakt. Chem.*, **138**, 55 (1933).

(4) F. F. Blicke and F. D. Smith, *J. Am. Chem. Soc.*, **51**, 3479 (1929).

trated and distilled. Acetic anhydride, 0.5 g. (49%), b.p. 136–137°, and tri-*n*-butylphosphine oxide, 1.9 g. (86%), b.p. 123–125° (0.2 mm.), were obtained.

Reaction of Phenylmercuric Acetate with Tri-*n*-Butylphosphine and Acetic Acid.—A mixture of phenylmercuric acetate (6.7 g., 0.02 mole), tri-*n*-butylphosphine (4.0 g., 0.02 mole), and glacial acetic acid (1.3 g., 0.02 mole) was heated with stirring at 65° for 2 hr. Mercury (3.4 g., 86%) was separated and the filtrate was distilled. Benzene, 1.4 g. (90%), b.p. 80–82°, acetic anhydride,[5] 1.63 g. (82 × 2%), b.p. 70–72° (92 mm.), and tri-*n*-butylphosphine oxide, 3.8 g. (94%), b.p. 123–125° (0.2 mm.), were obtained.

Reaction of Diphenylmercury and Tri-*n*-Butylphosphine with Acetic Acid.—A solution of diphenylmercury (5.3 g., 0.015 mole), tri-*n*-butylphosphine (3.0 g., 0.015 mole), and glacial acetic acid (1.8g., 0.03 mole) in 10 ml. of anhydrous benzene was refluxed for 2 hr. Then the liberated mercury (2.84 g., 94%) was filtered off and the filtrate was concentrated. The residue was distilled, giving acetic anhydride, 1.38 g. (80%), b.p. 134–136°, and tri-*n*-butylphosphine oxide, 2.6 g. (86%), b.p. 123–125° (0.2 mm.).

By a similar procedure, propionic, butyric, and benzoic anhydrides were obtained (see Table II).

Reaction of Diphenylmercury and Tri-*n*-Butylphosphine with Phthalic Acid.—A solution of diphenylmercury (5.3 g., 0.015 mole), tri-*n*-butylphosphine (3.0 g., 0.015 mole), and phthalic acid (2.5 g., 0.03 mole) in 10 ml. of anhydrous benzene was refluxed for 2 hr. Then a trace of liberated mercury was filtered off and the filtrate was cooled. The resulting white precipitate, 6.95 g., m.p. 128–133°, was filtered and the filtrate was concentrated *in vacuo*. An additional white precipitate, 2.35 g., m.p. 125–128°, was obtained. These were combined and recrystallized twice from benzene, m.p. 142–143°.

When 4.60 g. of these crystals was heated at 180° for 20 min., mercury, 0.90 g., was liberated and the residue solidified. This solid was washed with a small volume of dry ether and phthalic anhydride, 0.73 g., m.p. and m.m.p. 130–132°. From the filtrate, tri-*n*-butylphosphine oxide, 1.28 g., b.p. 123–135 (0.2 mm.), was obtained.

Reaction of Diphenylmercury and Tri-*n*-Butylphosphine with Phenyl Dihydrogen Phosphate.—A solution of diphenylmercury (3.5 g., 0.01 mole), tri-*n*-butylphosphine (2.0 g., 0.01 mole), and phenyl dihydrogen phosphate (3.4 g., 0.02 mole) in 15 ml. of anhydrous benzene was refluxed for 3 hr. After the liberated mercury, 1.70 g. (85%), was filtered off, a solution of barium chloride ($BaCl_2 \cdot H_2O$, 5 g.) in 20 ml. of water and pyridine (10 ml.) was added to the cold filtrate and allowed to stand in a refrigerator for about 30 min. The white precipitate was washed twice with acetone, dried, and then thoroughly washed with 50 ml. of water. The undissolved precipitate was filtered and dried *in vacuo* over phosphorus pentoxide, yielding 4.50 g. (86%) of barium diphenyl pyrophosphate, R_f 0.74 (*n*-PrOH:NH_3:H_2O = 6:3:1). From the filtrate, tri-*n*-butylphosphine oxide, 1.70 g. (78%), b.p. 121–122° (0.8 mm.), was obtained.

By a similar procedure, *sym*-di-*p*-chlorophenyl pyrophosphate and *sym*-di-*p*-nitrophenyl pyrophosphate were obtained.

Reaction of Diphenylmercury and Tri-*n*-Butylphosphine with *p*-Toluenesulfonic Acid.—Diphenylmercury (3.5 g., 0.01 mole), tri-*n*-butylphosphine (2.0 g., 0.01 mole), and *p*-toluenesulfonic acid (3.4 g., 0.02 mole) were dissolved in 15 ml. of anhydrous benzene and refluxed for 3 hr. Then the liberated mercury, 1.86 g. (93%), was filtered off and the filtrate was evaporated *in vacuo*. On addition of 0.9 g. (0.01 mole) of aniline to the residue, a white precipitate deposited. It was filtered off and washed with a small volume of water and dried *in vacuo*; 1.88 g. (76%) of *p*-toluenesulfonyl anilide, m.p. and m.m.p. 100–102°, was obtained. From the filtrate, tri-*n*-butylphosphine oxide, 1.92 g. (88%), b.p. 120–122° (0.2 mm.), was isolated.

(5) Acetic anhydride, derived from two sources, can not be determined separately; consequently, it is assumed that equal volumes are obtained from them.

Acknowledgment.—The authors wish to express their hearty thanks to Mr. Hirohiko Nambu for his kind advice during the course of this experiment.

Mechanisms of Hydrolysis of Several Atom-Bridged Bicyclic Anhydrides, N-Methylimides, and Lactones

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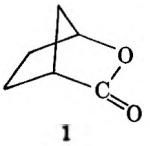
Several atom-bridged bicyclic carbonyl compounds were synthesized. The saponification or hydrolysis rates of these and related compounds were determined. Ground state strains were assessed by determining the position of the monomer–polymer equilibrium. The rates were interpreted using a postulate of Bruice and Pandit about the location of the transition states. Because these cage structures reacted readily in most cases, a configuration of the transition state wherein the hydroxyl ion is colinear with the carbonyl oxygen was rejected.

Interest in the mechanisms of hydrolysis and saponification reactions[1] prompted determination of the rates of these reactions for several atom-bridged bicyclic compounds prepared earlier[2] and for several new ones.

Results

Preparation of Compounds.—Ethyl 3-hydroxycyclopentanecarboxylate was prepared according to Vaughan[3] and Toki.[4] When heated with a trace of litharge,[2] ethanol was eliminated and the lactone, 2-oxabicyclo[2.2.1]heptan-3-one (**1**), distilled as a waxy solid.[5] 2-Oxabicyclo[3.2.1]octan-3-one (**2**) was prepared by Baeyer–Villiger oxidation of norcamphor.[6,7] 3-Oxabicyclo[3.2.1]octane-2,4-dione (**3**)[8] and 3-oxabicyclo[3.2.2]nonane-2,4-dione (**4**)[9] were prepared from corresponding dicarboxylic acids by literature procedures. N-Methyl-3-azabicyclo[3.2.1]octane-2,4-dione (**5**) and N-methyl-3-azabicyclo[3.3.1]nonane-2,4-dione (**6**) were prepared by treating *cis*-cyclopentane-1,3-dicarboxylic acid and *cis*,-



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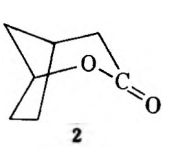


2

(1) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(2) H. K. Hall, Jr., *ibid.*, **80**, 6412 (1958).

(3) H. A. Vaughan, Jr., Ph.D. thesis, Columbia University, 1955; *Chem. Abstr.*, **51**, 16314 (1957).

(4) K. Toki *Bull. Chem. Soc. Japan*, **32**, 233 (1959).

(5) The same lactone has been reported by D. S. Noyce and J. Fessenden, *J. Org. Chem.*, **24**, 715 (1959).

(6) A. Rassat and G. Ourisson, *Bull. soc. chim. France*, 1133 (1959).

(7) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).

(8) K. Posspischill, *Ber.*, **31**, 1952 (1898).

(9) R. Malachowski and J. Jankiewiczowna, *ibid.*, **67**, 1783 (1934).

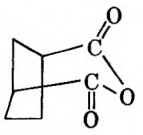
TABLE I

RATES OF SAPONIFICATION AND HYDROLYSIS IN WATER AT 25.0°

Acyl derivative	Ground state strain by polymerization criterion	Ref.	Initial concn., $M \times 10^3$, of acyl derivative	$k_1 \times 10^{3d}$	k_2^e	Ref.
Anhydrides						
Glutaric anhydride	0	[f]		2.80	11	
3-Oxabicyclo[3.2.1]octane-2,4-dione (3)	0	[c]	35.8	1.41[a]		[c]
			35.8	0.414[b]		[c]
3-Oxabicyclo[3.2.2]nonane-2,4-dione (4)	+	[g]	39.0	Insol.[a]		[c]
			39.0	0.381[b]		[c]
N-Methylimides						
N-Methylglutarimide	0	[c]			1.81	[f]
N-Methyl-3-azabicyclo[3.2.1]octane-2,4-dione (5)	0	[c]	5.14	8.51	1.65	[c]
			10.0	14.5	1.45	[c]
			19.4	30.1	1.55	[c]
N-Methyl-3-azabicyclo[3.3.1]nonane-2,4-dione (6)	0	[g]	12.0	8.97	0.75	[c]
Lactones						
γ-Butyrolactone	0	[g]			0.81	[f]
δ-Valerolactone	+	[g]			13.8	[f]
6-Oxabicyclo[3.2.1]octane-7-one (7)	+	[g]			0.36	[f]
2-Oxabicyclo[2.2.1]heptane-3-one (1)	+	[c]	15.5	3.80	.25	[c]
			35.6	9.00	.25	[c]
2-Oxabicyclo[2.2.2]octane-3-one (8)	+	[g]			.027	[f]
2-Oxabicyclo[3.2.1]octane-3-one (2)	0	[c]	13.2	0.0576	.0044	[c]
			79.7	.340	.0043	[c]

[a] Solvent 20% acetone–80% water by weight. [b] Solvent 40% acetone–60% water by weight. [c] Present work. [d] First-order rate constant in sec.$^{-1}$ for solvolysis in initially neutral water or pseudo first-order rate constant for disappearance of hydroxide ion[1]. [e] Second-order rate constant in l. mole^{-1} sec.$^{-1}$ for bimolecular saponification by hydroxide ion. [f] Ref. 1. [g] Ref. 2.

trans-cyclohexane-1,3-dicarboxylic acid, respectively, with methylamine and distilling the reaction mixtures.



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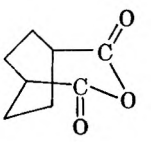

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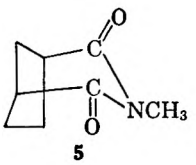

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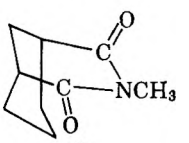

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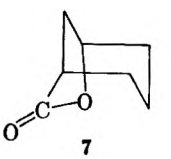
Polymerizations and Rate Measurements.—The ability of these atom-bridged bicyclic compounds to polymerize *via* ring-opening was established by the methods described earlier.[2] The results are presented in Table I. The saponification rates of the esters and N-methylimides were determined as described earlier.[1,10]

Discussion

Ground State Strains.—Ground state strains were assessed by ring-opening polymerizations since heat of combustion data for these compounds are lacking. As described earlier,[2] polymerization of a cyclic monomer is an equilibrium process. Destabilizing factors, mainly nonbonded hydrogen interactions or angle strain, favor the formation of polymer, which is usually unstrained.

The strained bicycloheptane system in 2-oxabicyclo-[2.2.1]heptan-3-one (1) favors polymerization. The bicyclo[3.2.1]octane system is marginal. None of the new compounds 2, 3, or 5 belonging to this class polymerized, although 6-oxabicyclo[3.2.1]octan-7-one (7) does so.[2]



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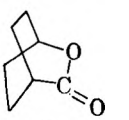

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3-Oxabicyclo[3.2.2]nonane-2,4-dione (4) polymerized as expected to relieve the strained boat form of the cyclohexane ring. The strainless two-chair form of N-methyl-3-azabicyclo[3.3.1]nonane-2,4-dione (6) did not polymerize, also as predicted.

Configuration of the Transition State.—Earlier work[1] suggested that the hydroxyl ion and carbonyl oxygen group might be at a 180° angle in the transition state. Such a transition state would not be possible for compounds 1, 3, 4, and 5 of the present study, yet they are quite reactive. Accordingly, the suggestion of a 180° transition state can be dropped[11] and the results can be discussed in terms of the 90° transition state suggested by Bender.[12]

Additionally, we shall use the postulate of Bruice and Pandit,[13] who suggest that the carbonyl group in anhydride hydrolysis is mostly sp^2 hybridized (the transition state is close to reactants), in N-methylimide saponification is intermediate in hybridization, and in lactone saponification is mostly sp^3 hybridized (the transition state possesses a fairly strong bond between the hydroxide ion and the lactone). Their proposal was based on the relative reactivities of six- and five-membered rings.

(10) J. Koskikallio, *Ann. Acad. Sci. Fennicae, Ser. A*, **57**, 1 (1954).

(11) The same conclusion was claimed recently for phthalamic acid by Zerner and Bender [*J. Am. Chem. Soc.*, **83**, 2267 (1961)], but their criterion, based on $k\ D_2O/k\ H_2O$ ratios, was apparently not decisive [M. L. Bender, E. J. Pollack, and M. C. Neveu, *ibid.*, **84**, 595 (1962)].

(12) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(13) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960).

Hydrolysis of Anhydrides.—The strained bicyclic anhydride **4** hydrolyzes at the same rate as the unstrained anhydride **3** and as monocyclic or acyclic-anhydrides. The ground state strain in **4** is, therefore, still present in the transition state. Since the latter resembles the reactants, the anhydride ring is not opening to provide relief of strain and enhancement of rate.

Saponification of N-Methylimides.—The particular compounds studied, **5** and **6**, were not strained. The transition state for these reactions is further along the reaction coordinate, but the hydroxyl group is still not firmly bonded or close enough to undergo steric crowding by the bridges. Accordingly, these compounds saponify at equal rates to each other and to monocyclic and acyclic N-methylimides.

Saponification of Lactones.—Here considerable bond formation between hydroxide ion and the reactant is present in the transition state. Steric crowding between the hydrated hydroxyl ion and the reactant will be more important for these compounds. We may ask whether the ring is being broken as the hydroxyl ion attacks the carbonyl group.[14] Strained lactones should saponify faster than unstrained ones if this were true. The strained compounds **1** and **7** saponify at rates similar to those of model compounds, while the strained lactone **8** saponifies quite slowly. Moreover, the unstrained lactone **2** reacts much more slowly than any of the others. Therefore, no significant cleavage of the ring has occurred at the transition state for the saponification of the lactones. The same conclusion can be reached by considering the fact that the saponification rates of the strained propiolactone and the unstrained γ-butyrolactone are equal.[1] The markedly lower reactivity of lactones **2** and **8** can be ascribed to drastic steric interference between the hydroxyl ion and the ethylene bridges of these molecules.

Experimental

2-Oxabicyclo[2.2.1]heptan-3-one (1).—Cyclopentanone-3-carboxylic acid was prepared according to literature procedures.[3,4] During the distillation of the product, it was difficult to maintain the vacuum, owing to slight decomposition in the boiler, and it was necessary to continue the distillation over several hours while gradually increasing the bath temperature in order to distil all of the acid. The product, obtained in 58.7% yield, melted at 54.0–60.5° (lit.[4] m.p. 64–65°) and was sufficiently pure for conversion to the ester. Ethyl cyclopentanone-3-carboxylate was prepared according to Toki[4] except that the reaction was terminated after 18 hr. Hydrogenation was carried out in ethanol over Raney nickel at 80°.

A mixture of 13.1 g. (0.0828 mole) of ethyl 3-hydroxycyclopentanecarboxylate and 0.16 g. of red Pb_3O_4 was held at 190–200° for 1 hr. under 150-mm. pressure. Ethanol, b.p. 42–47° (150 mm.), 4 ml., distilled. Pressure was reduced to 0.3 mm. and the lactone distilled slowly over a 3-hr. period, b.p. up to 80°. The product, a mixture of liquid and solid, weighed 4.5 g. It was crystallized from a mixture of 12 ml. of ether and 6 ml. of hexane at −80°, filtered onto a Dry Ice-chilled Allihn sintered glass funnel under nitrogen, and spun in a centrifuge until it attained room temperature.[15] There was obtained 2.44 g. (26.3%) of nicely crystalline, hygroscopic, 2-oxabicyclo[2.2.1]heptan-3-one (**1**), m.p. 51.0–56.0° (sealed cap.). The analytical sample had m.p. 56.5–60.5°[c] (lit.[5] m.p. 53.7–54.5°). Its infrared spectrum was consistent with the assigned structure, in particular showing carbonyl absorption at 1775 cm.$^{-1}$, which is characteristic of five-membered lactones.

Anal. Calcd. for $C_6H_8O_2$: C, 64.0; H, 7.0. Found: C, 64.3; H, 7.2.

2-Oxabicyclo[3.2.1]octan-3-one 2.—The procedure was that of Sauers,[16] starting from norcamphor. The lactone had b.p. 81° (0.20 mm.), m.p. 58.5–60.5° (sealed cap.) (lit.[6,7] m.p. 64°), 66.2% yield.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.9; H, 8.1.

The infrared spectrum was consistent with the assigned structure, the carbonyl absorption occurring at 1742 cm.$^{-1}$.

Attempted Preparation of 3-Oxabicyclo[3.2.1]octan-2-one.—Hydrogenolysis of 25 g. of *cis*-cyclopentane-1,3-dicarboxylic anhydride in dioxane over copper chromite at 200° gave 13.6 g. of *cis*-cyclopentane-1,3-dimethanol, b.p. 117° (0.55 mm.), $n^{25}D$ 1.4842.

Anal. Calcd. for $C_7H_{12}O_2$: C, 64.6; H, 10.8. Found: C, 63.8, 64.1; H, 10.5, 10.8.

The infrared spectrum was consistent with this formulation showing strong hydroxyl absorption but no carbonyl absorption.

3-Oxabicyclo[3.2.1]octane-2,4-dione (3).—This anhydride melted at 160.5–163.0° (lit.[8] m.p. 160–161.5°).

3-Oxabicyclo[3.2.2]nonane-2,4-dione (4).—A mixture[9] of 70 g. (0.406 mole) of *cis,trans*-1,4-cyclohexanedicarboxylic acid and 225 g. of acetic anhydride was refluxed for 5 hr. Acetic acid and acetic anhydride were removed by distillation. The resulting solid polyanhydride depolymerized smoothly when heated with a pale blue flame at 1–3 mm., head temperature 210°, to give 56.3 g. of solid distillate. Recrystallization from benzene–hexane containing a little acetone gave 28.8 g. (46.1%) of white crystals of the desired anhydride, m.p. 160–168°, on a heated bar (lit.[9] m.p. 150–160°) (polymerization occurs during the determination).

N-Methyl-3-azabicyclo[3.2.1]octane-2,4-dione (5).—The procedure was that of Grogan and Rice.[17] The imide (38.9% yield) had m.p. 43.5–47.0°.

Anal. Calcd. for $C_8H_{11}O_2N$: N, 9.14. Found: N, 9.04.

N-Methyl-3-azabicyclo[3.3.1]nonane-2,4-dione (6).—This imide has been prepared previously.[2]

Kinetics Methods.—The rates of hydrolysis of the lactone and imides were determined by the pH method previously described.[1] The anhydride rates were determined by the aniline titration method.[10] Because saponification and hydrolysis rate constants are very sensitive to solvent composition,[10,18,19] the rates were determined generally using water alone at 25° as the solvent. Only in the cases of the two bicyclic anhydrides was acetone added to form a homogeneous solution.

Polymerizations.—These were performed as previously described.[2] The lactones were sealed in glass tubes with traces of litharge or tetraisopropyl titanate and heated at 150° for 48 hr. 3-Oxabicyclo[3.2.1]octane-2,4-dione was heated similarly with water at 170°. Under these conditions 2-oxabicyclo[2.2.1]heptan-3-one became a rather viscous sirup on cooling. This was extracted twice with ether to remove most of the unreacted lactone. The remaining polymer, *ca.* 50% yield, had a molecular weight of 1100 (isopiestic in chloroform). Its infrared spectrum was consistent with the polyester structure and a little unchanged lactone was present also.

Acknowledgment.—The author is indebted to Mrs. Nancy Abbadini for excellent technical assistance, to Mr. I. D. Plank and his associates for the microanalyses, to Dr. Caryl Sly for the hydrogenations, to Professor J. Meinwald for information about the oxidation of norcamphor, and to Dr. D. R. Wilson for helpful criticism.

(14) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *J. Am. Chem. Soc.*, **83**, 4193 (1961), have shown that no tetrahedral intermediate is detectable in lactone saponification.

(15) S. I. Miller and R. M. Noyes, *J. Am. Chem. Soc.*, **73**, 2377 (1951).

(16) R. R. Sauers, *ibid.*, **81**, 975 (1959).

(17) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

(18) E. Tommila and M. P. O. Ilömaki, *Acta Chem. Scand.*, **6**, 1246 (1952), and other articles in this series.

(19) For example, Huisgen and Ott[20] showed that the saponification rate ratio *k* butyrolactone/*k* aliphatic ester was 1.8×10^2 in dioxane–water at 0°, whereas data obtained in water at 25°, give the same ratio *k* butyrolactone/*k* ethyl acetate as 7.3.

(20) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

3-Indolepropionic Acid. Some Reactions of Indole with Salts of Acrylic and Methacrylic Acids[1]

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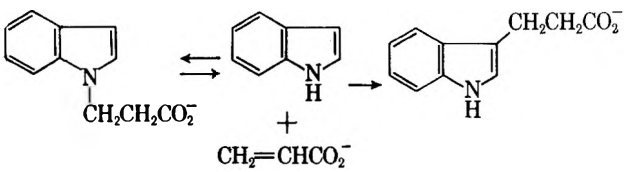
Indole and sodium acrylate react at 250° to give high yields of 3-indolepropionic acid. Methacrylate salts react similarly. The probable mechanism, origin of by-products, and limitations of this novel reaction are discussed.

The formation of 1-indolepropionic acid is reported[2,3] to proceed in high yield *via* the reaction of indole with sodium acrylate in aqueous solution at about 180°. Analogous to other reactions of amines with α,β-unsaturated esters and nitriles,[4] this reaction may be reversible. In contrast, 3-indolepropionate salts might be expected to be more stable. Therefore, by considering the 1-addition of sodium acrylate reversible and the 3-addition, if it occurs at all, irreversible reaction conditions should be possible to allow the formation of 3-indolepropionic acid from these reagents. This communication describes the syntheses of various 3-indolepropionic acid derivatives by the reaction of indole with salts of α,β-unsaturated acids at temperatures from 225–300°.



Experiments in which indole, potassium acrylate, and a catalytic quantity of potassium hydroxide were allowed to react at 250° for seventeen hours provided a 60% yield of 3-indolepropionic acid. Although an exhaustive study of the reaction conditions was not made, it was determined that reaction times from two to twenty-one hours were about equally effective in producing the desired product. The reaction temperature, however, was more critical: at 225° mixtures (approximately 1:1) of 1- and 3-indolepropionic acids were observed and at 300° some degradation of the indole nucleus was noted.[5] Best results were obtained by performing the reaction in the presence of sodium hydroxide at 260° for about seventeen hours and employing indole–acrylic acid–sodium hydroxide in a ratio of 1:0.90:1.35. In this manner there was obtained a 69% yield (based on indole charged) of light tan 3-indolepropionic acid having a melting point less than 5° below that of pure material. As 21% of the starting indole could be recovered, a 90% efficiency based on this reactant was realized. A small amount ($\leq$ 5%) of acidic impurities persist in the reaction product and most probably consist of acrylate polymers. These materials are difficultly removable by crystallization techniques; consequently, esterification followed by distillation was used to purify the reaction product. No β-(1-indolyl)propionate could be detected in the distillate.

Several variations in the reaction conditions produced results of interest. In particular, the reaction of indole, acrylic acid, and triethylamine at 260°, and in a mole ratio of 1:1:1.5, deserves mention. From this reaction was isolated, *inter alia*, N,N-diethylpropionamide (7%), 3-ethylindole (15%), **1,2,3,4-tetrahydrocarbazole** (5%), N,N-diethyl-β-(1-indolyl)propionamide (9%), N,N-diethyl-β-(3-indolyl)propionamide (8%), and considerable nonvolatile intractable residue. With the exception of the 1-propionamide, all of the reaction products were identified by comparison of a purified sample with authentic material. As this amide could not be obtained in a pure state its presence can only be inferred by comparison of the infrared spectrum of this fraction and the g.l.c. retention time of the major component to those of an authentic crystalline sample. Hydrolysis to β-(1-indolyl)propionic acid by prolonged heating with 40% aqueous potassium hydroxide was not successful; the 3-isomer behaved similarly.

A triethylacylammonium hydroxide may be an intermediate in the formation of 3-ethylindole and the diethylamides, as this base could be expected to decompose to an ethyl fragment (ethanol or ethylene) thus, producing the observed amides and 3-ethylindole. As indole and ethanol do not react at 250° in the presence of triethylamine, and indole and ethylene are unreactive in the presence of aqueous sodium hydroxide at temperatures to 250°, it is possible that the triethylacylammonium hydroxide catalyzes the reaction of indole and ethanol[6,7] as well as the acrylate additions.

The origin of 1,2,3,4-tetrahydrocarbazole remains obscure. However, methacrylic acid, when treated with indole and triethylamine under similar conditions, produced some 1-methyl-1,2,3,4-tetrahydrocarbazole, establishing that the presence of an acrylate is necessary for the formation of these carbazoles. The structure of this carbazole derivative was inferred by its n.m.r. spectrum and established by dehydrogenation to 1-methycarbazole.[8]

Large amounts of water added to the reaction mixture were found to be deleterious to the formation of 3-indolepropionic acid. Esterification of the crude acidic product, obtained as an oil, enabled the reaction products to be characterized as being predominantly 1-indolepropionic acid. Some 3,3-diindolylmethane was also formed and probably is derived from the base-catalyzed reaction of indole with formaldehyde.[9] Hy-

(1) Paper III in a series of Reactions of Indole. Papers by H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **25**, 569 (1960), and **28**, 1246 (1963), to be considered I and II of this series.

(2) W. Reppe and H. Ufer, U. S. Patent 2,195,974.

(3) W. Reppe and H. Ufer, German Patent 698,273.

(4) H. A. Bruson, Organic Reactions, Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 79.

(5) R. Weissgerber and C. Seidler, *Ber.*, **60**, 2090 (1927).

(6) B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933); *Chem. Abstr.*, **27**, 3933 (1933).

(7) R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 680 (1942).

(8) F. Ullman, *Ann.*, **332**, 82 (1904).

(9) J. Thesing, S. Klussendorf, P. Ballach, and H. Meyer, *Chem. Ber.*, **88**, 1295 (1955).

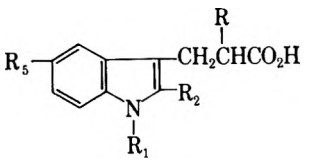
dration of acrylic acid followed by a reverse aldol condensation possibly accounts for the presence of formaldehyde.

It is worth noting that the reaction of methacrylate salts with indole at 300° produced appreciable amounts of 3-*n*-propylindole and *o*-toludine,[5] in addition to considerable quantities of the 3-acid derivative. At 280°, crotonate salts yielded some 3-ethylindole. Although no β-(3-indolyl)butyric acid was ever observed among the reaction products, at 250° some β-(1-indolyl)butyric acid could be isolated (*via* esterification of the crude acidic product).

The use of 2-methyl- and 2,5-dimethylindole produced the corresponding 3-propionic acids in 30 and 48% yields, respectively. 1,2-Dimethylindole, under the present conditions, was not reactive, presumably due to its inability to form a reactive anion. As expected, methacrylate salts and indole reacted to give α-methyl-β-(3-indolyl)propionic acid in 60–70% yield. The structure of this acid was substantiated by its identity to an acid prepared by the reaction of indole with methacrylic acid in the presence of acetic anhydride.[10] Crotonic, itaconic, maleic, and fumaric acids did not react noticeably with the 3-position of indole, employing the present reaction conditions. The indole acids prepared by this method are shown in Table I.

TABLE I

INDOLEPROPIONIC ACIDS



R	R_1	R_2	R_5	Yield, %	M.p., °C.	Other
H	H	H	H	70	134–136	Reported[a] m.p. 135–136°
CH_3	H	H	H	60	129–130	See Experimental
H	H	CH_3	H	30	135–136	Reported[b] m.p. 137–138°
H	H	CH_3	CH_3	48	169–170	*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.17; N, 6.38.
H	CH_3	CH_3	H			No reaction

[a] See ref. 11. [b] See ref. 12.

Experimental

Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer, ultraviolet spectra by a Cary Model 21 spectrophotometer, and nuclear magnetic resonance spectra by a Varian Associates Model A-60 spectrometer. G.l.c. analyses were performed at 200–250° with a 5-ft. column containing Apiezon-L supported on Fluoropak.

3-Indolepropionic Acid.—To a 3-l. stainless steel rocker autoclave was added 234 g. (2.0 moles) of indole, 144 g. (2.0 moles) of acrylic acid, and 180 g. (2.7 moles) of 85% potassium hydroxide. The reaction mixture was heated under autogenous pressure with rocking at 275° for 20 hr. and then cooled to about 100°. Eight hundred milliliters of water was added to dissolve the reaction product and, after cooling the mixture further, it was extracted with ether to remove unchanged indole and other neutral materials. Acidification of the aqueous phase followed by filtration and drying afforded 229 g. (61%) of light tan 3-indolepropionic acid, m.p. 121–125°. Repeated crystallization of a sample from water raised the m.p. to 134–136° (lit.[11] m.p. 135–136°), undepressed when mixed with an authentic sample. The nature of the acidic impurity in the crude reaction product is unknown and is difficultly removable by crystallization. A more satisfactory method for the purification of the crude reaction product consists of the preparation of the ethyl ester followed by fractional distillation and saponification, as described later for ethyl α-methyl-β-(3-indolyl)propionate.

In another experiment using 234 g. (2.0 moles) of indole, 130 g. (1.8 moles) of acrylic acid, and 108 g. (2.7 moles) of sodium hydroxide, 260 g. (76% based on acrylic acid, 69% based on indole) of very light tan 3-indolepropionic acid was obtained, m.p. 127–131°. Distillation of the neutral material recovered from the reaction mixture afforded 49 g. (21%) of indole. Increasing the amount of acrylic acid in the reaction mixture led to higher yields of reaction products; the quality, however, was poorer.

α-Methyl-β-(3-indolyl)propionic Acid. (a) **By the Reaction of Indole with Potassium Methacrylate.**—In the manner described before for preparation of 3-indolepropionic acid, 234 g. (2.0 moles) of indole, 172 g. (2.0 moles) of methacrylic acid, and 180 g. (2.7 moles) of 85% potassium hydroxide reacted at 280° for 19 hr. to give 244 g. (60%) of light brown product, m.p. 109–119°. Several crystallizations from water afforded an analytical sample as short off-white needles, m.p. 127–129°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.88; H, 6.38; N, 6.80.

From a similar experiment in which the reaction temperature was 300°, 250 g. (61%) of dark brown acid was obtained, m.p. 112–117°, and 101 g. of neutral material, b.p. 76–130° (3.0 mm.). Fractional distillation of this product afforded 6 g. of pure *o*-toluidine, b.p. 61° (3.0 mm.), $n^{30}D$ 1.5675; 58 g. (25%) of indole; and 10 g. of 3-(*n*-propyl)indole, b.p. 116° (1.25 mm.), $n^{30}D$ 1.5762, m.p. 26–27° (lit.[13] m.p. 29° and as an oil[7]). The infrared spectra of the toluidine and propylindole were identical in detail to the respective spectra of authentic samples and a mixture melting point of the two indole samples was undepressed.

(b) **By the Reaction of Indole with Methacrylic Acid in the Presence of Acetic Anhydride and Sodium Acetate.**[10]—A mixture of 240 g. (2.04 moles) of indole, 344 g. (4.0 moles) of methacrylic acid, 816 g. (8.0 moles) of acetic anhydride, 128 g. (1.56 moles) of sodium acetate, and 960 ml. of acetic acid was heated under reflux for 5 hr. All volatile material was removed quickly *in vacuo* and the remaining 853 g. of residue added to 360 g. of sodium hydroxide in 1.2 l. of water. Considerable nonacidic oil was present and was removed by extraction with ether. The aqueous phase was acidified with concentrated hydrochloric acid to give, after collection by filtering and drying, 129 g. (31%) of dark brown product, m.p. 118–125°. Crystallization from water raised the m.p. to 129–130°, which was undepressed when mixed with the acid as prepared in method a.

Ethyl α-Methyl-β-(3-indolyl)propionate.—A solution of 519 g. (2.54 moles) of α-methyl-β-(3-indolyl)propionic acid in 2 l. of ethanol containing 25 g. of *p*-toluenesulfonic acid monohydrate was prepared and heated under reflux for a total of 18 hr. The ethanol was removed by distillation under reduced pressure and the remaining residue dissolved in 1 l. of ether. After washing the ether solution successively with 5% sodium hydroxide solution and water, the ether was evaporated and the residue distilled. A total of 471 g. (80%) of slightly yellow distillate was obtained, b.p. 182–185° (1.5 mm.), $n^{30}D$ 1.5492. A portion was redistilled and analyzed, b.p. 165° (0.75 mm.), $n^{30}D$ 1.5504.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.47; H, 7.41; N, 5.99.

The Reaction of Indole with Sodium Crotonate.—As described for the preparation of 3-indolepropionic acid, 234 g. (2.0 moles) of indole, 155 g. (1.8 moles) of crotonic acid, and 80 g. (2.0 moles) of sodium hydroxide were heated at 250° for 21 hr. Acidification of the crude reaction mixture produced a thick oil that would not solidify. Ether extraction followed by evaporation led to 144 g. of acidic product which was esterified by treatment with ethanol and *p*-toluenesulfonic acid. From this reaction was obtained 66 g. of product, b.p. 123–160° (2.0 mm.). Fractional distillation provided 35 g. of colorless ester, b.p. 167° (4.0 mm.), $n^{30}D$ 1.5452. The analytical data, lack of an NH absorption at about 3 μ, and boiling point are consistent with ethyl β-(1-indolyl)butyrate.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.51; N, 6.22.

The Reaction of Indole with Acrylic Acid in the Presence of Triethylamine.—A mixture of 234 g. (2.0 moles) of indole, 144 g.

(10) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **25**, 569 (1960).
(11) A. Ellinger, *Ber.*, **38**, 2884 (1905).
(12) J. Harley-Mason, *J. Chem. Soc.*, 2433 (1952).
(13) G. F. Smith and A. E. Waters, *ibid.*, 940 (1961).

(2.0 moles) of acrylic acid, and 303 g. (3.0 moles) of triethylamine was prepared and heated, with agitation, at 260° in a 3-l. stainless steel autoclave. After 21 hr. the reaction mixture was cooled, diluted with 1 l. of water, and extracted with ether. Acidification of the aqueous phase provided only a trace of acidic material, which was not investigated further. Distillation of the ether extracts gave 227 g. of a mixture of reaction products, b.p. to 243° (1.0 mm.), and 140 g. of nonvolatile intractable residue. Fractional distillation of the volatile reaction products using a 3-ft. spinning band column produced the following major fractions: (A) 28 g., b.p. to 82° (1.0 mm.); (B) 46 g., b.p. 82–88° (1.0 mm.); (C) 30 g., b.p. 88–112° (1.0 mm.); (D) 11 g., b.p. 145–147° (1.0 mm.); (E) 44 g., b.p. 180–183° (1.0 mm.); (F) 37 g., b.p. 220–229° (1.0 mm.); and (G) 34 g. residue and mid-fractions.

Fraction A consisted of a multitude of products of which indole was found in minor amounts. No indoline was present. Further fractionation of this mixture afforded a pure sample of N,N-diethylpropionamide, b.p. 46° (1.85 mm.). Its infrared spectrum was found to be identical to the spectrum of an authentic sample, b.p. 62° (2.0 mm.), $n^{30}D$ 1.4351.

Fraction B was redistilled and identified as being predominantly indole from its g.l.c. retention time and physical constants, b.p. 82° (1.0 mm.) and m.p. 51–52°. Approximately 10% of a mixture of lower boiling materials also was present.

Fraction C contained 7.5% of lower boiling unidentified material, 17% of indole, 0.5% of skatole (by retention time only), and 75% of 3-ethylindole. Additional fractionation afforded pure 3-ethylindole as a colorless solid, m.p. 36–37°, undepressed when mixed with an authentic sample (lit.[7] m.p. 37°).

Fraction D solidified and was purified further by repeated crystallizations from hexane, m.p. 117–118°. Elemental analysis suggested a $C_{12}H_{13}N$ formula; infrared, ultraviolet, and n.m.r. spectra indicated the material to be 1,2,3,4-tetrahydrocarbazole. A mixture melting point with an authentic sample[14] of m.p. 118–119° was undepressed.

Fraction E was redistilled and a constant-boiling fraction was collected at 164° (0.06 mm.). G.l.c. indicated a purity of 82%; the material could not be induced to solidify. Further purification by chromatography on alumina resulted in an oily fraction, about 90% pure, which still would not crystallize, even when seeded with N,N-diethyl-β-(1-indolyl)propionamide (see col. 2). The retention time (63 min.) of this material was found to be the same as that of pure N,N-diethyl-β-(1-indolyl)propionamide and, with the exception of minor OH (2.90 μ), NH (3.02), and C=O (5.78) absorptions, the infrared spectra of these two materials were very similar.

Fraction F slowly solidified and an analytical sample was obtained as colorless microcrystals, m.p. 114–116°, after several crystallizations from isopropyl ether followed by toluene. A mixture melting point with authentic N,N-diethyl-β-(3-indolyl)-propionamide (see col. 2) was undepressed, and the infrared spectra of the two were found to be identical in detail.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.67; H, 8.40; N, 11.29.

Integration of the g.l.c. peak areas of all fractions and mid-fractions provided the following approximate yields of the reaction products: 7% N,N-diethylpropionamide; 7% indole; 15% 3-ethylindole; 5% 1,2,3,4-tetrahydrocarbazole; 9% N,N-diethyl-β-(1-indolyl)propionamide; and 8% N,N-diethyl-β-(3-indolyl)-propionamide.

(14) C. U. Rogers and B. B. Carson, *Org. Syn.*, **30**, 90 (1950).

The Reaction of Indole with Methacrylic Acid in the Presence of Triethylamine. Isolation of 1-Methyl-1,2,3,4-tetrahydrocarbazole.—In the manner described for the reaction of indole with acrylic acid and triethylamine, 234 g. (2.0 moles) of indole, 172 g. (2.0 moles) of methacylic acid, and 303 g. (3.0 moles) of triethylamine reacted to give 292 g. of distilled products, b.p. to 250° (0.75 mm.), and 79 g. of nonvolatile residue. Further fractionation produced 138 g. of a mixture containing indole (34%) and 3-ethylindole (66%), b.p. to 104° (0.75 mm.), and 20 g. (5%) of 1-methyl-1,2,3,4-tetrahydrocarbazole, b.p. 128–131° (0.5 mm.), $n^{30}D$ 1.6007. The sample slowly solidified but defied recrystallization (lit.[15] m.p. 65°), λ_{max}^{EtOH} mμ (ε), 278 (shoulder), 283 (7050), 292 (5850). Signals in the nuclear magnetic resonance spectrum were observed at 1.1 p.p.m. (doublet, methyl group), 1.75 p.p.m. (multiplet, 2,3-methylene groups), and 2.66 p.p.m. (multiplet, methine and 4-methylene group) in a ratio of 3:4:3. Resonance due to the 5,6,7,8, and N protons occurred at 7.0–7.5 p.p.m.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.42; H, 8.49; N, 7.43.

Dehydrogenation of 1-Methyl-1,2,3,4-tetrahydrocarbazole.—A 1.02-g. sample of the tetrahydrocarbazole from the reaction of indole, methyacrylic acid, and triethylamine and 0.10 g. of 5% palladium on carbon were mixed and heated to 300° until the evolution of hydrogen ceased. The cooled mixture was slurried with hot ethanol and filtered to remove the catalyst. Evaporation of the filtrate and crystallization of the residue from hexane afforded 0.72 g. of colorless plates, m.p. 117–118°. Further crystallization from the same solvent raised the m.p. to 120–121° (lit.[8] m.p. 120.5°).

N,N-Diethyl-β-(1-indolyl)propionamide.—Following the procedure of Shaw and Wooley,[16] 20 g. (0.1 mole) of 1-indolepropionic acid[3] and 23 g. (0.1 mole) of phosphorus pentachloride were mixed in 200 ml. of dry ether. After 30 min. at 0° and 30 min. at 25°, the mixture was poured over 100 g. of diethylamine and ice. The ether was evaporated in a stream of nitrogen to leave 22 g. (90%) of light brown solids, m.p. 40–44°. Several crystallizations from hexane (Dry Ice–acetone cooling) provided an analytical sample as colorless microcrystals, m.p. 42–44°.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 74.00; H, 8.32; N, 11.51.

N,N-Diethyl-β-(3-indolyl)propionamide.—This amide was prepared[17] in 95% yield by the procedure described for the synthesis of the 1-isomer. Several crystallizations from ethyl acetate gave a sample, m.p. 115–117°, identical in all respects to the material isolated from the reaction of indole, acrylic acid, and triethylamine.

Ethyl 1-Indolepropionate.—A solution of 115 g. (0.61 mole) of 1-indolepropionic acid,[3] 20 g. of *p*-toluenesulfonic acid monohydrate, and 1500 ml. of ethanol was refluxed for 17 hr. The ester (115 g., 88%) was isolated in the usual manner as a colorless liquid, b.p. 132–134° (0.75 mm.), $n^{30}D$ 1.5565.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.06; H, 7.20; N, 6.74.

Acknowledgment.—The authors are grateful to C. R. McClure for capable assistance and to Q. Quick and his associates for microanalyses and spectral data.

(15) G. Plancher, B. Cecchetti, and E. Ghigi, *Gazz. chim. ital.*, **59**, 334 (1929); *Chem. Abstr.*, **24**, 112 (1930).

(16) E. Shaw and D. W. Wooley, *J. Biol. Chem.*, **203**, 979 (1953).

(17) By J. A. Durden of this laboratory.

The Action of Ozone on the Trimethyl Ester of Maleopimaric Acid. Terpenes. VI[1,2]

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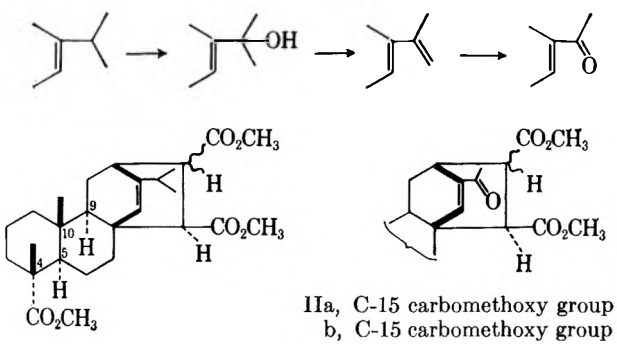
Ozonolysis of the trimethyl ester of maleopimaric acid (Ia) has been shown to yield, in addition to the previously reported α,β-unsaturated ketone II and diene III, the following crystalline products: a saturated ketone (IVa), an alcohol (IX), a γ-lactone (VIII), a δ-lactone (X), and two acids (XII and XIII). All of these compounds arise by attack of ozone on the isopropyl group, rather than the expected reaction at the double bond. Isolation of alcohol IX provides evidence for the oxidation scheme suggested earlier by Ruzicka and Kaufmann.[3] Nuclear magnetic resonance was employed in the structure and stereochemical elucidation of the various products.

In a study of the ozonolysis of the trimethyl ester of maleopimaric acid (Ia), Ruzicka and Kaufmann found that the reaction took an unusual course.[3,4] Oxidation of the isopropyl group occurred rather than cleavage of the double bond, as evidenced by the isolation of the α,β-unsaturated ketone II and the diene III.

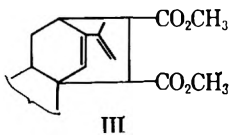
The stereochemistry of the Diels–Alder adduct of levopimaric acid and dimethyl maleate is now well established; the adduct possesses the absolute configuration as depicted in Ia.[5-9] An examination of a molecular model of Ia clearly indicates that both faces of the double bond are blocked, thus suggesting an explanation for the abnormal ozonolysis observed by Ruzicka and Kaufmann.[3] They suggested the following scheme to explain the reaction.



Ia, C-15 carbomethoxy group β
b, C-15 carbomethoxy group α

IIa, C-15 carbomethoxy group β
b, C-15 carbomethoxy group α

(The α-configuration signifies that the group lies behind the general plane of the ring system, where in the β-configuration the group lies in front of the plane.[10])

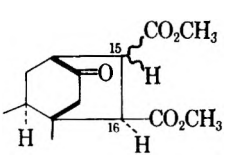


III

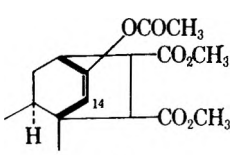
We have had occasion to repeat the ozonolysis of Ia and have found that IIa is indeed the major product of the reaction, but, in addition, six other crystalline compounds, previously unreported, have been isolated. All of these products arise by oxidation of the isopropyl group and offer strong support for the oxidation scheme proposed by the earlier workers.[3]

Following the previous procedure a solution of Ia in acetic acid was exposed to a steady stream of oxygen containing ozone for forty-eight hours. The crude product was separated into acidic (~20%) and neutral (~80%) fractions. The neutral fraction was further separated into nonketonic (~25%) and ketonic (~75%) fractions using Girard's T reagent. Hydrolysis of the Girard derivative gave the previously reported ketone IIa, together with a second ketone, IVa ($C_{24}H_{34}O_7$). Nuclear magnetic resonance spectroscopy proved to be particularly useful in arriving at the structure of IVa. Ayer, McDonald, and Stothers[6] have made a detailed study of the n.m.r. spectra of derivatives of maleopimaric acid. These workers observed that, in compounds such as I and II, the double bond at C-13–C-14 has a long range shielding effect on protons of the methyl group at C-10. These protons appear at ~δ 0.50 in compounds such as I and II, whereas the protons of the methyl group at C-4 appear at approximately δ 1.10. Removal of C-13–C-14 double bond results in a shift of the C-10 methyl protons to ~δ 1.0.

The signal at highest field in the n.m.r. spectrum of IVa appeared at δ 0.83, and the vinylic proton present in the spectra of Ia (δ 5.31) and IIa (δ 6.90) was absent. Both Ia and IIa gave a positive test for a double bond with tetranitromethane, but IVa did not. The n.m.r. spectrum of IVa also indicated the absence of an isopropyl group, and of a methyl group attached to a carbonyl group (as present in IIa at δ 2.36). On the basis of these facts together with the elemental analysis and infrared spectrum, it appeared likely that this ketone possessed structure IVa. Since the double bond in Ia was so hindered as to be unaffected by ozone, it seemed possible that the Baeyer–Villiger reaction on IIa would likewise proceed without attack on the double



IVa, C-15 β-carbomethoxy
b, C-15 α-carbomethoxy



V

(1) Generous support of this investigation by grant NSF-GP-233 of the National Science Foundation is gratefully acknowledged.

(2) "The Conversion of 2-Acetoxypulegone to Menthofuran. Terpenes. V," L. H. Zalkow, J. W. Ellis, and Sister M. Roger Brennan, *J. Org. Chem.*, **28**, 1705 (1963).

(3) L. Ruzicka and St. Kaufmann, *Helv. Chim. Acta*, **23**, 1346 (1940).

(4) Sir John Simonsen, "The Terpenes," Vol. 3, Cambridge University Press, Cambridge, England, 1952, p. 434.

(5) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem.*, **27**, 3535 (1962).

(6) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

(7) W. L. Meyer and R. W. Hoffman, *Tetrahedron Letters*, No. **16**, 691 (1962).

(8) W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.*, **83**, 2563 (1961).

(9) A. W. Burgstahler, H. Ziffer, and U. Weiss, *ibid.*, **83**, 4660 (1961).

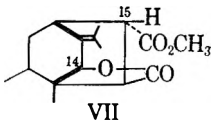
(10) Definitive rule for nomenclature of steroids, *ibid.*, **82**, 5577 (1960).

bond and would lead, therefore, to ester V. Hydrolysis of ester V should give IVa. This was found to be the case. Treatment of IIa with peroxytrifluoroacetic acid gave V in good yield. The n.m.r. spectrum of V showed the C-14 vinyl proton at δ 5.34, upfield from the C-14 proton in IIa, since in the latter compound the double bond is conjugated. The methyl protons of the acetoxy group in V appeared at δ 2.18 and the C-10 methyl protons at δ 0.75.

Acid-catalyzed hydrolysis of V at room temperature gave IVa identical in all respects with that isolated from the ozonolysis reaction. The optical rotatory dispersion curve of IVa showed a strong negative Cotton effect in methanol which was unchanged upon the addition of hydrochloric acid. This is characteristic of ketones which are unable to form ketals.[11] Thus, structure IVa is firmly established.

A second compound, VI, was isolated in low yield from the Baeyer–Villiger reaction. This substance was found not to be the tetramethyl ester resulting from the insertion of an oxygen atom on the methyl side of ketone IIa; the latter ester, XIIIa (following), was available for comparison. The infrared and n.m.r. spectra of VI showed it to be an alcohol and to contain three carbomethoxy groups. Since the C-10 methyl protons appeared at δ 0.67 in the n.m.r., the C-13–C-14 double bond was apparently still present. However, no vinylic protons were evident and an unexplained 3-proton signal was present at δ 3.05. No satisfactory structure for VI can be offered at this time.

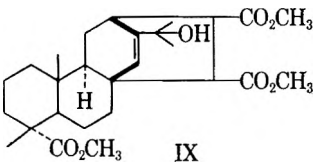
When Ia, IIa, and IVa were refluxed in alkaline solution, the resulting acids re-esterified with diazomethane, the respective, isomeric compounds Ib, IIb, and IVb were obtained. The trimethyl ester Ib was identical with that obtained from the Diels–Alder reaction between methyl abietate and fumaric acid followed by esterification with diazomethane. The more stable *trans* isomers have been assigned structures in which the C-15 carboxyl group is down (α), since Ayer, *et al.*,[6] reported the conversion of Ib to a γ-lactone, VII, with the oxygen atom attached at C-14. The corresponding isomer of VII with the C-15 carboxyl group up (β) has been reported from this laboratory previously.[5]



VII

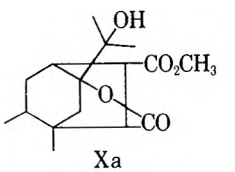
After chromatography on alumina, the nonketonic portion of the neutral fraction obtained from the ozonolysis of Ia yielded three previously unreported compounds, VIII (m.p. 220–221°), IX (m.p. 194–196°), and X (m.p. 264–265°). In addition, the ultraviolet spectrum of the noncrystalline part of this fraction indicated the presence of approximately 15% of the previously reported diene III.

Compound IX, when treated with phosphorus oxychloride in pyridine, gave a substance which had the same ultraviolet spectrum as III. The infrared and n.m.r. spectra of IX and its conversion to a diene with the ultraviolet chromophore of III support the structure shown later. The presence of a hydroxyl group was shown by the band at 3472 cm.$^{-1}$ in the infrared, and by n.m.r. (δ 5.0, which disappears on the addition of deuterium oxide). Three carbomethoxy groups were established by three sharp signals (three protons each) at δ 3.58, 3.60, 3.67 in the n.m.r., and by a band at 1727 cm.$^{-1}$ in the infrared. The double bond at C-13–C-14 was apparent from the position of the C-10 methyl protons at δ 0.62 and by the C-14 vinyl proton at δ 5.70. The double bond also gave a weak peak at 1638 cm.$^{-1}$ in the infrared. The two methyl groups flanking the carbon atom containing the hydroxyl group have n.m.r. signals at δ 1.22 and δ 1.28, downfield from where the isopropyl methyl protons appeared in I (δ 1.08). The isolation of IX provides strong support for Ruzicka's proposed oxidation scheme.

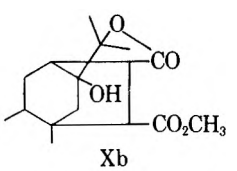


IX

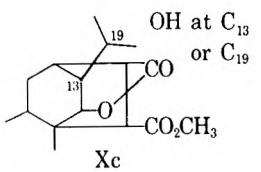
Compound X ($C_{26}H_{38}O_7$), obtained in very low yield, exhibited a hydroxyl group (3401 cm.$^{-1}$) and three carbonyl bands (1739, 1718, and 1691 cm.$^{-1}$) in its infrared spectrum. The band at highest wave length has been assigned to a δ-lactone and the other two are assigned to the A- and D-ring ester groups. Since X had no signals in its n.m.r. spectrum at field higher than δ 1.0, and gave a negative test with tetranitromethane, the absence of a double bond was concluded. On the basis of this evidence structures Xa and Xb are



Xa



Xb



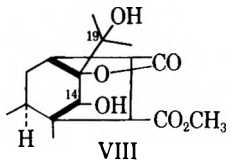
Xc

suggested for this compound. Another structure containing a δ-lactone (Xc) was not considered a likely possibility because of the absence of a signal in the n.m.r. corresponding to the C-14 proton.

The third crystalline compound isolated from the nonketonic fraction has been assigned structure VIII. Compound VIII exhibited a hydroxyl band (3448 cm.$^{-1}$) and a band due to a γ-lactone (1786 cm.$^{-1}$) in the infrared. The n.m.r. spectrum showed that it contained only two carbomethoxy groups and no C-13–C-14 double bond (tetranitromethane test was negative). Methyl protons of the isopropyl group were moved downfield (δ 1.35 and 1.47) showing that an oxygen atom was attached at C-19. The C-14 proton appeared at δ 4.35. If the lactone had been attached at C-14, then this latter proton would have been expected to give a signal at $\sim\delta$ 5.00; however, the attachment of a hydroxyl group at C-14 is completely consistent with the observed data.[5]

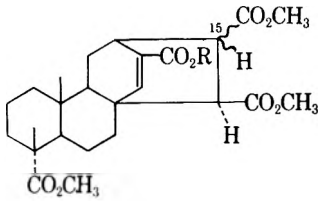
The acids XII and XIII were isolated from the acidic fraction of the ozonolysis product; after esterification

(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 143.



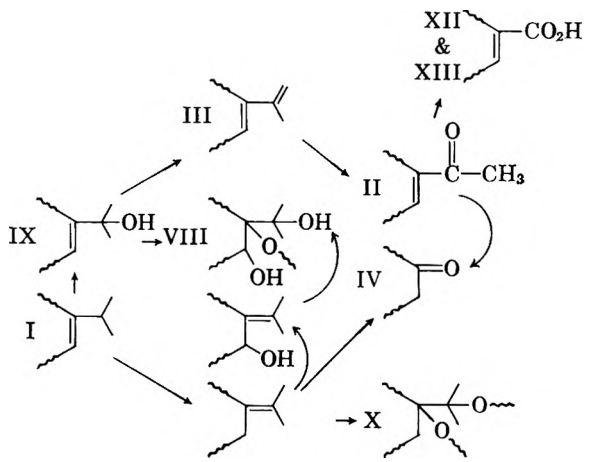
VIII

with diazomethane, they were separated by chromatography on alumina. The first material to be eluted from the column, XIIa, could also be prepared from XIIIa by alkaline isomerization followed by re-esterification. The haloform reaction of IIa, followed by esterification with diazomethane, gave XIIa identical in all respects with that isolated from the ozonolysis experiment. The n.m.r. spectra of XIIa and XIIIa were completely consistent with the suggested structures.



XII, C-15 α-carbomethoxy, R = H; XIIa, R = CH_3
XIII, C-15 β-carbomethoxy, R = H; XIIIa, R = CH_3

It is not possible to offer a detailed mechanism for the unusual ozonolysis observed in this case. However, it does appear likely that Ruzicka's original suggestion of a stepwise oxidation of the isopropyl group is valid. A scheme of oxidation as shown can be visualized.



Peracetic acid, formed by the prolonged action of ozone on the acetic acid solvent, may be the active oxidizing agent. If this were the case, then IV might arise from II *via* a Baeyer–Villiger reaction followed by hydrolysis in the work-up. However, XII and XIII must not arise from II by the action of peracetic acid, since in that case the methyl esters and not the free acids should have been isolated. Ketone IV may arise by a double bond migration to give an isopropylidine group, followed by cleavage of the double bond. Lactones VIII and X also may arise from the same intermediate by hydroxylation followed by lactonization. When a stream of oxygen containing no ozone was passed through an acetic acid solution of Ia under conditions identical to those used in the ozonolysis, no change in Ia occurred.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ 0) and deuteriochloroform as solvent. Ultraviolet spectra were obtained with the Beckman recording spectrometer, Model DK1.

Ozonolysis of Trimethyl Ester of Maleopimaric Acid (Ia).—The trimethyl ester Ia was prepared as previously described[6] and ozonized as follows. A rapid stream of ozone (approximately 3%) was passed through a solution of 29.8 g. of Ia in 225 cc. of glacial acetic acid for 48 hr. at room temperature. After the addition of 15 cc. of water, the solution was stirred for a short time and then taken to dryness on a steam bath using the water aspirator. The glassy yellow solid thus obtained was then separated into acidic and neutral fractions; it was dissolved in ether and the resulting solution was repeatedly extracted with 5% ice-cold sodium hydroxide solution until the alkaline extract was colorless. The ether layer, after drying over anhydrous sodium sulfate, was concentrated to give 22.7 g. of the yellow neutral fraction.

The aqueous sodium hydroxide extracts were combined, acidified with dilute hydrochloric acid, and extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the combined ether extracts were concentrated to yield 4.52 g. of glassy acidic fraction.

The Ketonic Fraction. Isolation of Ketones IIa and IVa.—A solution of 6.75 g. of previous neutral fraction in 70 cc. of anhydrous methanol containing 2 cc. of glacial acetic acid and 2.7 g. of Girard's T reagent was refluxed for 4 hr. The cooled reaction mixture was then poured into a solution of 2.8 g. of sodium bicarbonate in 280 cc. of water, and this solution was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to give 1.87 g. of the nonketonic fraction as a viscous gum. The separation of this fraction is described in the section on the nonketonic fraction.

The aqueous layer, which contained the ketones, was acidified by adding 10 cc. of 6 *N* hydrochloric acid. After standing for 1 hr., ketone IIa crystallized and was collected by filtration, washed with water, and dried to give m.p. 161–163° (3.5 g.). Two recrystallizations from methanol gave m.p. 163–169° (lit.[3] m.p. 168–169°); ν_{max}^{KBr} 1724, 1661, and 1610 cm.$^{-1}$; n.m.r. (p.p.m. downfield from tetramethylsilane), δ 0.50 (3 protons), 1.13 (3), 2.36 (3), and 6.90 (1).

The filtrate remaining after the removal of ketone IIa, on standing open to the atmosphere for 2 weeks, became turbid and then was extracted with ether. After washing with water and drying over anhydrous sodium sulfate, evaporation of the ether gave 1.1 g. of ketone IVa. Recrystallization from methanol gave 0.8 g., m.p. 193–194°; negative tetranitromethane test; ν_{max}^{KBr} 1745, 1740, and 1725 cm.$^{-1}$; n.m.r., δ 0.83 (3), 1.12 (3). This substance exhibited a strongly negative Cotton effect in methanol solution (*c* 0.0565) which was unchanged on the addition of a small amount of hydrochloric acid: $[\alpha]_{589}$ mμ −46°, $[\alpha]_{302}$ −1071°, $[\alpha]_{267}$ + 302°, $[\alpha]_{250}$ −250°.

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.33; H, 7.88. Found: C, 66.57; H, 7.95.

Ketone IVa also could be isolated by further acidification of the aqueous filtrate remaining after the removal of ketone IIa.

Alkaline Isomerization of IIa. Preparation of IIb.—A solution prepared by dissolving 0.34 g. of IIa in 10 cc. of methanol and 25 cc. of 2 *N* sodium hydroxide was refluxed for 10 hr. After cooling, it was diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the ether extract was concentrated to give the crystalline *trans* acid; after crystallization from aqueous acetic acid it had m.p. 287–289°; ν_{max}^{KBr} 3703–2127, 1709, 1661, and 1626 cm.$^{-1}$.

Treatment of the crystalline *trans* acid with ethereal diazomethane gave IIb as a viscous gum which could not be crystallized; n.m.r., δ 0.50 (3), 1.08 (3), 2.25 (3) and 6.88 (1).

Conversion of IIa into IVa.—A solution of peroxytrifluoroacetic acid was prepared by the dropwise addition of 3 cc. of trifluoroacetic anhydride to a suspension of 0.5 cc. of 90% hydrogen peroxide in 10 cc. of methylene chloride. This solution was added over a period of 15 min. to a stirred suspension of 7.86 g. of dry, finely powdered disodium hydrogen phosphate in a solution of 5.5 g. of ketone IIa in 30 cc. of methylene chloride. After addition

was complete, the solution was heated under reflux for 1 hr. The inorganic salts were removed by filtration and washed with methylene chloride. The combined methylene chloride layers were washed with 10% sodium carbonate, dried over anhydrous sodium sulfate, and the solution finally concentrated to give 5.4 g. of crude products.

Two recrystallizations from a mixture of methanol–dioxane gave 3.5 g. (61%) of V, m.p. 208–210°. The analytical sample of V obtained by recrystallization from methanol gave m.p. 210–212°; ν_{max}^{KBr} 1757, 1750, 1727, 1669 cm.$^{-1}$; n.m.r., δ 0.75 (3), 1.13 (3), 2.18 (3), 5.34 (doublet, 1 proton).

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.52; H, 7.61. Found: C, 65.41; H, 7.72.

Concentration of the mother liquor from which V was obtained gave a viscous gum which upon the addition of methanol gave 0.55 g. of VI. The analytical sample was obtained by recrystallization from methanol–acetone and had m.p. 268–271°; ν_{max}^{KBr} 3425, 1725 cm.$^{-1}$; n.m.r., δ 0.67 (3), 1.12 (3), 3.05 (3), and 4.10 (doublet which disappears on addition of deuterium oxide).

Anal. Calcd. for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 64.04; H, 7.55.

A solution containing 3.37 g. of V, 175 cc. of dioxane, 175 cc. of methanol, and 100 cc. of 6 *N* hydrochloric acid was allowed to stand at room temperature for 10 hr. Addition of 1200 cc. of water yielded 2.95 g. of ketone IVa, m.p. 191–193°. Recrystallization from methanol gave ketone IVa of identical melting and mixture melting point, infrared, and n.m.r. spectra, with IVa obtained by treatment of Ia with ozone.

Alkaline Isomerization of IVa. Preparation of IVb.—A solution prepared by the addition of 0.5 g. of IVa to 10 cc. of methanol, to which was added 15 cc. of 2 *N* sodium hydroxide, was refluxed for 3 hr. After cooling, it was diluted with 100 cc. of water and acidified with dilute hydrochloric acid, then extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the ether extract was concentrated to yield an amorphous solid which was treated directly with an excess of an ethereal solution of diazomethane. The crude product was crystallized from methanol to give 0.41 g. of ketone IVb, m.p. 148–149°; ν_{max}^{KBr} 1730 cm.$^{-1}$; n.m.r., δ 0.80 (3), 1.13 (3).

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.33; H, 7.88. Found: C, 66.56; H, 8.03.

The Nonketonic Fraction.—The fraction (1.87 g.) remaining after removal of the ketones with Girard's T reagent was chromatographed on neutral activated alumina (100 g.). Elution with 25% ether–75% benzene gave 1.26 g. of a viscous gum from which was obtained, on crystallization with benzene–*n*-heptane, 40 mg. of compound VIII. Further elution with ether gave 0.34 g. of a viscous gum which could be partially crystallized from aqueous methanol to give 70 mg. of compound IX. Rechromatography of the noncrystalline material (1.08 g.) on 60 g. of neutral activated alumina gave as crystalline material 35 mg. of ketone IVa (which apparently escaped reaction with Girard's T reagent), 10 mg. of a new crystalline compound X, and a further 50 mg. of VIII; these were all eluted with 25% ether–75% benzene. The remainder of the material could not be crystallized, but its ultraviolet spectrum (λ_{max}^{EtOH} 240 mμ, ϵ 2392) indicated the presence of 15% of the previously reported diene III (λ_{max} 240 mμ, ϵ 17,780).

Compound VIII.—This substance, obtained as described before, after recrystallization from benzene–*n*-heptane and drying at 140° and 1-mm. pressure for 10 hr., had m.p. 220–221° and gave a negative tetranitromethane test; ν_{max}^{KBr} 3448, 1786, and 1712 cm.$^{-1}$; n.m.r., δ 1.10, 1.17, 1.35, 1.47, 3.65, 3.70, 4.35, and 7.36.

Anal. Calcd. for $C_{26}H_{38}O_8 \cdot 0.5H_2O$: C, 64.05; H, 8.06. Found: C, 63.82; 64.12, H, 7.82, 7.99.

Maleopimaric acid and related substances have been shown to hold tenaciously solvents of crystallization and to form hydrates.[12]

Compound IX.—Recrystallization from methanol and drying for 12 hr. at 140° and 1-mm. pressure gave m.p. 194–196° and a positive tetranitromethane test; ν_{max}^{KBr} 3472, 1727, 1638 cm.$^{-1}$; n.m.r., δ 0.62, 1.15, 1.22, 1.33, 3.58, 3.60, 3.67, 5.0 (disappears with deuterium oxide), and 5.70 (doublet, 11 c.p.s.).

Anal. Calcd. for $C_{27}H_{40}O_7 \cdot H_2O$: C, 65.56; H, 8.55. Found: C, 65.83; H, 8.33.

(12) L. H. Zalkow and M. L. Corser, *Proc. Oklahoma Acad. Sci.*, **42**, 190 (1962).

Reaction of IX with Phosphorus Oxychloride.—A solution prepared by dissolving 0.132 g. of IX in 5 cc. of pyridine and 1 cc. of phosphorus oxychloride was heated on the steam bath for 4 hr., then allowed to stand at room temperature for 12 hr. The reaction mixture was diluted with water and then extracted with ether. The ether extract was washed with dilute hydrochloric acid, then with water, and finally dried over anhydrous sodium sulfate. Removal of the solvent yielded 0.070 g. of a glassy product which resisted attempts at crystallization. The infrared spectrum of this material showed no O–H absorption and gave λ_{max}^{EtOH} 240 mμ (log ϵ 3.84). Reported for diene III, λ_{max} 240 mμ (log ϵ 4.25).

Compound X.—Compound X, eluted from alumina with 15% ether–85% benzene, had m.p. 264–265° after recrystallization from benzene–*n*-hexane and drying for 10 hr. at 60° and 1 mm., and gave a negative test with tetranitromethane; ν_{max}^{KBr} 3401, 1739, 1718, and 1691 cm.$^{-1}$; n.m.r., due to the small size of sample available, a strong spectrum could not be obtained, but there were no signals at field higher than δ 1.0.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.50; H, 8.28. Found: C, 67.43; H, 8.01.

The Acid Fraction. Isolation of Tetraesters XIIa and XIIIa.—The glassy acidic fraction (4.52 g.) obtained as described earlier was treated with an excess of an ethereal solution of diazomethane. After the usual work-up, the crude ester mixture (4.7 g.) was chromatographed directly on 200 g. of neutral activated alumina. Crystallization of the glassy fraction, eluted with 10% ether–90% benzene, gave 160 mg. of XIIa, m.p. 155–156° (lit.[3] m.p. 152–153°); ν_{max}^{KBr} 1724, 1709 and 1634 cm.$^{-1}$; n.m.r., δ 0.50 (3), 1.10 (3), 3.57 (3), 3.64 (3), 3.70 (3), 3.74 (3), and 6.93 (1). The remainder of the noncrystalline material eluted from the column was rechromatographed on neutral alumina. Elution with ether–benzene and crystallization from benzene–hexane gave an additional 60 mg. of pure XIIa and 340 mg. of pure XIIIa. Recrystallization of XIIIa from *n*-hexane–benzene gave m.p. 177–178°; ν_{max}^{KBr} 1754, 1712, and 1628 cm.$^{-1}$; n.m.r., δ 0.53 (3), 1.11 (3), 3.49 (3), 3.52 (3), 3.64 (3), 3.75 (3), and 6.92 (1).

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.52; H, 7.61. Found: C, 65.93; H, 7.68.

The rest of the material eluted in the chromatography could not be crystallized. Infrared spectra of the noncrystalline fractions indicated the presence of hydroxyl-containing compounds and γ-lactones.

Preparation of XIIa and XIIIa by Alkaline Isomerization.—A solution prepared by mixing 40 mg. of XIIIa, 5 cc. of methanol, and 10 cc. of 2 *N* sodium hydroxide was refluxed for 8 hr. The cold reaction mixture was diluted with 50 cc. of water, acidified with dilute hydrochloric acid, and extracted with ether. The ether layer, after drying over anhydrous sodium sulfate, was concentrated to give a white solid, which was immediately esterified with a solution of diazomethane in ether. Evaporation of the ether and crystallization of the residue from ether–*n*-hexane gave 34 mg. of XIIa, m.p. 155–156° identical in all respects with that obtained as already described.

Preparation of XIIa from IIa by the Haloform Reaction.—Using the procedure reported by Ruzicka and Kaufmann[3] ketone IIa was oxidized with sodium hypobromite. The crude acid product was esterified directly with ethereal diazomethane to yield XIIa, m.p. 155–156°, m.m.p. 155–156° (lit.[3] m.p. 152–153°), identical in all respects with XIIa isolated as described earlier.

Alkaline Isomerization of Ia. Preparation of Ib.—A solution prepared by dissolving 0.30 g. of Ia in 10 cc. of methanol and 25 cc. of 2 *N* sodium hydroxide, was refluxed for 10 hr., then cooled, diluted with 150 cc. of water, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to give the crystalline acid. Recrystallization from aqueous acetic acid gave m.p. 252–253°, with previous melting at 190–210°, followed by resolidification.[12] This substance was identical in mixture melting point and infrared spectrum with the product obtained from the Diels–Alder reaction of abietic acid and fumaric acid.[12]

Treatment of the acid with ethereal diazomethane gave Ib as a viscous gum which could not be crystallized. The n.m.r. spectra of Ia and Ib were almost identical, the C-10 methyl protons appearing at δ 0.60, and the C-14 vinylic proton at δ 5.34.

The Synthesis of 5a,8,8-Trimethyl-3,10a-ethanoperhydrophenanthrene. Terpenes. VII[1]

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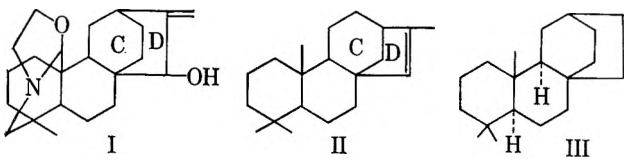
The synthesis of 5a,8,8-trimethyl-3,10a-ethanoperhydrophenanthrene (III, $C_{19}H_{32}$), which contains the same structure and relative stereochemistry as found in the diterpenoid skeleton of the atisine alkaloids is described.

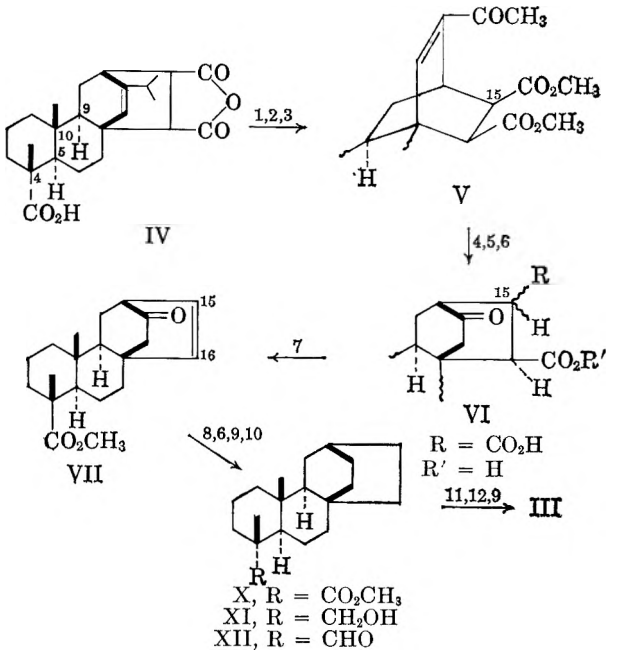
Atisine (I) and related diterpenoid alkaloids contain a bicyclo[2.2.2]octane C,D ring system, whereas the closely related Garrya alkaloids and the diterpenes of the phyllocladene group possess a bicyclo[3.2.1]-octane C,D ring structure.[2-5] A synthesis of phyllocladene (II) was reported recently by Turner and Ganshirt.[6] We wish now to report the synthesis of the hydrocarbon III, which contains nineteen of the twenty carbon atoms of the diterpenoid skeleton of atisine, and in addition contains a *trans-anti* ring fusion as found in the naturally occurring alkaloids.



I II III

Maleopimaric acid (IV) was the starting material for the synthesis of III. It is readily prepared from maleic anhydride and abietic acid, and the latter compound has been totally synthesized.[7,8] The stereochemistry shown for maleopimaric acid (IV) is now well established.[9-14] The conversion of IV into III involves three phases: first, the removal of the isopropyl group of ring C; second, removal of the anhydride moiety of ring D; and finally, conversion of the C-4 carboxyl group to a methyl.[15]

The ozonolysis of the trimethyl ester of IV has been found to proceed in an unusual manner, leading to attack on the isopropyl group rather than the hindered double bond, to give as the major product the methyl ketone V.[14,16] The Baeyer–Villiger reaction on V followed by hydrolysis led directly to the ketone VI.[14] Again, the hindered double bond in V was not affected;



1. PCl_5
2. CH_3OH
3. O_3
4. CF_3CO_3H
5. H^+
6. OH^-
7. $Pb[OAc]_4$
8. H_2, Pd/C
9. Wolff–Kishner
10. CH_2N_2
11. $LiAlH_4$
12. CrO_3, Pyridine

DIAGRAM 1

peroxytrifluoroacetic acid converted V into an enol acetate which on hydrolysis gave the desired ketone.[14] Thus, the isopropyl group of the starting material could be removed readily.

The most obvious method of removing 1,2-dicarboxyl groups is that of oxidative bisdecarboxylation. However, this method has been known to be quite unreliable.[17-19] A recent modification[20] of the oxidative bisdecarboxylation procedure which utilizes lead tetraacetate in pyridine was found to give VII in good yield. The n.m.r. spectrum of VII showed the protons of the C-10 methyl group at δ 0.93, no noticeable shielding effect being exerted by the carbonyl group. In contrast, the C-10 methyl protons in IV and V appear at δ 0.59 and 0.50, a much larger shielding effect resulting from the C-13–C-14 double bond. Thus the n.m.r. spectrum of VII provides additional support for the assignment of the double bond at C-15–C-16. The C-15 proton in VII appeared as a doublet at δ 6.07 (J = 3) and the C-16 proton as a sharp singlet at δ 6.13, while the protons of the C-4 methyl group appeared at δ 1.12 and the protons of the carbomethoxy group at δ 3.62.

(1) This work was supported generously by the National Science Foundation through grant GP-233.

(2) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. 16, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1958, p. 26.

(3) E. S. Stern, "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chap. 22, p. 473.

(4) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961).

(5) D. Dvornik and O. E. Edwards, *ibid.*, **14**, 54 (1961).

(6) R. B. Turner and K. H. Ganshirt, *Tetrahedron Letters*, No. **7**, 31 (1961).

(7) A. W. Burgstahler and L. R. Worden, *J. Am. Chem. Soc.*, **83**, 2587 (1961).

(8) G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962).

(9) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem.*, **27**, 3535 (1962).

(10) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

(11) W. L. Meyer and R. W. Hoffman, *Tetrahedron Letters*, No. **16**, 691 (1962).

(12) W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.*, **83**, 2563 (1961).

(13) A. W. Burgstahler, H. Ziffer, and U. Weiss, *ibid.*, **83**, 4660 (1961).

(14) L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2033 (1963).

(15) F. E. King, D. H. Godson, and T. J. King, *J. Chem. Soc.*, 1117, (1955).

(16) L. Ruzicka and St. Kaufmann, *Helv. Chim. Acta*, **23**, 1346 (1940).

(17) W. Von E. Doering, M. Farber, and A. Sayigh, *J. Am. Chem. Soc.*, **74**, 4370 (1952).

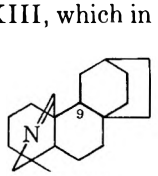
(18) C. A. Grob, M. Ohta, and A. Weiss, *Angew. Chem.*, **70**, 343 (1958).

(19) W. von E. Doering and M. Finkelstein, *J. Org. Chem.*, **23**, 141 (1958).

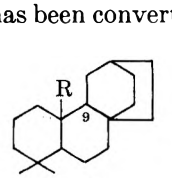
(20) E. Grovenstein, D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc.*, **83**, 1705 (1961).

The further conversion of VII to III was accomplished as follows. The double bond of VII was reduced smoothly using palladium-on-charcoal catalyst to give VIII. Under identical conditions the double bond of IV was unaffected. The C-10 methyl protons of the saturated ketone VIII appeared slightly upfield (δ 0.82) from the corresponding protons in VII, while C-4 methyl protons in VIII (δ 1.10) were in almost the identical position to the corresponding protons in VII. The carbonyl group showed an absorption band at exactly the same wave length (1724 cm.$^{-1}$) in both VII and VIII. Compound VIII was saponified to give the keto acid IX in order to prevent reaction of the ester grouping with hydrazine during the Wolff–Kishner reaction. The carbonyl group of the keto acid IX was removed smoothly by the Huang-Minlon procedure to give an acid which was converted directly into the ester X with diazomethane. The n.m.r. spectrum of X showed the C-10 methyl protons at δ 0.95, while C-4 methyl protons appeared at δ 1.10. Reduction of X with lithium aluminum hydride gave the alcohol XI, which showed two sharp, three proton singlets at δ 0.73 (C-4 methyl) and 0.97 (C-10 methyl), and a pair of doublets (J = 10 c.p.s.) at δ 2.98 and 3.36 corresponding to the two protons attached to the carbon bearing the hydroxyl group; the hydroxyl proton appeared at δ 2.18 and this signal disappeared on the addition of deuterium oxide. Oxidation of alcohol XI with chromic anhydride in pyridine gave aldehyde XII which was characterized by infrared only (ν_{max}^{KBr} 2680, 1724 cm.$^{-1}$) because of its rapid oxidation. Huang-Minlon reduction of XII gave hydrocarbon III (87%) as white needles, m.p. 86–87°, $[\alpha]D$ + 38.7°. The n.m.r. spectrum of III showed three sharp, three proton singlets at δ 0.82, 0.85, and 0.93 corresponding to the two methyl groups at C-4 and the one at C-10, respectively.

Hydrocarbon III, of absolute configuration shown, is potentially a useful intermediate for correlation with the atisine alkaloids. Atisine and ajaconine have both been degraded to the oxygen-free azomethine base, XIII, which in turn has been converted to XIV.[4]



XIII



XIV

R = CH_2OH, CHO, or CO_2H

The atisine alkaloids recently have been reported to possess a configuration at C-5, C-9, and C-10 which is the mirror image of that found in the resin acids and steroids.[21] Therefore, conversion of the carbonyl group of XIV (R = CHO) to a methyl group should give a hydrocarbon which is the enantiomer of III.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using the Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ 0) and carbon tetrachloride as solvent (except where indicated).

Preparation of VII.—A mixture of ketone VI[14] (R = β CO_2CH_3, R′ = CH_3) (11.1 g.), methanol (55 cc.), sodium hydroxide (2.1 g.), and water (66 cc.) was refluxed for 45 min. After cooling, the reaction mixture was diluted with water (250 cc.), acidified with 6 N hydrochloric acid, and finally extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 10.9 g. of glassy solid which solidified on the addition of ethyl acetate. The solid (VI, R = α CO_2H, R′ = H) had m.p. 260–268° after recrystallization from ethyl acetate–acetone; ν_{max}^{KBr} 3279 broad, 1730–1695 broad; n.m.r., δ 0.95 (3 protons), 1.22 (3), and 3.89 (3) (run in CF_3CO_2H).

The noncrystalline residue was converted to the previously described trimethyl ester VI (R = α CO_2CH_3, R = CH_3), with ethereal diazomethane; this latter ester could be partially saponified as described earlier to give VI (R = α CO_2H, R = H).

The diacid ester VI (R = α CO_2H, R = H), 8.1 g., was dissolved in 150 cc. of pyridine maintained at 70° and 8.8 g. of lead tetraacetate was added to the stirred solution under an atmosphere of nitrogen. After 10 min., when the initial reaction had subsided, an additional 4.4 g. of lead tetraacetate was added and the reaction mixture allowed to reflux for 1.5 hr. The pyridine was removed on the steam bath with a water aspirator and the dark brown residue was acidified with 6 N hyrdochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 6.3 g. of a brown solid. This solid was chromatographed on 100 g. of neutral alumina. Elution with 750 cc. of benzene and 9:1 benzene–ether (200 cc.) gave 3.46 g. of VII, m.p. 166–168°; positive tetranitromethane test; ν_{max}^{KBr} 1724, 1616, 1248 cm.$^{-1}$; n.m.r., δ 0.93 (3), 1.12 (3), 3.62 (3), 6.06 (doublet J = 3 c.p.s., 1 proton), and 6.13 (1).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.90; H, 8.92.

Hydrogenation of VII. Preparation of VIII.—The unsaturated ketone VII (3.46 g.) was hydrogenated with 0.37 g. of 10% palladium-on-charcoal catalyst in 130 cc. of ethyl acetate at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 45 min. Filtration of the catalyst followed by evaporation of the ethyl acetate gave a quantitative yield of VIII, m.p. 128–130°. The analytical sample, prepared by recrystallization from hexane, had m.p. 129–130°, and gave a negative tetranitromethane test; ν_{max}^{KBr} 1724, 1248 cm.$^{-1}$; n.m.r., δ 0.82 (3), 1.10 (3), and 3.60 (3).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.36; H, 9.49.

Preparation of X.—A suspension of 3.5 g. of the saturated keto ester VIII in a mixture of 100 cc. of 5% sodium hydroxide and 100 cc. of methanol was refluxed for 10 hr. The clear, cooled solution was diluted with 500 cc. of water and extracted with ether to remove unchanged VIII. The remaining aqueous alkaline solution was made acidic with 6 N hydrochloric acid and then extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the ether was evaporated to give 2.68 g. of keto acid IX, m.p. 238–240°.

Keto acid IX (2.63 g.) was added to a solution of 5 g. of potassium hydroxide in 30 cc. of diethylene glycol and 5 cc. of 95% hydrazine. The reaction solution was refluxed for 4 hr., after which the temperature of the mixture was raised to 240° by distilling water and hydrazine. Hydrazine (5 cc.) was again added to the residue and refluxing was continued an additional 12 hr. After the addition of 250 cc. of water, the reaction mixture was made acidic with 6 N hydrochloric acid and extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the ether extract was evaporated to give a solid which was immediately treated with an excess of an ethereal solution of diazomethane. Removal of the solid gave crude X, which on recrystallization from methanol gave 2.5 g. (95%) of pure X, m.p. 97–98°; ν_{max}^{KBr} 1724, 1253 cm.$^{-1}$; n.m.r., δ 0.95 (3), 1.10 (3), and 3.59 (3).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.54; H, 10.28.

Ester X (2.18 g.) in 75 cc. of anhydrous ether was added dropwise to a well stirred suspension of 600 mg. of lithium aluminum hydride in 100 cc. of anhydrous ether. After refluxing the reaction mixture for 3 hr., the excess hydride was decomposed by the addition of ethyl acetate and then water. The solution was acidified with cold 6 N hydrochloric acid and extracted with ether. The ether layer, after washing with water and drying over anhydrous magnesium sulfate, was evaporated to give 1.9 g. of residue which on crystallization from methanol gave 1.8 g. (91%) of XI (m.p. 129–130°). The analytical sample was ob-

(21) H. Vorbrueggen and Carl Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

tained by further recrystallization from *n*-hexane and gave m.p. 129–130°; ν_{max}^{KBr} 3311, 1038 cm.$^{-1}$; n.m.r., δ 0.73 (3), 0.97 (3), 2.18 (disappears on the addition of deuterium oxide), 2.98 (doublet, 1 proton), 3.36 (doublet, 1 proton).

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.93; H, 11.57.

A solution of 0.79 g. of XI in 10 cc. of anhydrous pyridine was added to a stirred mixture of 1 g. of chromic anhydride in 10 cc. of pyridine, and the entire mixture was then stirred at room temperature for 2 hr. After pouring into ice–water the solution was extracted with ether; the ether extract was washed successively with 5% hydrochloric acid and 5% sodium hydroxide, and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation and 0.7 g. of crude product was obtained. Crystallization from methanol gave the air-sensitive aldehyde (0.5 g.), m.p. 85–92°; ν_{max}^{KBr} 2680, 1724 cm.$^{-1}$. The aldehyde was reduced to III without further purification.

Potassium hydroxide (1.5 g.) was heated with 1.5 cc. of 95% hydrazine and 10 cc. of diethylene glycol until it dissolved. The aldehyde XII (400 mg.) was added to this solution and the reaction mixture was refluxed for 3 hr. Some of the product sublimed into the condenser during this period. Excess hydrazine and water were distilled until the temperature of the residue reached 240°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine (1.5 cc.) was again added to the residue and refluxing continued for an additional 12 hr. The reaction mixture, distillate, and ether washings were combined, added to water (150 cc.), and the entire mixture was extracted with ether. The ether extract was thoroughly washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave 350 mg. of hydrocarbon III, m.p. 75–79°. Recrystallization from acetone gave 320 mg., m.p. 84–86°. The analytical sample was obtained by two recrystallizations from acetone and had m.p. 86–87°; $[\alpha]_D$ +38.7° (*c* 0.036 in CCl_4); ν_{max}^{KBr} 2941, 1460, 1390, 1370 cm.$^{-1}$; n.m.r., δ 0.82 (3), 0.85 (3), and 0.93 (3).

Anal. Calcd. for $C_{19}H_{32}$: C, 87.61; H, 12.38. Found: C, 87.96; H, 12.41.

Pyrolysis of Trityl Esters Possessing β-Hydrogen. II[1,2]

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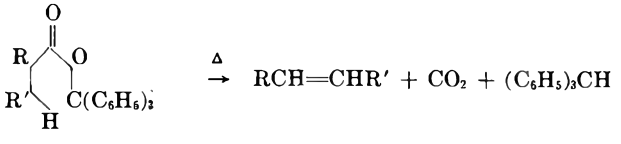
Pyrolysis of trityl propionate, trityl hydrocinnamate, and trityl pivalate has been examined over a temperature range of 225–430°. Nearly complete decomposition was observed in all examples whose reaction mixtures were analyzed meticulously by gas chromatography. Except in the case of trityl pivalate, the pyrolysates of the trityl esters were complex. The presence of tritan, tritanol, and benzophenone in the mixtures testified to the occurrence of both alkyl–oxygen and acyl–oxygen fission. Only with trityl pivalate was a degree of specificity observed, since isobutylene, carbon dioxide, and tritan were produced in high yields. Rather copious quantities of the respective acids were found in the other two pyrolysates, and only minor amounts of olefins were obtained. Mechanistic considerations involving radicals are proposed to explain the degradation results.

Trityl esters have been made readily accessible by a method described recently.[2] We now wish to report the pyrolysis studies of three trityl esters all of which possess at least one β-hydrogen atom in the acid portion of the molecule. Examination of the pyrolysate of trityl triphenylmethylacetate[5] appears to be the first recorded example in the area of trityl-substituted carbonyl compounds.[6] Tritan and carbon dioxide were the only components identified unequivocally in the reaction mixture.[5] Although stable at room temperature, trityl formate decomposed rapidly near 49° to give tritan and carbon dioxide.[7] Similarly, trityl fluoromethylacetate melted at 106° with decomposition but no details of a product analysis were presented.[8] In a study of the pyrolysis of several benzyl esters, Jones and Ritchie followed the thermal degradation of trityl benzoate.[9] The ester decomposed at 225° and 500° to give pyrolysates of nearly identical composition. The major pathway of cleavage involved aryl–acyl and alkyl–oxygen bond severance to give carbon dioxide and tetraphenylmethane. Minor products included benzoic acid, benzene, and triphenylmethane.[10]

Pyrolysis of acetates and xanthates has become a preferred method for preparation of olefins.[11] A decomposition process similar to that described in the acetate elimination reaction could be envisioned for the thermal collapse of a trityl ester whose structure is shown. Moreover, the absence of acidic products was an attractive possibility since a neutral medium at elevated temperatures would provide for minimum rearrangements.



Thermal decomposition of trityl propionate (1) was examined in a static system over the range 220–310°, which was above the boiling point of the ester. Contents of the pyrolysate were virtually unaltered at temperatures studied within the preceding range. Neither a bromine trap nor direct infrared analysis of the gaseous products from 1 indicated more than a trace of ethylene formed.

Clearly a concerted, intramolecular decomposition is not operative here as is known in acetate pyrolysis.[11] Table I contains pertinent data of a typical run on the type and weight of components in the pyrolysate from

(1)(a) We gratefully acknowledge the support of the National Science Foundation, grant G-19733. Partial support by the Oklahoma State University Research Foundation is acknowledged. (b) Presented at the Southwest Regional Meeting of the American Chemical Society, Dallas, Tex., December 6–8, 1962.

(2) For paper I in the series, see *J. Org. Chem.*, **27**, 3595 (1962).

(3) To whom inquiries should be addressed.

(4) National Science Foundation teacher training participant, summer, 1962; on leave from the Department of Chemistry, Augustana College, Rock Island, Ill.

(5) R. Anschutz, *Ann.*, **359**, 196 (1908).

(6) For a review of pyrolysis reactions of trityl ketones, see R. C. Fuson and K. D. Berlin, *J. Am. Chem. Soc.*, **81**, 2130 (1959).

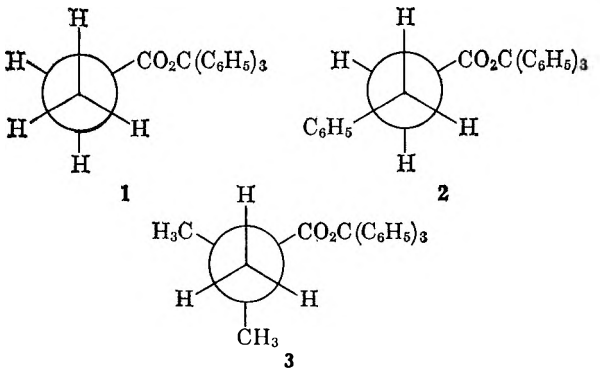
(7) S. T. Bowden and T. F. Watkins, *J. Chem. Soc.*, 1333 (1940).

(8) P. W. Sharp and N. Shephard, *ibid.*, 674 (1957).

(9) E. Jones and P. D. Ritchie, *ibid.*, 4141 (1960).

(10) The use of vapor phase chromatography was not referenced as an analytical tool in this research.

(11) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).



1. Below 220° little decomposition of **1** occurred after four hours since analysis of the residue by infrared spectroscopy and gas chromatography indicated nearly pure starting material. Noteworthy is the substantial amount of propionic acid isolated. This is reminiscent

$$\mathbf{1} \longrightarrow CH_3CH_2CO_2\cdot + (C_6H_5)_3C\cdot$$

of the behavior of other simple aliphatic propionates. For example, pyrolysis of **4** gave 4-methyl-2-butene and propionic acid in good yields.[12]

Similarly, *t*-butyl propionate (**5**) was converted to

$$(CH_3)_2CHCH_2CHOCCH_2CH_3 \longrightarrow C_2H_5CO_2H + (CH_3)_2CHCH{=}CHCH_3$$

4

$$(CH_3)_3COCCH_2CH_3 \xrightarrow{240^\circ} (CH_3)_2C{=}CH_2 + C_2H_5CO_2H$$

5

isobutylene and propionic acid at 240°.[13] Since decomposition was heterogeneous and not reproducible in clean glass vessels and some polymerization of isobutylene was implied, the reaction may be radical in nature.

Analysis of the pyrolysate from **1** revealed tritan, tritanol, benzophenone, benzene, styrene, ethylbenzene, ethane, ethylene, and butane as the major components in addition to propionic acid. However, some polymeric material also could be obtained and it was carefully isolated and characterized. The weight of products separated by column chromatography totaled more than 90% of the initial weight of ester. Such complexity in the pyrolysate has been reported when esters of triphenylacetic acid were thermally decomposed.[14] Tritan, carbon dioxide, and a mixture of saturated and unsaturated hydrocarbons were obtained, and an intermediate trityl radical was postulated.

Initial homolytic fission of the alkyl–oxygen bond to give trityl and propionoyloxy radicals seems probable for several reasons: (1) the low yield of ethylene detected precludes a concerted intramolecular abstraction of hydrogen by the trityl radical; (2) the high yields of tritan and propionic acid; (3) a probable low O–C bond dissociation energy[15]; and (4) the presence of benzophonone in the pyrolysate.[16] In addition, an effort was made to trap trityl radicals by conducting a stream of molecular oxygen through the melt of **1** at 300°. Discoloration of the liqiud in this experiment was essentially the same as when the pyrolysis was performed under nitrogen, namely from clear to yellow to red to brown. A marked increase in the amount of benzophenone was observed along with propionic acid in high yield. The interpretation here is that trityl radicals are oxidized to triphenylmethylperoxy radicals which might be expected to couple with trityl radicals to give trityl peroxide. However, trityl peroxide is known to decompose in solution below 150°[17] and thus it is reasonable that a similar reaction could occur in the melt to give phenyl radicals and benzophenone. Tritan also was formed, but the yield was reduced, as expected, by approximately 50%. Therefore, this observation lends credence to the postulate that initial homolytic cleavage occurs in pyrolysis of **1**, to give trityl and propionyloxy radicals.

Pertinent to this discussion are the results of Rembaum and Szwarc who investigated the degradation of propionyl peroxide in the gas phase near 245°.[18] In spite of the low, comparable O–O bond dissociation energy (*ca.* 30 kcal./mole) and the similar over-all rate of decomposition of acetyl peroxide and propionyl peroxide, it was suggested that the efficiency at which the corresponding acyloxy radicals decay must differ markedly. Loss of carbon dioxide from the propyl derivative and formation of butane was rationalized on the supposition that ethyl radicals were created; this was supported further by the detection of ethane and ethylene.[19] These same three hydrocarbons were isolated from the decomposition of **1** in addition to styrene and ethylbenzene. The data suggest that propionyloxy radicals from **1** decay by a route similar to that shown in the decomposition of propionyl peroxide. Formation of the latter two compounds may well be dependent upon the presence of phenyl radical whose evolution from collapse of triphenylmethoxy radical is well documented.[16] A general scheme for the pyrolysis under nitrogen is provided.

Propionic acid is formed early in the decomposition as it could be isolated from a static pyrolysis after one hour at 250°. The acid is reported to be stable to 460° and decomposes near 600°.[20] Stability of the alkyl radical, which results from loss of carbon dioxide, may

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

(13) E. Warrich and P. Fugassi, *J. Phys. Colloid Chem.*, **52**, 1314 (1948).

(14) J. F. Norris and A. Cresswell, *J. Am. Chem. Soc.*, **56**, 423 (1934).

(15) The low bond dissociation energy of trityl compounds has been determined in a few cases: see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chap. 18; C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957; M. Szwarc, *Proc. Soc.* (London), **A207**, 5 (1951); and W. A. Waters, "The Chemistry of Free Radicals," Oxford University Press, New York, N. Y., 1946.

Attempts were made to assemble a molecular model of **1** from Courtauld models. The system could only be made when the normal 0.5-Å. brass link was extended to 0.6 Å. The van der Waals envelope of each atom causes molecular crowding between the trityl group and the oxygen atoms of the carboxyl function with the normal brass links. It is implied that perhaps the O–C bond may be stretched somewhat. For example, this is the apparent situation in $(C_6H_5)_3CBr$ where the C–Br distance is 1.99 Å. as compared to C–Br value of 1.91 ± 0.06 in CH_2Br; see L. E. Sutton, "Tables of Interatomic Distances and Configurations in Molecules and Ions," S.P. 11, The Chemical Society, London, England, 1958.

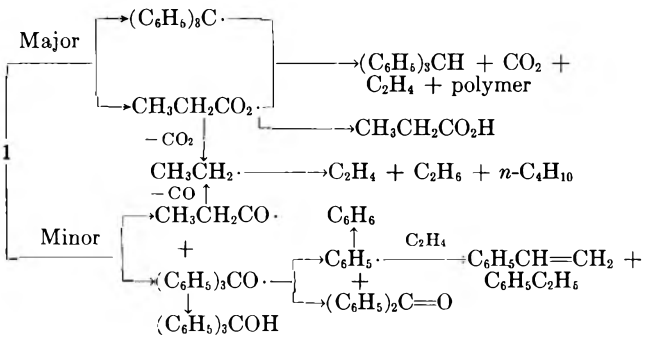
(16) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959); on p. 274 the simultaneous formation of phenyl radical is discussed in regard to the decomposition of triphenylmethoxy radicals.

(17) M. Gomberg, *J. Am. Chem. Soc.*, **22**, 757 (1900); see also ref. 16.

(18) A. Rembaum and M. Szwarc, *J. Chem. Phys.*, **23**, 909 (1955); for a general review of this type of decomposition, see J. O. Edwards, Ed., "Peroxide Reaction Mechanisms," Interscience Publishers, Inc., New York, N. Y., 1962.

(19) For a recent review on the degradation of ethyl radicals, see M. Matsuoka, P. S. Dixon, A. P. Stefani, and M. Szwarc, *Proc. Chem. Soc.*, 304 (1962).

(20) C. D. Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., New York, N. Y., 1929, Chap. 13.



SCHEME I

well govern the process. As will be seen later trityl pivalate undergoes thermal collapse rather specifically at 420° and pivalic acid is not isolated. For comparison, phenyl propionate is only slightly decomposed at 500° at short contact time but suffers complete degradation at 650°. Styrene, carbon dioxide, ethylene, ethane, phenol, and several other volatile products were recorded.[21] Although phenyl acrylate was suggested as the precursor of styrene,[20] the ester is known to yield acetylene, carbon monoxide, and phenol in a sealed tube at 320°.[22] However, the pyrolysate of phenyl propionate did contain some methyl ketene,[21] a product also possible from **1** if acyl–oxygen fission occurred and an α-hydrogen atom was removed. Tritanol was iso-

$$CH_3CH_2CO\cdot + R\cdot \longrightarrow CH_3CH{=}C{=}O + RH$$

lated from the reaction mixture, but a ketone or a ketene dimer was not detected in the evolved gases by infrared or gas chromatographic analysis with a hydrogen flame detection unit. Lifetime of the propionoyl radical is probably short and disintegration to carbon monoxide and ethyl radical would be predicted although trace quantities of ketenes may have been undetected.

Styrene and ethylbenzene most likely arise from disproportionation of two β-phenethyl radicals[23] which could conceivably result from attack of phenyl radicals on ethylene. Direct coupling of phenyl radicals with ethyl radicals is also possible since ethane and ethylene are gaseous products. Szwarc and co-workers have noted also that ethyl radicals produced from propionyl peroxide can add to aromatic systems to form an unknown hydrogen donor.[24] Ethylbenzene may be formed *via* this route. Careful analysis of the amount of benzene recovered in the residue and traps from pyrolysis of **1** revealed the quantity was always less than the total benzophenone obtained. Thus it is attractive to consider that the origin of phenyl radical occurs primarily from collapse of triphenylmethoxy radical. Consequently, the yield of ethylbenzene and styrene should never exceed the benzophenone isolated as is actually observed.

Infrared analysis of the glassy, polymeric material (melting range 70–90°) isolated from the residue of **1** contains peaks for the hydroxyl group (3448 cm.$^{-1}$), a carbonyl group (1715 cm.$^{-1}$ broad), and monosubstituted benzene (701 cm.$^{-1}$). Attempted methanolysis of the polymer in pure methanol did not result in the formation of a trityl methyl ether which would be expected if a trityl ester was present.[25] Solution of the polymer occurred slowly in cold, aqueous sodium hydroxide and suggested a carboxyl function. Esterification of the acidic group was accomplished in ethanol with concentrated hydrochloric acid as catalyst. The new polyester exhibited bands for a carbonyl group (1730 cm.$^{-1}$) and monosubstituted benzene (699 cm.$^{-1}$), but the hydroxyl band had vanished. In view of the infrared absorption for a monosubstituted phenyl group in the polymer and the fact that styrene is a component of the pyrolysate, the obvious assumption is for a copolymer structure. The infrared spectrum and physical appearance of the polymer and polyester also suggest an acrylate repeating unit.[26] Support of the postulated copolymer structure was afforded by comparison of its infrared spectrum with that of a copolymer prepared from ethyl methacrylate and styrene. Except for a few peaks of low intensity the spectra were nearly superimposable. Acrylic acid and styrene polymerize readily with radical catalysts[27] and by thermal initiation.[28]

The unsaturation necessary in the pyrolysate to provide the stoichiometry for hydrogen balance in the formation of tritan and propionic acid is partially accounted for by the monomers required in the copolymerization. Assuming styrene was formed by disproportionation of β-phenyl radicals with another radical, one-half mole of hydrogen would be produced per mole of styrene. Likewise, assuming propionic acid furnished one mole of hydrogen when converted to acrylic acid, a total of 0.025 mole of hydrogen made available can be calculated from data in Table I. Certainly, if the ratio of acrylic acid to styrene was greater than one in the copolymer, the value for total moles of hydrogen available would be increased. From weights of tritan and propionic acid in Table I, a total of 0.037 mole of hydrogen is calculable as needed to convert trityl radicals and propionyloxy radicals to the hydrocarbon and acid, respectively. The approximately 30% hydrogen deficiency cannot be due entirely in the residual styrene, and we estimate it may be found in the 5–10% (by weight) of trace materials unidentified.

Trityl hydrocinnamate (**2**) should possess active benzylic hydrogen and, consequently, styrene, carbon dioxide, and tritan might be anticipated as major products. Unfortunately, the pyrolysis residue is much more complex as indicated in the scheme with many parallelisms to the decomposition of trityl propionate (**1**).

(21) C. D. Hurd, P. Perletz, and S. S. Drake, *J. Org. Chem.*, **10**, 62 (1945).

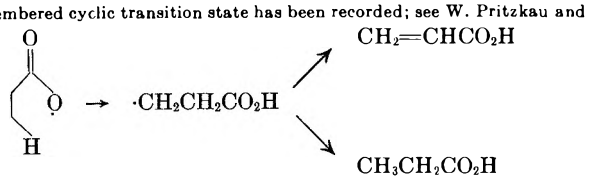
(22) See ref. 20, p. 532.

(23) W. A. Waters, "The Chemistry of Free Radicals," Oxford University Press, New York, N. Y., 1946, p. 212.

(24) J. Smid and M. Szwarc, *J. Am. Chem. Soc.*, **78**, 3322 (1956).

(25) See ref. 2 for a discussion of this reaction.

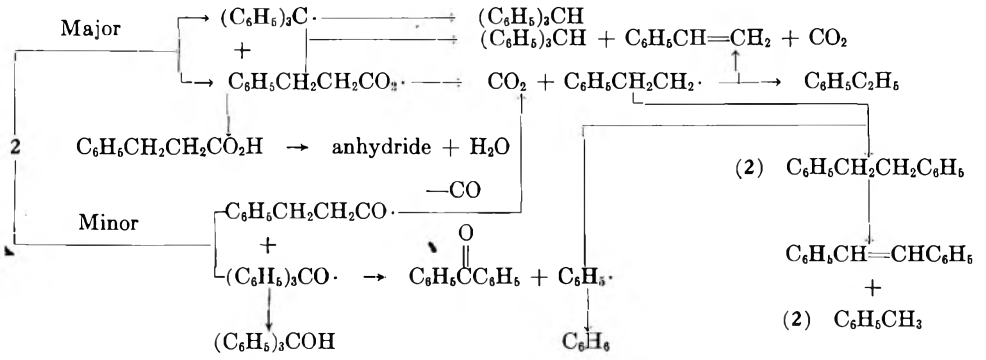
(26) A referee has suggested that the radicals produced in the initial homolytic bond cleavage process may never be free with special emphasis on the probable instability of the acyloxy radicals at the pyrolysis temperature. An intramolecular hydrogen transfer in the acyloxy radical *via* a five-membered cyclic transition state has been recorded; see W. Pritzkau and



K. Dietzsch, *Ber.*, **93**, 1733 (1960). Disproportionation of the alkyl radical could lead to propionic acid and acrylic acid in the case of ester **1**. To be sure the alkylcarboxylate radical could be attacked by trityl radical to give acrylic acid also. In any event the intramolecular hydrogen shift is reasonable and would reduce the acyloxy radical population, but not exclusively. For a summary of transfer reactions in radical processes, see T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, **27**, 3067 (1962).

(27) F. R. Mayo and F. M. Lewis, *J. Am. Chem. Soc.*, **66**, 1594 (1944).

(28) C. Walling, "Free Radicals In Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 180.



SCHEME 2

TABLE I

PYROLYSIS OF TRITYL PROPIONATE IN A STATIC SYSTEM

(Temperature, 300–310°; time, 6 hr.)

Products	Wt., g.	Moles product/ mole ester
Carbon dioxide	0.3343	0.12
Carbon monoxide	.2053	
n-Butane		
Benzene	.047	.01
Water	.021	.01
Ethylbenzene	.103	.01
Styrene	.010	.001
Propionic acid	2.120	.60
Tritan	10.952	.77
Benzophenone	1.408	.13
Tritanol	0.299	.001
Copolymer	2.886	.27
Trace materials (mixture)	0.316	
Total weight of products	18.8016	
Initial weight of ester **1**	18.960	

TABLE II

PYROLYSIS OF TRITYL HYDROCINNAMATE IN A STATIC SYSTEM

(Temperature, 290–310°; time, 6 hr.)

Products	Wt., g.	Moles product/ mole ester
Carbon dioxide	0.413	0.22
Carbon monoxide plus other volatiles	0.423	
Benzene	.053	.017
Toluene	.069	.018
Ethyl benzene	.021	.004
Styrene	.579	.13
Water	Trace	
Diphenylmethane	0.278	.04
1,2-Diphenylethane	.072	.009
trans-Stilbene	.830	.039
Hydrocinnamic acid / Hydrocinnamic anhydride	2.874	
Tritan	8.340	.807
Benzophenone	1.036	.147
Traces of unknowns plus tritanol	0.090	
Total weight of products	15.078	
Initial weight of ester **2**	15.680	

As in the propyl analog **1**, components from the minor route probably decay in part to products which also arise from the major alkyl–oxygen cleavage process. Table II contains a summary of the quantities of components found in the pyrolysis of **2**. Several compounds must serve as sources of hydrogen for the trityl radical since with the two main products, tritan and hydrocinnamic acid; the yield of acid did not exceed 50% although tritan was isolated in yield of 85–90%. Styrene could result from disproportionation of β-phenethyl radicals as described previously. In addition toluene and/or ethylbenzene are reported to yield small quantities of the olefin at high temperature.[29] Hydrocinnamic anhydride was found in the residue from **2**, which is in agreement with the recorded preparation of the anhydride from the acid.[30] Confirmation of this dehydration process to form the anhydride was achieved in this laboratory. Hydrocinnamic acid is relatively stable being only slightly decomposed at 370° in a sealed tube.[31a]

trans-Stilbene, 1,2-diphenylethane, and toluene make appearances in the pyrolysate of **2**, all of which probably originate from the acid portion of the ester.[31b] Related to this situation is the moderate yield of benzophenone found. The significance of this is that an equal amount of phenyl radical must have formed simultaneously. It was observed that in all runs the total yield of stilbene and toluene never exceeded the total return of benzophenone. The inference is that 1,2-diphenylethane may be created primarily *via* a coupling of β-phenethyl and phenyl radicals.

In view of the reported tendency of trityl peroxide to decompose in xylene,[16] an attempt was made to effect a decomposition of **2** in boiling *p*-xylene with ultraviolet light. A stream of dry oxygen was passed through a 50% solution of the ester which was irradiated with a 100-watt Hanovia lamp for seventy-two hours. As anticipated, hydrocinnamic acid and benzophenone were major constituents of the decomposition with more than 50% recovery of starting material.[32] The similarity of these results to those obtained from the oxidation of the melt of **1** is consistent with a radical mechanism for the decompositions.

Surprisingly, the exhaustive analyses of pyrolysates from **1** and **2** by gas chromatography did not divulge the presence of 1,1,1-triphenylpropane or 1,1,1,4-tetraphenylpropane, respectively. Two factors which must be considered as influential are the rate of hydrogen abstraction by the trityl group[33] and the availability of the alkyl radicals. Diffusion of radicals formed initially seems probable in view of the high yields of tritan and

(29) See ref. 20, pp. 103–104.

(30) D. Davidson and P. Newman, *J. Am. Chem. Soc.*, **74**, 1515 (1952).

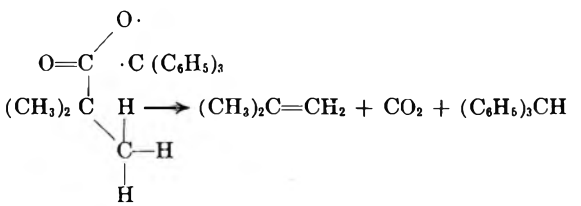
(31) (a) See ref. 20, p. 336; (b) see ref. 22, p. 98.

(32) Further results of the photolysis experiments will be reported at a later date.

(33) Rapid abstraction of hydrogen by trityl radical has been recorded on several occasions; see ref. 25, p. 52, and F. Benington, "Third Symposium on Combustion, Flame and Explosion Phenomena," Williams and Wilkens Co., Baltimore, Md., 1949, p. 448; also, D. Y. Curtin and T. C. Miller, *J. Org. Chem.*, **25**, 885 (1960).

respective acid in each case. Although trityl radical is known to add to aromatic systems,[34] no tetraphenylmethane was observed in pyrolysates of **1** and **2** is spite of the presence of benzene. All trace materials unidentified in each pyrolysate were extremely volatile and, therefore, probably of low molecular weight. Apparently the rate of hydrogen abstraction is great at pyrolysis temperatures. Moreover, loss of carbon monoxide and carbon dioxide is small which suggests a low population of alkyl radicals. Such an observation has been made recently with trityl benzoate in which presumably only aromatic hydrogen is available to trityl radical.[9] Considerable tritan was extracted from the pyrolysis residue.

Trityl pivalate as observed in Table III decomposed in a clean manner to give tritan, carbon dioxide, and isobutylene in high yields. Remarkably little decomposition occurred below 300° in a static system after three hours.[35] However, a smooth pyrolysis resulted at 430° in a rapid flow system (see Experimental). Since pivalic acid is known to be stable at 450°,[12] it probably does not form in the pyrolysis of **3**. The



marked affinity of trityl radical to abstract hydrogen prompts an immediate postulation that the decomposition involves attack of this radical on pivaloyloxy radical. A particularly attractive feature of this theory is that it allows for a reasonable explanation for the high yields of all three products. Some charring does occur in the pyrolysis chamber, and the yields of products were influenced by the degree of charring. Courtauld molecular models imply a close proximity of the trityl moiety to a hydrogen atom on a methyl group. In view of the ease of formation of trityl radical in esters **1** and **2**, a completely concerted mechanism is unattractive. Whether or not carbon dioxide is lost with simultaneous abstraction of hydrogen to yield isobutylene cannot be stated definitively. It should be pointed out, however, that the *t*-butyl radical, if formed, could be expected to abstract hydrogen as has been shown in the photolysis of trimethylacetaldehyde.[36]

TABLE III

PYROLYSIS OF TRITYL PIVALATE IN A RAPID FLOW SYSTEM

(Temperature, 430 ± 10°.)

Products	Wt., g.	Moles product/mole ester
Tritan	12.484	0.921
	2.6656	.858
Isobutylene	1.9639	.804
Carbon dioxide		
Tritanol	0.9114	.056
Benzophenone and biphenyl	Trace	
Initial weight of ester **3**	19.1165	

(34) R. A. Benkeser and W. Schroeder, *J. Am. Chem. Soc.*, **80**, 3314 (1958).

(35) Traces of pivalic acid and tritan were isolated but infrared analysis of the residue indicated nearly pure starting material **3**.

(36) J. B. Conant, C. N. Webb, and W. C. Mendum, *J. Am. Chem. Soc.*, **51**, 1246 (1929).

No isobutane was found in the gaseous products of **3**. Tritanol and benzophenone in the pyrolysate testify to a minor acyl-oxygen fission process.

Experimental[37]

Trityl Esters.—The esters were prepared as described previously.[2] Some improvements in yields were noted when anhydrous carbon tetrachloride was used as a solvent.

Pyrolysis of Trityl Propionate (1) and Trityl Hydrocinnamate (2) in a Static System.—The pyrolyses were conducted in a Pyrex system in a nitrogen atmosphere. All volatile components were swept into Dry Ice–acetone traps except for components gaseous at room temperature which were collected over salt water or in liquid nitrogen traps. Liquid components were analyzed directly on the hydrogen flame gas chromatographic unit. Gases were analyzed by gas chromatography and infrared spectrometry. Solution of the individual residues was essentially complete in ether–benzene. Extraction of the acid (and anhydride in **2**) was accomplished with a known quantity of standard aqueous base. Titration of the excess base and salt with standard hydrochloric acid afforded standard titration curves for propionic and hydrocinnamic acids, respectively. This was checked with the known acids in this laboratory. In the pyrolysate of **1** the copolymer also dissolved in aqueous base, but was precipitated by the addition of acid.

Analysis of the extracted residue was completed by gas chromatography. Columns which proved superior were 10% SE-30 on Chromosorb W, 20% Apiezon L on Chromosorb W, and Lac-32-728 on Chromosorb W. Gaseous products could be analyzed reasonably well with a 10% di-*n*-butyl phthalate on Fluoropak 90. Pure samples of all components were injected to verify all retention times under a particular set of conditions with a column. The weights given in Table I and II for products obtained from **1** and **2** were typical of more than a dozen runs in each case. Some fluctuation of individual yields of products was noted over the range 225–330° but no other compounds were detected by the methods employed. Carbon dioxide was absorbed in an Ascarite trap and weighed. Carbon monoxide was detected by means of infrared analysis as mentioned and by reaction with palladium chloride.[38] Chromatography of the residues was most convenient on alumina with a cyclohexane–benzene–petroleum ether system.

Interestingly, the liquid β-form of benzophenone was obtained directly from the pyrolysates of **1** and **2** rather than the more common α-modification which melts at 48°.[39] Since the α-form can be distilled at 190° (15 mm.),[40] it is possible that the β-form is produced specifically although the temperature differential may be significant here.[39] Cristol and Leffler have noted the decomposition of trityl nitrate in a sealed tube at 110° gave the α-form of benzophenone from the collapse of triphenylmethoxy radicals.[41]

Pyrolysis of Trityl Pivalate (3).—Since little decomposition of **3** occurred below 300° in 3 hr. in a static system, a rapid flow apparatus was utilized. It consisted of a Vycor tube mounted vertically in heavy-duty hinged, electric, combustion tube furnace; i.d., 2.375 in.; length, 12 in. An addition funnel with gas inlet tube was placed on top of the combustion tube which was packed with Pyrex helices; o.d., 0.094 in. Ice, Dry Ice–acetone traps, an Ascarite absorber, and a liquid nitrogen trap were used to capture all products. A calibrated pyrometer controller[42] maintained the pyrolysis temperature of 430 ± 10° during the runs. A 10% solution of the ester in benzene was added dropwise (*ca.* 1.5 ml. per minute) over a 5-hr. period to a helium-purged system.

(37) All melting points are corrected. All boiling points are uncorrected. All infrared spectra were recorded on a Beckman IR-5 and/or IR-7 instrument. All gas chromatographic analyses were performed with a Wilkens Model A-550 Hy Fi hydrogen flame unit and a Wilkens Model A-350 with a dual column system and linear temperature programmer.

(38) V. J. Altieri, "Gas Analysis," American Gas Association, Inc., New York, N. Y., 1945, p. 257.

(39) Isomerization of the α-form to the β-form was observed on a silicone column at 210° in a gas chromatograph. When heated at 220°, the α-form is converted to the β-compound (80%); see K. Schaum, K. Schaeling, and F. Klausing, *Ann.*, **441**, 161 (1916).

(40) C. S. Marvel and W. M. Sperry, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 95.

(41) S. J. Cristol and J. E. Leffler, *J. Am. Chem. Soc.*, **76**, 4468 (1954).

(42) Model 478 is available from the Bristol Co., Waterbury 20, Conn.

Tritan, tritanol, benzophenone, and biphenyl were caught in the ice trap, but isobutylene was found in all containers including the liquid nitrogen trap. After rinsing the column with dry benzene, the solution of pyrolysate in the ice trap was made up to a total volume of 500 ml. The solid products caught in the ice trap were chromatographed on alumina as described previously, and were analyzed by gas chromatography with columns cited earlier. The remaining cold traps were warmed and purged with helium through a gas scrubber to dissolve residual isobutylene in benzene. All solutions were combined and made up to a volume of 500 ml. with benzene. Isobutylene proved more difficult to determine, but with meticulous effort a modification of the Fritz and Hammond method[43] was developed which gave reproducible results. Bromine was generated in an evacuated system by introducing 5 ml. of 6 *N* sulfuric acid into the bromination flask containing a known quantity of standardized potassium bromate solution (*ca.* 15% excess). After 3 min. a sample (20-ml. aliquot) from the ice trap solution was introduced into the dark bromination flask. Enough benzene was added to bring the volume to 40 ml. and an additional 20 ml. of acetic acid was introduced. The mixture was stirred and shaken vigorously for 9 min. and 15 ml. of 20% potassium iodide solution was added. After another minute, vacuum was alleviated in the system, and the excess free iodine was titrated at once with standard sodium thiosulfate solution to a starch end point. Triplicate runs were performed on aliquots from both the ice traps and the combined contents of the other cold traps. In several determinations an average yield of 86% was obtained for isobutylene. Duplicate blanks were also run in benzene to check the fading end point and to establish the small correction factor for the end point observed in titration of the aliquot from the ice trap solution. Moreover, to ascertain the reliability of the method a sample of 1-heptene (98% pure by gas chromatography) served as a test substrate. An average recovery of 97% was realized. To complete the determination, a sample of the pyrolysate was treated with bromine and 1,2-dibromo-2-methylpropane was actually isolated from the mixture. Comparison of the dihalide with the bromination product from pure isobutylene showed them to be identical.

(43) J. L. Fritz and G. S. Hammond, "Quantitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 275.

Polarographic Reduction of Some Alkyl-, Alkylene-, and Polymethylnaphthalenes[1]

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Polarography was conducted on naphthalene and twenty-seven substituted naphthalenes (bearing monoalkyl, dimethyl, trimethyl, allyl, and alkylene substituents) in 0.1 *M* tetra-*n*-butylammonium iodide in 75% dioxane–water. Using naphthalene as a standard of comparison the change in the half-wave reduction potential, $-\Delta E_{1/2}$, for the single wave obtained for each of the derivatives is positive, consistent with a decrease in ease of electroreduction due to the substituent(s). For the monoalkyl derivatives plots of $-\Delta E_{1/2}$ *vs.* σ^*, the polar substituent constant, for the 1- and for the 2-series are linear. There is no indication of a steric effect due to the bulkiness of the alkyl group. For dimethylnaphthalenes approximate additivity in $-\Delta E_{1/2}$ exists, except for the cases of the 1,8- and 2,3-isomers, where an enhancement potential must be included in order to retain additivity. For trimethylnaphthalenes, acenaphthene, and hexahydropyrene, $-\Delta E_{1/2}$ is an additive function of the effects of the individual substituents and the over-all geometric pattern of substitution.

In a previous paper[3] data were reported on the polarographic reduction of some alkyl- and polymethylanthracenes in 0.1 *M* tetra-*n*-butylammonium iodide in 75% dioxane–25% water as solvent–electrolyte. The present paper concerns an extension of this study to polarographic reduction of alkyl-, allyl-, alkylene-, and polymethylnaphthalenes.

Used in these studies were the parent naphthalene itself, as well as nine monoalkyl, the two allyl, all of the ten possible dimethyl, four trimethyl, and two alkylene derivatives. Six of these compounds were synthesized by new or modified procedures. Thus, the allylnaphthalenes were obtained by coupling the naphthylmagnesium bromides with allyl bromide (62% crude yield for 1-isomer). Catalytic hydrogenation of the allyl substituents occurred readily using glacial acetic acid and platinum to form the *n*-propylnaphthalenes. 1-*t*-Butylnaphthalene resulted in 13% yield from dehydration (with alumina at 380°) and subsequent dehydrogenation of the carbinol obtained by interaction of α-tetralone and *t*-butylmagnesium bromide. Chloromethylation of 1,8-dimethylnaphthalene produced 1-chloromethyl-4,5-dimethylnaphthalene, hydrogenolyzable to 1,4,5-trimethylnaphthalene in good yield.

Polarography was conducted in the same manner as employed for the anthracenes. Polarograms, obtained for three different concentrations of each hydrocarbon, showed the presence of only one wave out to a cathode potential of *ca.* −2.8 v. (*vs.* the saturated calomel electrode), where the solvent–electrolyte undergoes reduction. In contrast to the regular waves found for the anthracenes the upper portions of the sigmoid-shaped waves for the naphthalenes increased linearly with increasing *E*, the applied cathode potential, instead of levelling off or paralleling the slightly rising line for the residual current. Onset of electrolysis of the solvent–electrolyte prevented checking this upper linear portion over a sufficiently extensive range in *E* so as to allow determination of the true asymptotic diffusion current, i_d. Under these circumstances an approximate diffusion current, i_d' (where $i_d' < i_d$), was measured (*cf.* Experimental) and used in calculations. Polarographic diffusion current constants, I_d', average values (reproducible to ±3 mv.) of $-E_{1/2}$, and values of $-\Delta E_{1/2}$ (the difference between $-E_{1/2}$ for a substituted naphthalene and that for naphthalene itself as a standard of comparison) are presented in Table I. On the basis of the fact that values of I_d' do not vary markedly from one compound to another it is presumed that all of the waves correspond to the uptake of two electrons (as found by coulometry for naphthalene)[4] to produce 1,4-dihydronaphthalenes, compounds which should not be

(1) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research under contract AF 49(638)-473. It is paper V in the series on polarography of aromatic hydrocarbons. For paper IV see ref. 3.

(2) Research Associate, 1959–1962.

(3) L. H. Klemm, A. J. Kohlik, and K. B. Desai, *J. Org. Chem.*, **28**, 625 (1963).

(4) L. H. Klemm, C. D. Lind, and J. T. Spence, *ibid.*, **25**, 611 (1960).

TABLE I

POLAROGRAPHIC AND OTHER DATA FOR SOME ALKYL-, ALLYL-, AND ALKYLENE-SUBSTITUTED NAPHTHALENES

Substituent(s) on naphthalene	Half-wave reduction potential, $-E_{1/2}$ (v. *vs.* S.C.E.)	$\frac{i_d'}{Cm^{2/3}t^{1/6}}$ (μamp. mmole^{-1}-l. mg.$^{-2/3}$ sec.$^{1/2}$)	$-\Delta E_{1/2}$[a] (mv.) Found	$-\Delta E_{1/2}$[a] (mv.) Calcd.[b]	$\Delta\nu$[c] (cm.$^{-1}$) Most intense central band[d]	$\Delta\nu$[c] (cm.$^{-1}$) Longest wave length α-band[e]	Mean methyl affinity,[f] k_2/k_1	Picrate stability constant[g] (l. mole^{-1})
None	2.437	3.71	0	0	0	0[l]	9.4	1.13
1-Methyl	2.458	3.87	21	19	900	300[l]	8.1	1.47
1-Ethyl	2.470	3.24	33	(33)[j]	900	300[l]	8.0	1.41
1-*n*-Propyl	2.471	3.24	34	(34)[k]	1000	300[l]		
1-*t*-Butyl	2.493	3.10	56		800	200		
1-Allyl	2.447	3.46	10		900	300		
2-Methyl	2.460	3.06	23	21	200	800[l]	13.0	1.76
2-Ethyl	2.468	3.05	31		200	700[m]	8.9	1.45
2-*n*-Propyl	2.471	3.03	34		200	800		
2-*i*-Propyl	2.476	2.97	39		−100	800		1.35
2-*t*-Butyl	2.482	2.67	45		−100	600		1.16
2-Allyl	2.444	3.13	7		0	800		
1,2-Dimethyl	2.479	3.01	42	40	1500	1100[l]		
1,3-Dimethyl	2.483	3.19	46	40	1100	1100[l]		
1,4-Dimethyl	2.471	3.28	34	38	1800	1000[l]		
1,5-Dimethyl	2.475	3.99	38	38	1400	1000[l]	5.8	
1,6-Dimethyl	2.476	3.03	39	40	900	1100[l]		
1,7-Dimethyl	2.469	2.86	32	40	800	1100[l]		
1,8-Dimethyl	2.521	3.69	84	38	1400	1100[l]		
2,3-Dimethyl	2.501	2.87	64	42	600	700[l]	10.5	
2,6-Dimethyl	2.476	3.22	39	42	−100	1300[l]	13.9	
2,7-Dimethyl	2.485	3.09	48	42	100	1000[l]		
1,3,7-Trimethyl	2.496	3.03	59	56	800	1600[n]		
1,4,5-Trimethyl	2.529	3.23	92	99	2200	1600[n]		
2,3,5-Trimethyl	2.515	2.67	78	74	1100	700		
2,3,6-Trimethyl	2.523	2.81	86	88	600	1300		
1,8-Dimethylene[h]	2.549	3.57	112	(112)[j]	1800	1000[l]	4.7	
1,8;4,5-Bis(trimethylene)[i]	2.66	...	220	(220)[k]	2700	1800		

[a] Compared to $E_{1/2}$ for naphthalene taken as a standard. [b] By means of equations 2 and 3 in text, where δ_j is taken as zero for mono- and disubstituted naphthalenes only. [c] Shift from corresponding band for naphthalene (measured in alkane or cyclohexane solvent) taken as a standard of comparison. [d] In naphthalene this band falls at 274.5 mμ (36,500 cm.$^{-1}$). It is designated as an α'-band (E. Clar, "Aromatische Kohlenwasserstoffe," Springer Verlag, Berlin, 1952, p. 134) and as a ^1L_a-band [J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949)]. [e] In naphthalene this band falls at 311 mμ (32,200 cm.$^{-1}$). It has been designated as a ^1L_b-band by Platt (footnote *d*). [f] See ref. 12. [g] See ref. 15. [h] Common name, acenaphthene. [i] Common name, 1,2,3,6,7,8-hexahydropyrene. [j] The value calculated for acenaphthene is based on the assumption that acenaphthene ≃ 1,8-diethylnaphthalene. [k] The value calculated for hexahydropyrene is based on the assumption that hexahydropyrene ≃ 1,4,5,8-tetra-*n*-propylnaphthalene. [l] Solvent, isooctane; American Petroleum Institute, "Catalog of Ultraviolet Spectral Data." [m] Solvent, cyclohexane; Ramart-Lucas and M. J. Hoch, *Bull. soc. chim.* (France), [5] **19**, 422 (1952). [n] Solvent, petroleum ether; E. Heilbronner, U. Fröhlicher, and P. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949).

further electroreducible under the experimental conditions used. If the electroreducible and thermodynamically more stable 1,2-dihydronaphthalenes had been formed as intermediates the reduction wave should have involved uptake of four electrons.[5] In Fig. 1, I_d' is plotted *vs.* the total number of carbon atoms in the side chain(s) on the naphthalene ring. It is apparent that compounds containing α-substituents only have higher values of I_d' than do those of the same molecular weight bearing one or more β-substituents. From the polarogram for the most dilute solution of each hydrocarbon, a plot (over the region of the reduction wave) was made of E *vs.* $\log\left[\frac{(i_d' - i)}{i}\right]$. All plots conformed closely to straight lines of slope 0.0519 ± 0.0078 (average 0.0514).[6]

Observation of Table I shows that all of the substituted naphthalenes studied were more difficultly electroreducible than naphthalene itself. For the monoalkyl- and allylnaphthalenes (except the *t*-butylnaphthalenes) there is no experimentally significant difference between $-\Delta E_{1/2}$ for corresponding 1- and 2-isomers. Again, as in the case of alkylanthracenes, relative conjugative power of the aryl group would thus seem to be of little or no pertinence in determining electroreducibility (as measured by $E_{1/2}$) of an alkyl-substituted alternant arene. Comparison of data for methyl or ethyl derivatives in both arene series shows the order 2-alkylanthracene > 2-alkylnaphthalene ≃ 1-alkylnaphthalene > 9-alkylanthracene ≃ 1-alkylanthracene in $-\Delta E_{1/2}$ from the corresponding parent arene.

In Fig. 2 are plotted values of $-\Delta E_{1/2}$ for the monoalkylnaphthalenes *vs.* Taft's polar substituent constants σ^* for the alkyl groups.[7] Excluding the point for naphthalene itself (R = H), the data fit two straight lines within the accuracy of the experimental method. As with the alkylanthracenes these lines fit equation 1.[3]

(5) It is possible that i increases following the reduction wave due to partial conversion of 1,4-dihydronaphthalenes to 1,2-dihydronaphthalenes at the high negative potentials involved.

(6) L. Meites and Y. Israel, *J. Am. Chem. Soc.*, **83**, 4903 (1961).

(7) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 13.

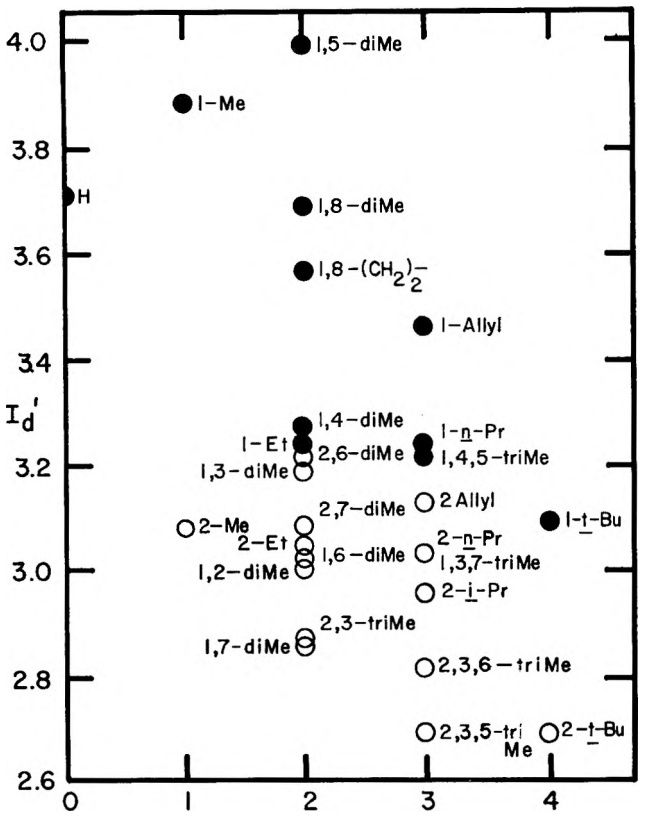

Fig. 1.—Plot of apparent polarographic diffusion current constant, I_d', *vs.* the total number of carbon atoms in the side chain(s) of alkyl- and alkylene-substituted naphthalenes.

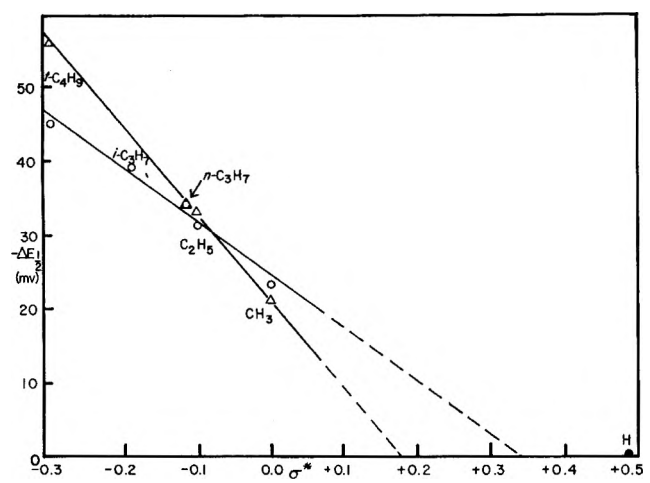

Fig. 2.—Plot of the difference between the polarographic half-wave reduction potential of an alkylnaphthalene and that of naphthalene *vs.* Taft's polar substituent constant for the alkyl group. Circles are for 2-alkyl groups; triangles for 1-alkyl groups.

$$\frac{n\mathcal{F}}{2.303\,RT}\,\Delta E_{1/2} = \rho^*(\sigma^* - c) \qquad (1)$$

where (if n is taken as 1) ρ^* equals +1.2 for the 1-alkylnaphthalene series (the same as for the combined 1- and 9-alkylanthracene series) and equals +1.9 for the 2-alkylnaphthalene series [as compared to +1.6 for the second wave of 1-alkyl-1-(2-naphthyl)ethenes[8] and to +0.58 for the 2-alkylanthracene series], and c is a constant which represents the intercept on the σ^* axis in each case. The considerable difference between the 2-alkylanthracene series ($c \simeq +1.0$, *i.e.*, $c > \sigma^*$ for H), on the one hand, and the four other series (c varies from +0.18 to +0.34, *i.e.*, $c < \sigma^*$ for H), on the other, is readily apparent. The fact that ρ^* has a positive value in every case is consistent with the action of alkyl groups in increasing electronic charge in the π-system and, hence, in making more difficult the addition of an electron during the polarographic process.[9]

From Table I one notes that the allyl substituent shows a much smaller $-\Delta E_{1/2}$ than does the corresponding *n*-propyl (or even the methyl) group. It is clear that the low value in $-\Delta E_{1/2}$ cannot result from the transformation, allyl (unconjugated) → propenyl (conjugated), for then the product should exhibit two waves (in contrast to only one found) with the first wave at $-E_{1/2} < 2.2$ v.[10] and I_d' should be nearly twice as large as found (corresponding to the uptake of four electrons rather than of two). A σ^* value for the allyl group is not available from Taft's tables.[7] If the allyl group were to fit the Taft relationship of Fig. 2 it should have $\sigma^* = +0.18 \pm 0.1$, a value consistent with that of +0.13 reported for the 1-(2-butenyl) group.

In two cases, those of 2-ethyl- and 2-isopropylnaphthalenes, $E_{1/2}$ can be compared with $E_{1/2}''$ for the second reduction wave of the corresponding conjugated 2-alkenylnaphthalene, previously investigated under the same experimental conditions.[8] The first wave for a conjugated 2-alkenylnaphthalene is believed to relate to transformation a, 2-alkenylnaphthalene → 2-alkylnaphthalene; and the second wave to concern transformation b, 2-alkenylnaphthalene → 2-alkyldihydronaphthalene. Transformation b is commonly visualized as occurring in two discrete steps at $E_{1/2}''$, *viz.* a followed by c, 2-alkylnaphthalene → 2-alkyldihydronaphthalene. If this concept is strictly correct, then $E_{1/2}''$ should be determined by the energetically less facile conversion c and one should find $E_{1/2} = E_{1/2}''$. Comparison shows that such relationship is approximately, but not exactly, true. In both cases $-E_{1/2}''$ is 6–8 mv. greater than $-E_{1/2}$. This discrepancy is slightly larger than the experimental error of ±3 mv. in the measurements. Although the exact reason for this discrepancy is not clear at this time, one possible explanation is that the addition of a third electron to the 2-alkenylnaphthalene may, on the average, start to occur slightly before addition of the second proton has been completed.

For various methylated naphthalenes one can represent $-\Delta E_{1/2}$ by equation 2, where n_α is the number of

$$-\Delta E_{1/2} = 19n_\alpha + 21n_\beta + \delta_j \qquad (2)$$

α-substituents, n_β is the number of β-substituents, δ_j is a potential associated with the geometric arrangement of substituents (*e.g.*, j = 137 for 1,3,7-trisubstitution), and all values are expressed in units of millivolts. Although δ_1 and δ_2 (for the monomethyl derivatives) are presumed to be zero, coefficients of 19 and 21 (rather than the measured values of 21 and 23, respectively) are used in equation 2 in order to give the best fit of all data. Values of δ_j may be considered as discrepancies from additivity in $-\Delta E_{1/2}$ (as based solely on the total

(8) L. H. Klemm, W. C. Solomon, and A. J. Kohlik, *J. Org. Chem.*, **27** 2777 (1962).

(9) It is not clear at this time whether the linear Taft relationships are to be ascribed to an equilibrium addition of the first electron, to a subsequent rate process, or to a combination of the two.

(10) Predicted from the observation that $-E_{1/2} = 2.164$ v. for 1-methyl-1-(2-naphthyl)ethene (see ref. 8).

numbers of α- and β-substituents). In order to ascertain the magnitudes of δ_j for dimethylnaphthalenes, the calculated values shown for these compounds in Table I are based on the approximation that $\delta_j = 0$. Comparison of found and calculated values for $-\Delta E_{1/2}$ then shows that the 1,2-, 1,4-, 1,5-, 1,6-, 2,6- and 2,7-isomers appear to be normal ($\delta_j = 0 \pm 6$), while the 1,7-isomer shows a slight repression potential ($\delta_{17} = -8$) and the 2,3- and 1,8-isomers show large enhancement potentials ($\delta_{23} = +22$; $\delta_{18} = +46$). The same enhancement potential for the 1,8-disubstitution pattern is observed for acenaphthene where the value of $-\Delta E_{1/2}$ may be rationalized in terms of the relationship 1,8-dimethylene $\approx$ 1,8-diethyl or $-\Delta E_{1/2} = 2 \times 33 + 46 = 112$. For the trimethylnaphthalenes and hexahydropyrene, the calculated values of $-\Delta E_{1/2}$ are not based on the assumption that $\delta_j = 0$, but rather on the assumed relationship shown in equation 3, where the subscript kl represents all possible combinations of two

$$\delta_j = \sum_j \delta_{kl} \qquad (3)$$

digit numbers contained in the subscript j, and kl is expressed in the lowest possible numbering for the corresponding pattern of disubstitution. Thus, for example, $\delta_{137} = \delta_{13} + \delta_{17} + \delta_{26}$; where $\delta_{26} \equiv \delta_{37}$. For a tetrasubstituted naphthalene δ_j will be given by the summation of six δ_{kl} terms. The calculated value of $-\Delta E_{1/2}$ for hexahydropyrene is based on the relationship hexahydropyrene $\approx$ 1,4,5,8-tetra-*n*-propylnaphthalene. Use of equations 2 and 3 gives good agreement between found and calculated values in all cases except 1,4,5-trimethylnaphthalene, where there is a difference of only seven millivolts.

Amongst the dimethylanthracenes studied an enhancement potential was associated with methyl groups situated in the two *meso*-positions and not with any combination of β-positions. In contrast, amongst dimethylnaphthalenes enhancement potentials are associated with the *peri*- and the vicinal β-positions. It is clear that the general effects on $-\Delta E_{1/2}$ of substitution patterns in the anthracene and naphthalene series are different, but more di- and polymethylanthracenes must be investigated before relationships can be clarified further.

In Table I are recorded values for the change in frequency, $-\Delta\nu$ (with respect to naphthalene taken as a standard), for the most intense central absorption maximum, and for the longest wave-length α-band in the ultraviolet spectrum (measured in alkane or cyclohexane as solvent) for each of the substituted naphthalenes studied here. Consistent with assignments (for these bands) of directions of polarization in the molecule[11] is the fact that the bathochromic effect of a 1-alkyl group is larger in the former band, whereas that of a 2-alkyl group is larger in the latter band. In fact, in the case of the former band the groups 2-allyl, 2-*i*-propyl, and 2-*t*-butyl give either no shift or else a hypsochromic one. The dimethylnaphthalenes bearing at least one α-substituent show a consistent bathochromic effect ($-\Delta\nu$ 1000–1100 cm.$^{-1}$) in the α-band. All other shifts appear irregular insofar as correlation with molecular structure is concerned.

(11) H. Zimmermann and N. Joop, *Z. Elektrochem.*, **64**, 1215 (1960); **65**, 61 (1961).

As in the alkylanthracenes[3] there is no apparent correlation between $-\Delta E_{1/2}$ and $-\Delta\nu$ (for either band) or between $-\Delta E_{1/2}$ values and methyl affinities as measured by Gresser, Binks, and Szwarc.[12] There is, however, qualitatively the same general inverse relationship[3] between the ionization potential, I_z, and $-E_{1/2}$ in that alkyl groups lower the former, but raise the latter. Values of I_z have been ascertained for naphthalene and the monomethylnaphthalenes by means of the charge-transfer spectra of the trinitrobenzene complexes (for naphthalene and 1-methylnaphthalene only)[13] and by means of photoionization.[14] Although precision in measurement of $E_{1/2}$ is at least an order of magnitude greater than in that of I_z, the 1- and 2-methylnaphthalenes give experimentally indistinguishable results by both methods.

Gardner, *et al.*,[15] have measured the stability constants of the picrates of naphthalene and monoalkylnaphthalenes in chloroform solution (see Table I). These molecular complexes (presumably present preferentially in parallel planar structures) exhibit the counteracting effects of electron donation and steric hindrance by the alkyl group to specific adsorption (on a molecular basis) of the electron-donating naphthyl moiety onto the electron-accepting picric acid surface. Similar effects of alkyl groups on adsorbability (presumably preferentially flatwise) of 2-alkylnaphthalenes and 9-alkylanthracenes onto an electron-accepting alumina surface have been noted by Klemm, *et al.*[16] In polarography the cathode surface differs from that of alumina or of a polynitroaromatic complexing agent in that it is an electron donor, rather than an electron acceptor. If specific adsorption (especially in a flatwise manner) of the alkylarene onto the cathode surface were pertinent to the polarographic process, polar and steric effects by the alkyl groups should reinforce one another with the excepted result that values of $-\Delta\Delta E_{1/2}$ should increase in progressing through the series in the order H, Me, Et, *i*-Pr, *t*-Bu. As observed in Table I $-\Delta\Delta E_{1/2}$ decreases in this progression, instead. Combined with the observed linear σ^* relationship for monoalkylnaphthalenes and anthracenes as well as the general additivity of substituent and geometric factors,[17] these data indicate that steric hindrance between the electroreducible molecule and the mercury cathode surface is of little or no pertinence to the electron-transfer process (at least as measured by $E_{1/2}$) and that specific adsorption of the hydrocarbon does not occur. Breiter, Kleinerman, and Delahay[18] have considered electrode processes which occur with and without specific adsorption of the electroreducible entity onto the electrode and, in the latter case, have suggested that the reacting species would approach the cathode no closer than the outer boundary of the Helmholtz

(12) J. Gresser, J. H. Binks, and M. Szwarc, *J. Am. Chem. Soc.*, **81**, 5004 (1959).

(13) G. Briegleb and J. Czekalla, *Z. Elektrochem.*, **63**, 6 (1959).

(14) K. Watanabe, *J. Chem. Phys.*, **26**, 542 (1957); ASTIA report no. AD 152 934 [A. Streitweiser, *J. Phys. Chem.*, **66**, 368 (1962)].

(15) P. D. Gardner, R. L. Brandon, N. J. Nix, and I. Y. Chang, *J. Am. Chem. Soc.*, **81**, 3413 (1959).

(16) L. H. Klemm, D. Reed, L. A. Miller, and B. T. Ho, *J. Org. Chem.*, **24**, 1468 (1959). The general preference for flatwise adsorption of aromatic hydrocarbons on alumina has been corroborated by the studies of L. R. Snyder, *J. Chromatog.*, **6**, 22 (1961); *J. Phys. Chem.*, **67**, 234 (1963).

(17) As shown by equations 2 and 3 in this paper and by equation 2 in ref. 3.

(18) M. Breiter, M. Kleinerman, and P. Delahay, *J. Am. Chem. Soc.*, **80**, 5111 (1958).

double layer; *i.e.*, presumably the molecule would remain largely within the diffuse double layer during the electron-transfer process.

Experimental[19]

Source and Purification of Hydrocarbons.—Except as otherwise noted, all hydrocarbons were purchased from Aldrich Chemical Company and purified by the same general procedure. 1-Methylnaphthalene (purum grade) was obtained from Fluka, A. G. Hydrocarbons of m.p. <75° were purified by conversion to the picrate (or sometimes the 1,3,5-trinitrobenzene) derivatives, which were recrystallized to constant melting point from ethanol and dissociated chromatographically by adding a solution of the complex in the minimum amount of benzene to a column of Alcoa F-20 alumina and eluting with petroleum ether (30–60°). The effluent was evaporated in an atmosphere of nitrogen and the residue was fractionally distilled *in vacuo*. Those products which were solid were also recrystallized to constant melting point. Generally for solids of m.p. >75° only direct recrystallization was used. Naphthalene (Distillation Products Industries, reagent grade) was purified by a combination of direct recrystallization, sublimation, and the picrate procedure. Although 1,6-dimethylnaphthalene was purified through its picrate this complex was rather unstable. Purified hydrocarbons were stored at 0–10° until use.

Where information to the contrary is not given, melting points, boiling points, and refractive indices of our products agreed closely with those reported in the literature. One exception was found for 1,3,7-trimethylnaphthalene, n^{20}D 1.6010 (reported[20] n^{20}D 1.5759). This compound did, however, show data for melting point, boiling point, and melting point of picrate consistent with those reported. Moreover, it gave the expected elemental analysis. Although 2,3-dimethylnaphthalene gave consistent data on melting points of the hydrocarbon and its picrate, its identity was checked further by microanalysis and mass spectra[21] (mol. wt. found: 156).

Hydrocarbons listed in subsequent paragraphs were synthesized in this laboratory and purified as noted in each case.

1-Allylnaphthalene.—To the cold (−30°) stirred Grignard reagent prepared from 2.75 g. of magnesium turnings, 23.3 g. (0.112 mole) of 1-bromonaphthalene, and 100 ml. of ether was added dropwise a solution of 13.6 g. (0.111 mole) of freshly distilled allyl bromide in 50 ml. of ether, maintained at −25°. The mixture was processed in the manner used for 3-(1-naphthyl)-cyclopentene[22]; crude yield 11.7 g. (63%), b.p. 140–141° (15 mm.). For use in polarography the hydrocarbon was converted to a 1,3,5-trinitrobenzene complex, m.p. 79–80°, after two recrystallizations from ethanol. The hydrocarbon was recovered by chromatographic dissociation of the complex using benzene and Alcoa F-20 alumina and fractional distillation of the effluent, b.p. 126.5–127° (10 mm.); n^{25}D 1.6081, reported[23] n^{25}D 1.6089.

1-*n*-Propylnaphthalene.—A solution of 6.0 g. of 1-allylnaphthalene in 150 ml. of glacial acetic acid was shaken with 0.1 g. of platinum oxide for 7 min. under hydrogen at 3-atm. pressure. The filtered solution was evaporated and the residue was converted to its 1,3,5-trinitrobenzene complex, obtained as yellow needles, m.p. 86–87°, after four recrystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{17}N_3O_6$: N, 10.96. Found: N, 11.13.

The hydrocarbon, recovered from the complex, distilled at 126–127° (10 mm.); n^{20}D 1.5920, reported[24] n^{20}D 1.5928.

1-*t*-Butylnaphthalene.—To the cold (0°) stirred Grignard reagent prepared from 15.8 g. of magnesium turnings, 79.2 g. (0.58 mole) of *t*-butyl bromide, and 65 ml. of ether was added dropwise a solution of 84.5 g. (0.58 mole) of α-tetralone in 80 ml. of ether. The mixture was refluxed for 2 hr. and processed further as for 1-allylnaphthalene; yield 80 g. of distillate, b.p. 133–165° (15 mm.). This crude carbinol was dehydrated by distillation *in vacuo* (0.3 mm.) through a column of Alcoa F-1 alumina[8] maintained at 370–385° over a period of 2.5 hr. An infrared spectrum of the red, viscous distillate showed the presence of both hydroxyl and carbonyl bands. Chromatography of this red liquid using a column (4.2 × 71 cm.) packed with Alcoa F-20 alumina and 2 l. of reagent grade petroleum ether (30–60°) as eluent gave three main fractions. Fraction no. 1 (1.2 l.) yielded a colorless liquid residue on evaporation; no. 2 (90 ml.), liquid plus some crystals; and no. 3 (240 ml.), white crystals (presumably naphthalene).[25] Infrared spectra of these residues showed neither hydroxyl nor carbonyl bands. A mixture of 15.8 g. of combined residues from fractions no. 1 and 2 (total 35.8 g.) and 1.6 g. of 30% palladium on charcoal was heated at 250° for 5 hr. in a stream of nitrogen. Tests of the effluent gases showed the presence of considerable permanganate-oxidizable product (isobutene?). Rechromatography partially separated 1-*t*-butylnaphthalene (liquid residue) from the more strongly adsorbed naphthalene.[25] Distillation of the liquid residue gave 5.8 g. (12%) of 1-*t*-butylnaphthalene, b.p. 148–149° (15 mm.), purified further by means of the picrate, m.p. 100.5–102°, after two recrystallizations from ethanol, chromatography, and distillation, b.p. 135–135.5° (12 mm.); n^{20}D 1.5914, reported[26] n^{20}D 1.5726.

2-Allylnaphthalene.—This compound, prepared from 2-bromonaphthalene by the procedure used for the 1-allyl isomer,[27] was purified by chromatography on Alcoa F-20 alumina, distillation, b.p. 95–96° (2 mm.), conversion to its picrate (m.p. 72–73° after two recrystallizations from ethanol), chromatographic dissociation of the picrate, and redistillation, b.p. 128° (14 mm.); n^{25}D 1.6027.

Anal. Calcd. for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.80; H, 7.05.

2-*n*-Propylnaphthalene.—This compound was prepared by catalytic hydrogenation of 2-allylnaphthalene in the same manner as employed for the 1-isomer and was purified in the manner used for 2-allylnaphthalene, b.p. 135–136° (15 mm.); n^{25}D 1.5852.

2-Isopropylnaphthalene.—2-Isopropenylnaphthalene[8] was hydrogenated as described by Bergmann and Weizmann.[28] The hydrogenated product was purified in the manner used for 2-allylnaphthalene, b.p. 125–126° (12 mm.); n^{20}D 1.5864, reported[26] n^{20}D 1.577.

2-*t*-Butylnaphthalene.—This compound was prepared[29] by the Friedel–Crafts method of Bromby, Peters, and Rowe[30] using *t*-butyl chloride and naphthalene. It was purified through the picrate.

1,4-Dimethylnaphthalene.—The Grignard reagent from 2.4 g. of magnesium, 60 ml. of ether, and 22.1 g. of 1-methyl-4-bromonaphthalene[31] (purified by recrystallization of its picrate, chromatography, and distillation) was refluxed with 20 ml. of methyl iodide for 2 hr. Treatment of the reaction mixture with ice and hydrochloric acid and evaporation of the ethereal layer gave a yellow liquid which was chromatographed on alumina and converted to a trinitrobenzene complex. The hydrocarbon was then processed in the usual manner, b.p. 125–126.5° (12 mm.); m.p. 8–9°; $n^{16.4}$D 1.6154, reported[32] $n^{16.4}$D 1.6157.

1,8-Dimethylnaphthalene.—Naphthalic anhydride (Aldrich Chemical Co., recrystallized from acetone, m.p. 265–268°) was reduced to 1,8-dihydroxymethylnaphthalene by the lithium aluminum hydride method of Boekelheide and Vick.[33] The diol was hydrogenolyzed to 1,8-dimethylnaphthalene as described by Beyler and Sarett.[34] The hydrocarbon was purified first *via* the picrate (m.p. 154–156°) and then by recrystallization thrice from

(19) Melting points are uncorrected. Unless otherwise noted microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were determined by means of a Perkin-Elmer Model 137 spectrophotometer.

(20) O. Kruber, *Ber.*, **72**, 1972 (1939).

(21) We are indebted to Klaus Biemann of the Massachusetts Institute of Technology for this measurement.

(22) L. H. Klemm, B. T. Ho, C. D. Lind, B. I. MacGowan, and E. Y. K. Mak, *J. Org. Chem.*, **24**, 949 (1959).

(23) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 1658 (1938).

(24) R. Y. Levina, L. E. Karelova, and I. A. El'yashberg, *J. Gen. Chem. USSR*, **10**, 913 (1940); *Chem. Abstr.*, **35**, 2479 (1941).

(25) From the adsorbability rules previously proposed,[16] 1,2-dihydronaphthalene, 1-*t*-butyl-3,4-dihydronaphthalene, and 1-*t*-butylnaphthalene should all be less strongly adsorbed than naphthalene.

(26) I. P. Tsukervanik and I. Terent'eva, *J. Gen. Chem. USSR*, **7**, 632 (1937); *Chem. Abstr.*, **31**, 5780 (1937).

(27) Prepared by S. K. Airee.

(28) F. Bergmann and A. Weizmann, *J. Org. Chem.*, **9**, 352 (1944).

(29) Prepared by J. T. Spence.

(30) N. G. Bromby, A. T. Peters, and F. M. Rowe, *J. Chem. Soc.*, 144 (1943).

(31) L. F. Fieser and D. M. Bowen, *J. Am. Chem. Soc.*, **62**, 2103 (1940).

(32) "Elsevier's Encyclopaedia of Organic Chemistry," Vol. 12B, F. Radt, Ed., Elsevier Publishing Co., Inc., New York, N. Y., 1948, p. 135.

(33) V. Boekelheide and G. K. Vick, *J. Am. Chem. Soc.*, **78**, 653 (1956).

(34) R. E. Beyler and L. H. Sarett, *ibid.*, **74**, 1406 (1952).

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA FOR SOME ALKYL- AND ALKYLENE-SUBSTITUTED NAPHTHALENES[a]

Substituent(s) on naphthalene	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε
1-*t*-Butyl	225	4.98	(262	3.59)	270	3.78	280	3.87	288	3.70	291	3.70			313	2.53
1-Allyl	225	4.95	(262	3.59)	271	3.78	281	3.87	289	3.69	292	3.69			313	2.57
2-*n*-Propyl	225	5.10	(266	3.67)	275	3.71			(286	3.53)			305	2.64	318	2.64
2-*i*-Propyl	224	5.09	(265	3.67)	274	3.71			(285	3.54)			304	2.64	318	2.60
2-*t*-Butyl	224	5.09	264	3.67	274	3.72			(282	3.56)			303	2.56	317	2.43
2-Allyl	225	5.09	266	3.69	275	3.72			(286	3.55)			304	2.64	318	2.56
2,3,5-Trimethyl	229	4.94	(265	3.58)	274	3.74	283	3.79			295	3.61			318	2.44
2,3,6-Trimethyl	229	5.08	268	3.66	278	3.66							309	2.81	323	2.87
1,8;4,5-Bis(trimethylene[b]	(228	4.70)	234	4.83	285	3.84	296	3.96	(301	3.88)	308	3.82	315	3.67	329	3.48

[a] Solvent, isooctane. Data in parentheses are for shoulders, not true maxima. [b] Common name, 1,2,3,6,7,8-hexahydropyrene. Other maxima at λ_{max} 214 mμ, ε 4.33; 306, 3.80; and 323, 3.19.

75% ethanol, m.p. 62.5–64°; intense infrared bands (Nujol) in the region 670–850 cm.$^{-1}$ at *ca.* 774 and 817.

1-Chloromethyl-4,5-dimethylnaphthalene.—Into a mixture of 3.13 g. of 1,8-dimethylnaphthalene, 3.3 g. of paraformaldehyde, and 36 ml. of hydrogen chloride-saturated dioxane–water (6:1, v./v.), maintained at 85°, was passed a stream of hydrogen chloride gas for 2 hr. The resultant solution was refluxed for 9 hr., whereupon two liquid phases were present. Evaporation of the upper layer yielded 4.0 g. of liquid which crystallized on cooling, m.p. 57–65°. Three recrystallizations from petroleum ether (b.p. 30–60°) gave prisms, m.p. 71–72°; intense infrared bands (Nujol) in the region 670–850 cm.$^{-1}$ at 692, 759, 765, and 810 and medium bands at 749 and 835.

Anal. Calcd. for $C_{13}H_{13}Cl$: C, 76.26; H, 6.40; Cl, 17.3. Found[35]: C, 76.25; H, 6.52; Cl, 16.6.

1,4,5-Trimethylnaphthalene.—A solution of 7.53 g. of the preceding chloromethyl compound in 400 ml. of methanol was shaken for 1 hr. with 1.2 g. of 5% palladium on charcoal in the presence of hydrogen gas at 3-atm. pressure. Evaporation of the filtered solution and chromatography of a petroleum ether (b.p. 30–60°) solution of the residue on Alcoa F-20 alumina gave 5.34 g. (86%) of crystalline product. It was recrystallized thrice from methanol, m.p. 61.5–62° (reported[36] m.p. 63°) and purified further through the picrate, m.p. 144–145.5° (reported[36] m.p. 144–145°). The hydrocarbon showed intense infrared bands (Nujol) in the region 670–850 cm.$^{-1}$ at *ca.* 762 and 825 and relatively weak bands, at *ca.* 793 and 807.

Polarography.—Only analytically pure hydrocarbons were used in the polarographic studies. The polarographic apparatus, the procedure, and the general reproducibility (±3 mv.) in $E_{1/2}$ were the same as previously described.[3,8] Only in the case of hexahydropyrene did $E_{1/2}$ fall at such a negative value as to cause serious overlapping of the reduction wave for the solvent–electrolyte with the limiting current portion of the polarogram. For this reason $-E_{1/2}$ is reported to only the closest 0.01 v. for this one substrate. Otherwise, all polarograms showed only one reduction wave and were regular in shape except for the fact that the slope of the straight line representing the limiting current was greater than that of the straight line representing the residual current, where such lines were drawn through the maxima of the pen oscillations. $E_{1/2}$ was ascertained graphically by construction of a rectangle on the polarogram (as described in the "point method" of Willard, *et al.*)[37] and determination of the center of gravity (at $E_{1/2}$) of this rectangle by bisection of its diagonal. The diffusion current i_d' was determined for the most dilute solution of the hydrocarbon and was calculated as six-sevenths of the vertical height of the rectangle. Polarographic data are given in Table I.

Ultraviolet Spectra.—Ultraviolet absorption spectra of those hydrocarbons for which such data were not readily available were determined in spectral grade isooctane using a Cary Model 11 spectrophotometer. Data on the absorption maxima are presented in Table II.

(35) Analysis for chlorine was performed by A. J. Kohlik using a method described for benzyl chloride by G. S. Tsypin and A. I. Chekalina, *Org. Chem. Ind. (USSR)*, **6**, 504 (1939); *Chem. Abstr.*, **34**, 2288 (1940).

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Thermal Reactivity of Polynuclear Aromatic Hydrocarbons[1]

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Much recent interest has been directed toward understanding the reactivity characteristics of polynuclear aromatic systems. The major emphasis has pertained to simple radical substitution and oxidation–reduction reactions. Relatively little work has been applied to studies of self-condensation sequences, which are generally accomplished thermally and lead to the formation of complex carbonaceous residues from the typical polynuclear aromatic hydrocarbon. We report herein investigations of the thermal reactivity for eighty-four polynuclear aromatic hydrocarbons. Our approach has employed differential thermal analysis (d.t.a.) to categorize and delineate thermal reactivity. These results emphasize the importance of intermolecular thermal hydrogen transfer for the polynuclear aromatics. Thermal condensation reactivity is found to be dependent on molecular structure and correlates with other reactivity criteria but includes the additional parameter of molecular size.

Much recent chemical interest has been directed toward studies in the field of polynuclear aromatic hydrocarbons. Special emphasis has been placed on theoretical treatments of these materials[2a,b] and the relationship of theoretical parameters to spectroscopic,[3] reactivity,[4-6] and physiological[8] criteria. Chemical reactivity investigations for the polynuclear aromatics have been restricted largely in the past to radical substitution,[4] oxidation–reduction,[5,6] and electrophilic substitution.[7] The thermal reactivity characteristics of these compounds also have been the subject of recent studies.[9] Many of the aromatic hydrocarbons are known to be thermally reactive both individually and as constituents of complex mixtures. These thermal reactions are believed to involve condensation or polymerization sequences to produce complex carbonaceous products.[10]

Rapid developments in instrumental analytical techniques and in dynamic methods of measuring changes in materials during heating and cooling make a detailed study of carbonization reactions possible and practical at this time. This report is a survey of the thermal reactivity characteristics for a wide variety of aromatic hydrocarbons. Differential thermal analysis (d.t.a.) has been used to categorize the high temperature behavior of these hydrocarbons. This technique has been used extensively in investigations of polymers and inorganic solids.[11] It has found relatively little use, however, in the study of thermally reactive organic compounds.

D.t.a. gives a continuous thermal record of reactions occurring in a sample, although it does not indicate what these reactions are nor does it sort out simultaneously occurring reactions. By comparing the temperature in a sample with the temperature in an inert reference material such as anhydrous alumina as both are heated at a uniform rate in a furnace, temperature regions where heat is absorbed (endothermic reactions) or evolved (exothermic reactions) by the sample can be observed.

Thermal reactivity behavior as derived from d.t.a. is interpreted in terms of reactivity parameters derived from electronic spectra and the adjunct of molecular size.

Experimental

D.t.a. Apparatus.—Differential thermal analysis is the technique of measuring the difference in the temperature between a thermocouple embedded in a sample and a thermocouple in a standard inert material such as aluminum oxide while both are heated at a uniform rate. These temperature differences arise when phase transformations or chemical reactions in the sample evolve or absorb heat. Experimentally, it is desirable thermally to match and isolate the sample and reference holders and to maintain a uniform heating rate.

The basic design of the apparatus used in this study has been described in detail elsewhere.[12] A sketch of the sample holder and a block diagram of the controlling, detecting, amplifying, and recording systems are shown in Fig. 1A and 1B, respectively.

The d.t.a. thermocouple assembly shown in Fig. 1A consists of two matched chromel–alumel thermocouples supported in a porcelain tube, which is held in position in a furnace combustion tube. The sample and reference cups are Inconel cylinders with a thermocouple well extending into the center of the cup from the bottom. With this arrangement, the thermocouples are protected from the embrittling action of the hydrocarbons during carbonization and can be used repeatedly. This extended life justifies very careful matching of the thermocouples and Inconel cups. The sample and reference cups are also isolated from each other and independent of the thermocouples. This arrangement permits weighing before and after heating so that weight changes can be determined. In most cases, the quantity of sample and of reference anhydrous alumina was standardized at 100 mg. The heating rate was also arbitrarily standardized at 10° per minute. All experiments were run at atmospheric pressure in continuously flowing purified argon.

The argon and volatile products were swept into a potassium bromide-filled condensate trap[13] for collecting the condensable volatile reaction products and unchanged starting material. The noncondensible gases then pass through a sulfuric acid bubbler which seals the system. Samples were heated to 750° and the carbon yields reported were determined on the 750° residues.

Normally the d.t.a. experiments were carried out by heating continuously to 750° at which point the residue is essentially carbon. However, since the d.t.a. thermogram provides an excellent visual method of detecting reactions and determining end points, a number of runs were terminated at a temperature just preceding or following a reaction peak and the products were cooled

(1) Presented at "Symposium on Aromatic Hydrocarbons," Division of Petroleum Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

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(12) I. C. Lewis and T. Edstrom, "Proceedings of the Fifth Carbon Conference," Pergamon Press, London, 1962.

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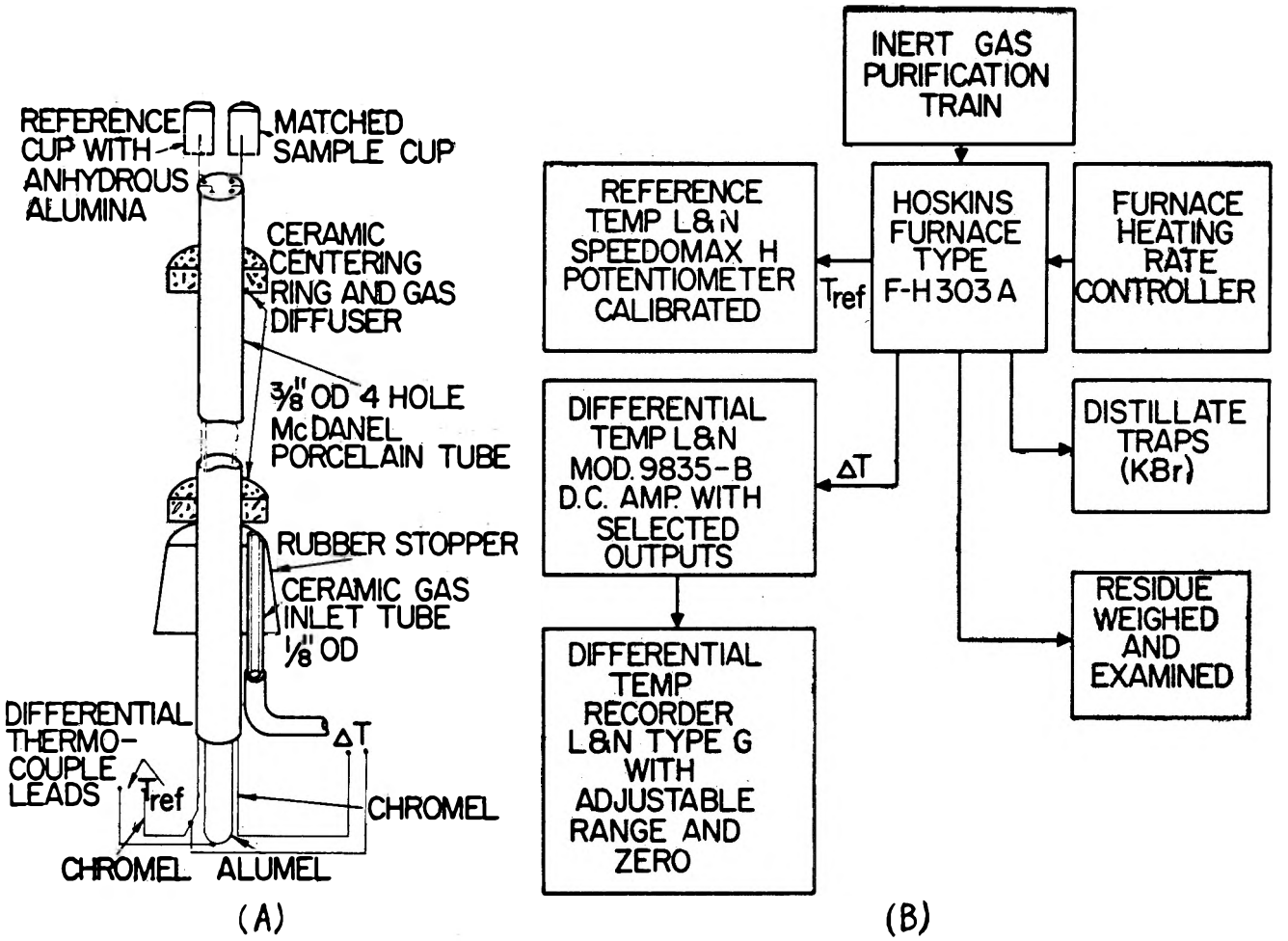


Fig. 1.—(A) D.t.a. thermocouple assembly; (B) block diagram of d.t.a. apparatus.

and analyzed. These experiments are discussed under the heading "Interrupted D.t.a. runs" in the following section.

Analytical Techniques. Chromatography.—Elution chromatography on alumina or silica gel columns has been extremely useful in the purification of reference compounds for this study, usually producing a much higher degree of purity than repeated recrystallization or sublimation and with less effort.

Infrared Absorption Spectra.—The infrared absorption spectra were measured on a Perkin-Elmer Model 21 or Model 221 double-beam spectrometer using conventional sampling techniques.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were measured on a Beckman DK-1 double-beam spectrometer using solution methods with 10-mm. matched silica cells exclusively.

Molecular Weight.—A Mechrolab Osmometer, Model 301, was used to determine number average molecular weights of those compounds and fractions soluble in benzene.

Electron Spin Resonance.—Electron spin resonance measurements were made on a number of the low temperature residues obtained in the d.t.a. apparatus. These measurements were made by L. S. Singer of this laboratory using methods and apparatus previously described.[14]

Materials.—The polynuclear aromatic compounds examined in this work were obtained through commercial chemical supply houses and in many cases were used as received. Infrared and ulatraviolet absorption spectra of each compound were compared with published spectra to ascertain purity. In those cases where thermally reactive compounds appeared to be contaminated, chromatographic purification was carried out and the purified material was re-examined in the d.t.a. apparatus. The impurity level after careful chromatographic purification is estimated to be in the parts per million range.

The solvents used in the chromatographic separations and for spectroscopic analysis were all Spectro-Grade solvents. The potassium bromide powder used in trapping the d.t.a. condensates and for infrared sampling was infrared quality powdered potassium bromide. The anhydrous alumina used in chromatographic columns and as the d.t.a. reference material is chromatographic grade anhydrous alumina, 80 to 200 mesh. The alumina used for d.t.a. reference is specially treated by heating to 800°. It is stored in a sealed dispenser to avoid exposure of the bulk of the material to the atmosphere when transferring to the d.t.a. cup.

(14) L. S. Singer and J. Kommandeur, *J. Chem. Phys.*, **34**, 133 (1961).

Results

D.t.a. Thermograms for Thermally "Unreactive" Aromatic Hydrocarbons.—For the purposes of this study the aromatic hydrocarbons have been designated as either thermally "reactive" or thermally "unreactive." The thermally "reactive" species possess sufficient reactivity in an atmospheric pressure system to undergo a condensation sequence in the liquid phase and yield a measurable amount of polymerized carbonaceous residue at 750°.

The thermally "unreactive" entities have sufficient stability so that such condensation reactions do not occur prior to complete volatilization. Hence, for these compounds no carbonaceous residues are observed at 750°.

Shown in Fig. 2 are the d.t.a. thermograms obtained for some representative aromatic hydrocarbon members of the thermally "unreactive" category. All of these thermograms exhibit common characteristic features. For solid compounds two major endothermic peaks corresponding to the melting and boiling processes are invariantly obtained. For liquid compounds a simple major endotherm representative of the distillation process is always evident. Additionally no carbonace-

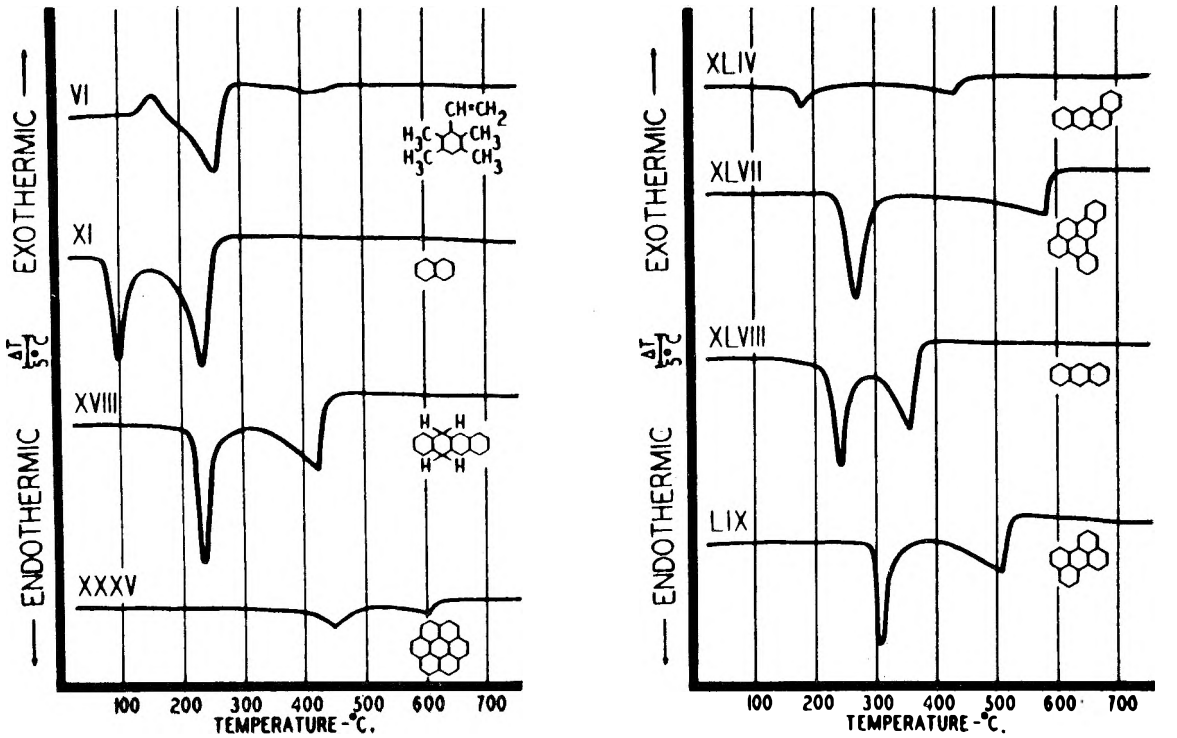


Fig. 2.—Typical d.t.a. thermograms of unreactive hydrocarbons.

ous residues are obtained in the d.t.a. sample cups at 750° and no products besides starting materials were observed in the condensed distillates.

For such materials d.t.a. offers a convenient if not precise method for measuring melting and boiling points. The initial inflection point of the melting endotherm has been found to be the most reliable method for ascertaining the melting points in our system. The melting points thus determined for the "unreactive" aromatic hydrocarbons are listed in Table I and compared with the appropriate literature values. In most cases the agreement is quite good.

The boiling endotherms are generally broad and have no specifically defined inflection temperature. The shape of the endotherm reflects the increasing vapor pressure of the sample with increasing temperature. The gradual approach to the boiling endothermic minimum indicates slow but increasing vaporization. The calculated values of the boiling points listed in Table I are the endothermic minima. Very few literature values are available for direct comparison although in cases where such comparisons are possible the agreement appears to be quite good. D.t.a. offers a suitable method of determining atmospheric boiling temperatures of extremely high boiling organic materials such as the aromatic hydrocarbons.

Also listed in Table I are the frequencies of the long wave-length p-bands determined from the measured electronic spectra by the procedure of Clar.[3] These wave lengths can readily be determined within 1%. The Hückel relationship (equation 1) as employed by Matsen[15] has been utilized to calculate ionization parameters for the respective aromatic hydrocarbons from the p-band wave lengths.

$$\text{i.p.} = 4.39 + 0.857\,\lambda\text{p} \qquad (1)$$

i.p. = ionization potential in electron volts
λp = wave length of long wave-length p-band in electron volts

These values are given in the last column of Table I. The compounds are listed in order of decreasing ionization potential.

In several instances the p-band definition from ultraviolet spectra was uncertain and the ionization potential data have been omitted. Such compounds have been placed in Table I in the approximate position based on a judicial estimate of the p-band.

D.t.a. Thermograms for Thermally "Reactive" Aromatic Hydrocarbons.—The thermograms for several representative aromatic hydrocarbons designated as thermally "reactive" are shown in Fig. 3. All of these compounds undergo thermal condensation and lead to carbonaceous residues at 750° in our d.t.a. system.

The thermograms for these "reactive" aromatics differ appreciably from those of the previous category. The major melting endotherms are, however, still evident. The d.t.a. melting points have again been calculated from the inflection temperatures and are compared with the literature values in Table II.

The boiling endotherms are observed to be either completely absent or largely diminished in these thermograms. In a large number of cases an exothermic peak indicative of polymerization or condensation is found. In nearly every instance new chemical species in addition to starting material were obtained in the condensed distillate. These have been examined spectrophotometrically.

Further listed in Table II for the "reactive" aromatics are the per cent carbonaceous residues obtained at 750° and the temperatures of indicated d.t.a. reaction peaks. These latter may be exothermic or endothermic depending on the combination of physical and chemical changes proceeding at the reaction temperature. Also given in Table II are the λ of the long wave-length p-bands and the ionization potentials computed as described previously. Again the compounds have been listed in order of decreasing ionization potential.

TABLE I

THERMALLY STABLE AROMATIC HYDROCARBONS

Compound no.	Hydrocarbon, source no.	M.p., °C. lit.	M.p., °C. d.t.a.	B.p., °C. d.t.a.	λ p-band, mμ	Calcd. i.p., e.v.
I	Benzene	5.5	...	...	208	>10.0
II	Styrene	...	...	170	...	...
III	Biphenyl	70	64	268	247	8.69
IV	Allylbenzene	...	...	180	260	8.47
V	Vinylmesitylene	<25	<25	235	260	8.47
VI	Vinyldurene	...	...	255	...	...
VII	Fluorene	114	122	314	261	8.46
VIII	9,10-Dihydroanthracene	108	98	328	271	8.31
IX	2-Methylfluorene	104	113	332	278	8.21
X	Benzo[*l*]phenanthrene	198	197	450	284	8.14
XI	Naphthalene	80	77	245	285	8.12
XII	Vinylxylene	<25	<25	235	286	8.10
XIII	Phenanthrene	100	93	348	292	8.03
XIV	*p*-Quarterphenyl	320	317	495	292	8.03
XV	Vinyltoluene	<25	<25	200	298	7.96
XVI	4,5-Methylenephenanthrene	116	120	375	299	7.95
XVII	3-Methylphenanthrene	65	45	370	304	7.88
XVIII	5,12-Dihydronaphthacene	...	214	420	306	7.86
XIX	*m*-Quinquephenyl	...	110	545	308	7.84
XX	1,1′-Binaphthyl	156	140	418	313	7.78
XXI	Tetraphenylethylene	227	230	424	315	7.77
XXII	1-Allylnaphthalene	...	...	295	315	7.77
XXIII	Acenaphthene	95	91	280	319	7.72
XXIV	Chrysene	254	260	460	319	7.72
XXV	9-Benzylidenefluorene	76	80	440	325	7.66
XXVI	Picene	365	370	535	329	7.62
XXVII	Dibenzo[*c,g*]phenanthrene	178	145	490	329	7.62
XXVIII	Benzo[*e*]pyrene	179	179	496	331.5	7.60
XXIX	Pyrene	150	146	386	335	7.56
XXX	4,5,9,10-Tetrahydropyrene	138	142	383	300	7.94
XXXI	4-Methylpyrene	143	153	425	338	7.54
XXXII	Benzo[*a*]fluorene	187	200	420	340	7.52
XXXIII	Benzo[*b*]fluorene	209	220	420	340	7.52
XXXIV	Azulene	99	99	285	...	...
XXXV	Coronene	430	438	600	342	7.50
XXXVI	1,1,4,4-Tetraphenylbuta-1,3-diene	202	215	460	344	7.48
XXXVII	1-Methylpyrene	72	78	372	344	7.48
XXXVIII	Dibenz[*a,c*]anthracene	205	208	520	349	7.43
XXXIX	Benzo[*b*]fluoranthene	168	170	490	350	7.42
XL	Dibenz[*a,h*]anthracene	265	265	520	350	7.42
XLI	Tetrabenzonaphthalene	215	220	565	350	7.42
XLII	4,6,8-Trimethylazulene	...	85	344	...	...
XLIII	Fluoranthene	110	110	386	359	7.35
XLIV	Benz[*a*]anthracene	159	166	430	359	7.35
XLV	Dibenzo[*a,h*]phenanthrene	294	308	537	362	7.32
XLVI	Benzo[*a*]pyrene	178	170	495	364	7.31
XLVII	Dibenzo[*a,e*]pyrene	225	237	580	375	7.23
XLVIII	Anthracene	217	215	350	376	7.22
XLIX	2-Phenylanthracene	207	221	465	383	7.17
L	9-Phenylanthracene	153	150	416	383	7.17
LI	Benzo[*g,h,i*]perylene	281	285	560	383	7.17
LII	9-Methylanthracene	80	77	370	386	7.14
LIII	1,10-*o*-Phenylenepyrene	...	160	538	386	7.14
LIV	9,9′-Bianthryl	320	322	520	389	7.12
LV	9,10-Diphenylanthracene	247	230	485	393	7.10
LVI	9,10-Dimethylanthracene	181	177	400	398	7.06
LVII	Benzo[*j*]fluoranthene	217	225	495	400	7.05
LVIII	Dibenzo[*a,l*]pyrene	227	225	522	400	7.05
LIX	Perylene	275	295	505	534	6.84

Identification of Condensates Trapped from D.t.a. Runs.—Spectrophotometric examination of the d.t.a. condensate traps showed that for nearly all the "unreactive" aromatic hydrocarbons only starting material could be identified.

In contrast, the majority of the "reactive" aromatic hydrocarbons showed evidence of new volatile aromatic species in the condensate trap. In a number of cases these products have been identified by spectral and physical property comparison with known hydrocarbons.

Summarized in Table III are the results of examina-

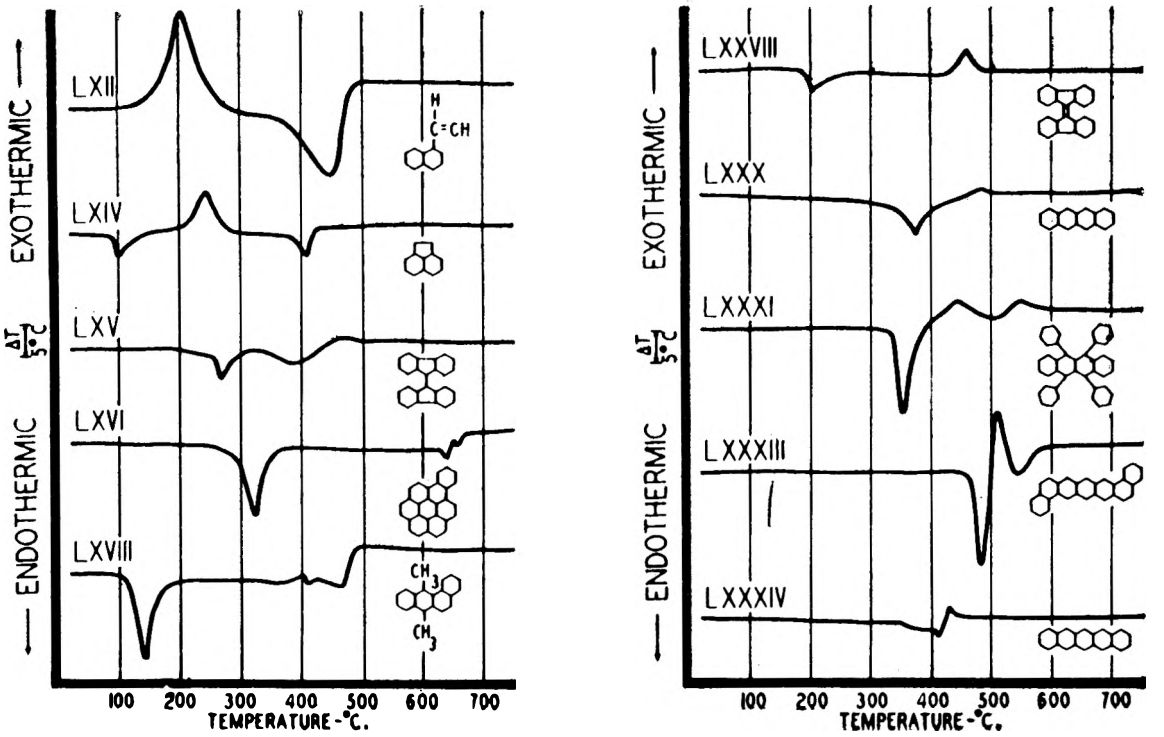


Fig. 3.—Typical d.t.a. thermograms of reactive hydrocarbons.

tion of the condensate traps for the "reactive" aromatic compounds.

Interrupted D.t.a. Runs.—The properties of residues obtained from the interrupted d.t.a. runs of acenaphthylene (LXIV) and 9,9′-bifluorenylidene (LXXVIII) are listed in Table IV. The temperatures at which heating was interrupted is given in the second column. Reference to the original thermograms in Fig. 3 shows the reaction stage at which these residues have been obtained. Also listed in Table IV are the general appearance of the residue, melting point, per cent yield, number average molecular weight, and the presence or absence of free radicals as measured by e.p.r.

Discussion of Results

The thermal stability of the aromatic hydrocarbons shows a marked dependence on structure. In this investigation eighty-four aromatic hydrocarbons have been designated as either thermally "unreactive" or thermally "reactive." The d.t.a. method examines thermal behavior of materials in the solid and liquid phases. The reactivity classifications are, therefore, applicable to solid and liquid phase pyrolysis only. This classification, although internally consistent within our system, will be affected, as will also the actual reaction temperatures and residue yields, by the experimental conditions employed. For example, anthracene can be made to react by prolonged heat treatment in a confined pressure system.

The application of the d.t.a. method to these compounds is extremely useful in permitting the detection of thermal physical and chemical changes. For thermally unreactive entities it permits the measurement of atmospheric melting and boiling points. The presence of impurities in the sample in general can be readily determined from the d.t.a. thermogram by either observation of separate melting endotherms or general lowering of the melting endotherm of the major constituent. Additionally, d.t.a. is effective in measuring crystal transformations, polymerizations, and degradations and hence provides an important tool for organic sample identification.

The categorization of the aromatic hydrocarbons within the respective "unreactive" and "reactive" categories conforms fairly well with their respective classification with regard to general reactivity characteristics. The ionization potential parameters as empirically determined from the measured electronic spectra appear to offer a convenient and readily obtainable reactivity parameter for these materials. The hydrocarbons of high ionization potential generally fall in Table I for the "unreactive" species. These aromatics on the whole possess i.p. values >7.10 e.v. The few compounds, which are listed in Table I and have i.p. ≦7.10 e.v., are borderline cases and can be made to undergo some thermal condensation sequences by slightly modifying reaction conditions.

The aromatic hydrocarbons listed in Table II as thermally "reactive" fall into two categories. The major class contains species which possess i.p. less than about 7.10 e.v. These materials would be classed as highly reactive on almost any chemical scale and are shown in this study to contain sufficient energetic character readily to undergo thermal condensation sequences prior to volatilization.

The second class of compounds listed in Table II have high i.p. values, >7.20 e.v., which should normally situate them with the unreactive species of Table I. These compounds, however, have the extraneous structural feature of a readily polymerizable vinyl double bond in addition to an aromatic structure. These hydrocarbons may initially undergo a vinyl type polymerization to yield large polymer species. This thermal vinyl polymerization sequence differs in kind from the subsequent aromatic condensation sequence or carbonization. For these structural types of aromatics,

TABLE II

THERMALLY REACTIVE AROMATIC HYDROCARBONS

Compound no.		M.p., °C. lit.	M.p., °C. d.t.a.	Reaction[a] Temp., °C.	% Residue 750°	λ p-band, mμ	Calcd. i.p., e.v.
LX	4-Vinylbiphenyl	...	120	203 (430)	8.1	278	8.21
LXI	10,15-Dihydro-5*H*-diindeno-[1,2-a:1′2′-c]fluorene	370	375	(570)	32.9	298	7.96
LXII	1,Vinylnaphthalene	<25	...	200 (445)	4.2	299	7.94
LXIII	10,15-Dihydro-5*H*-diindeno-[2,1-α:1′,2′-c]fluorene	...	175	(550)	13.5	336	7.55
LXIV	Acenaphthylene	92	89	245 (405)	20.9	339	7.53
LXV	9,9′-Bifluorenyl	247	250	(380)	5.8	364	7.31
LXVI	Benzo[a]coronene	...	291	(637) (652)	30.9	372	7.24
LXVII	9-Cinnamylidene fluorene	154	169	400 (435)	9.3	376	7.22
LXVIII	7,12-Dimethylbenz[a]anthracene	122	111	400 (405) (460)	4.7	381	7.18
LXIX	Tribenzo[a,e,i]pyrene	297	342	(525)	13.7	384	7.16
LXX	Dibenzo[a,i]pyrene	280	284	(560)	9.8	397	7.07
LXXI	9,10-Dibenzylanthracene	242	251	(445)	8.9	399	7.06
LXXII	Diacenaphtho[1,2-j:1′,2′-l]fluoranthene	388	377	610	66.3	402	7.04
LXXIII	Dibenzo[b,k]chrysene	400	412	(571)	22.3	414	6.95
LXXIV	Dibenzo[def,mno]chrysene	257	272	(535)	18.5	430	6.86
LXXV	Benzo[1,2,3-cd:4,5,6-c′d′]diperylene	...	295	(455) (680)	91.8	437	6.82
LXXVI	1-Methyl-dibenzo[b,i]pyrene	...	327	(548)	22.7	456	6.72
LXXVII	Pyranthrene	360	400	600 (606)	60.1	458	6.71
LXXVIII	9,9′-Bifluorenylidene	188	188	456	31.5	460	6.70
LXXIX	1,6-Dimethyl-dibenzo[b,i]pyrene	373	372	488 (525) (557)	33.6	464	6.68
LXXX	Naphthacene	343	340	480	13.9	471	6.64
LXXXI	5,6,11,12-Tetraphenylnaphthacene	333	333	442, 545	43.9	489	6.57
LXXXII	Rubicene	306	315	(551)	9.0	524	6.42
LXXXIII	Dibenzo[a,i]pentacene	440	460	505 (540)	53.2	529	6.40
LXXXIV	Pentacene	270	...	426 (411)	42.8	576	6.23

[a] Temperatures in parenthesis refer to endothermic reaction peaks. Unenclosed temperatures are those for exothermic peaks.

however, the former process is a prerequisite to the latter. Some vinyl derivatives may undergo a polymerization and depolymerization process to yield noncarbonizable products as exemplified by vinyl durene, the thermogram of which is shown in Fig. 2. Several borderline compounds in Table II consist of aromatics with intermediate i.p., namely, benzo[a]coronone and tribenzo[a,e,i]pyrene. For such species one must take into account the added variable of molecular size in addition to general reactivity. The former parameter induces sufficient physical stability in the molecule to permit reaction before volatilization. General reactivity parameters such as i.p. values can, therefore, only serve as qualitative measures of thermal reactivity as defined here.

The activating effect of alkyl substituents on aromatic carbonization has been noted earlier by Madison and Roberts[9] and is evident in the reactivity of 7,12-dimethylbenz[a]anthracene, as contrasted to the nonreactivity of benz[a]anthracene.

Certain consistent features are apparent in the chemical thermal transformations for many of the "reactive" aromatic hydrocarbons. As shown in Table III, a large number of the volatile products obtained from the reacting aromatic hydrocarbons are hydrogenated derivatives of the parent material.

Carbonization of aromatics essentially involves a dehydrogenation and concomittant condensation process to produce complex hydrogen deficient aromatic species. At least initially, these dehydrogenations are accomplished internally in many instances and involve intermolecular hydrogen transfers between reacting molecules. Such a mechanism previously has been proposed for catalytically induced carbonization reactions.[16] Our results indicate that this sequence is important in pure thermal uncatalyzed carbonization reactions.

Such hydrogen transfers could lead to the simultaneous formation of hydrogenated, less reactive (higher ionization potential) derivatives and more reactive aromatic derivatives or radicals, capable of undergoing further condensations. This pattern of thermal condensation may be discerned from the data for the interrupted d.t.a. residues of the reactive hydrocarbons, acenaphthylene, and 9,9′-bifluoroenylidene as summarized in Table IV.

Acenaphthylene provides an example of an aromatic hydrocarbon of high ionization potential possessing an unusually reactive site in the form of a vinyl double bond. At 300° an extensive polymerization has proceeded as evidenced by the exotherm in the thermogram in Fig. 3. At 360° a thermal depolymerization has begun. Paramagnetism is observed for the residue. At higher temperatures rearrangement of aromatic structures to form larger species is indicated. Dehydrogenations are accomplished internally resulting in formation and distillation of the volatile derivative acenaphthene. Increased concentrations of aromatic radicals are observed in the residues with increasing temperatures.

This reaction sequence may be generally summarized (see equation 2, p. 2056).

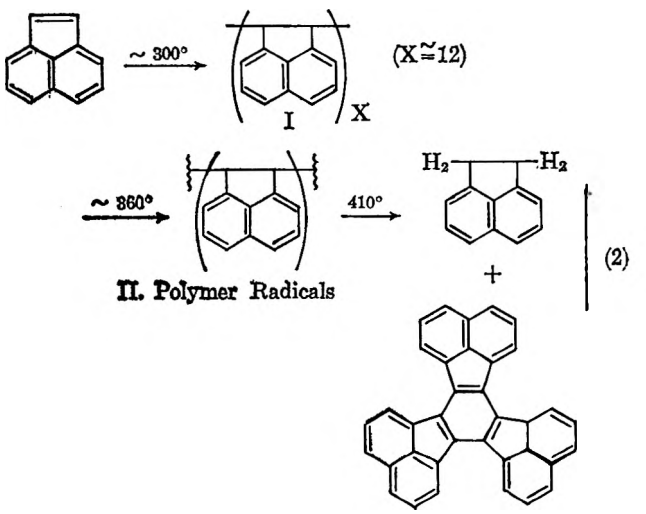
(15) F. A. Matsen, *J. Chem. Phys.*, **24**, 602 (1956).

(16) W. G. Appleby, J. W. Gibson, and G. M. Good, Preprints of Division of Petroleum Chemistry of American Chemical Society, Vol. 5, No. 4, pp. B-71.

TABLE III

CONDENSED NEW PRODUCTS FROM D.T.A. RUNS OF "REACTIVE" AROMATIC HYDROCARBONS

	Starting material	New product
LX	4-Vinylbiphenyl	Unknown aromatic hydrocarbons
LXI	10,15-Dihydro-5*H*-diindeno[1,2-*a*:1′,2′,*c*]-fluorene	None
LXII	1-Vinylnaphthalene	1-Vinylnaphthalene (monomer)
LXIII	10,15-Dihydro-5*H*-diindeno[2,1-a:1′,2′-*c*]-fluorene	None
LXIV	Acenaphthylene	Acenaphthene + unknown hydrocarbons
LXV	9,9-Bifluorenyl	Fluorene, 9,9′-bifluorenylidene, tetrabenzonaphthalene, and unknown hydrocarbon
LXVI	Benzo[*a*]coronene	Slight amount of hydrogenated derivative
LXVII	9-Cinnamylidenefluorene	Fluorene and major unknown hydrocarbon product
LXVIII	7,12-Dimethylbenz[*a*]anthracene	Slight amount of structurally similar hydrocarbon, (monomethyl?)
LXIX	Tribenzo[*a*,*e*,*i*]pyrene	Structurally similar hydrogenated derivative
LXX	Dibenzo[*a*,*i*]pyrene	Major amount of new products including large proportion of hydrogenated derivatives
LXXI	9,10-Dibenzylanthracene	Unknown hydrocarbon products
LXXII	Diacenaphtho[1,2-*j*:1′,2′-*l*]fluoranthene	Acenaphthylene + acenaphthene
LXXIII	Dibenzo[*b*,*k*]chrysene	None
LXXIV	Dibenzo[*def*,*mno*]chrysene	None
LXXV	Benzo[1,2,3-*cd*:4,5,6-*c*′*d*′]diperylene	Unknown hydrogenated derivative
LXXVI	1-Methyldibenzo[*b*,*i*]pyrene	Major unknown but structurally similar product
LXXVII	Pyranthrene	None
LXXVIII	9,9′-Bifluorenylidene	Fluorene + major amount of unknown aromatic hydrocarbon
LXXIX	1,6-Dimethyldibenzo[*b*,*i*]pyrene	Identical product to that obtained for LXXVI
LXXX	Naphthacene	5,12-Dihydronaphthacene
LXXXI	5,6,11,12-Tetraphenylnaphthacene	Unknown aromatic hydrocarbons
LXXXII	Rubicene	Slight amount of hydrogenated derivative
LXXXIII	Dibenzo[*a*,*l*]pentacene	Unknown hydrocarbons
LXXXIV	Pentacene	Isomeric dihydropentacenes

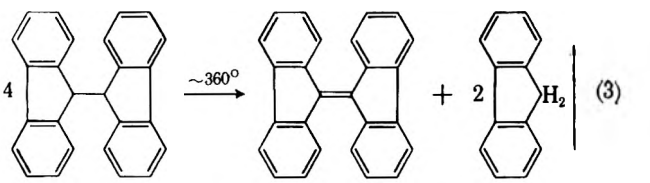


Decacyclene
+ highly condensed aromatic hydrocarbon and radical species

This reaction has been investigated previously by Dziewonski.[17] Identification of the trimer decacyclene as a product conforms to his early conclusions although the structural identification of the more complex products is still uncertain.

The hydrocarbon 9,9′-bifluorenylidene has been shown in this study to be formed as a thermal reaction product from the 9,9′-bifluorenyl by a hydrogen transfer disproportionation scheme as shown in equation 3.

The hydrocarbon fluorene is the volatile hydrogenated derivative produced.



9,9′-Bifluorenyl 9,9′-Bifluorenylidene Fluorene

The properties of progressive thermal condensation sequence products of 9,9′-bifluorenylidene are summarized in Table IV. Again with increasing temperature a continued increase in complexity of product and growth in size is apparent. At 750° an ultimate 31% infusible carbonaceous residue results. The concentration of free radicals also increases with heat-treatment temperature.

The initial thermal sequence for 9,9′-bifluorenylidene appears to involve a dehydrogenation and rearrangement to more condensed aromatic structures with concurrent formation of fluorene as a hydrogenated product. The hydrocarbon tetrabenzonaphthalene has been identified as one of the rearrangement products. This compound also has been reported to be a product of the pyrolysis of fluorene.[18] The generalized reaction scheme is shown in equation 4.

The pyrolysis of the reactive aromatic hydrocarbons are invariably accompanied by the formation of free radical species. It is felt that these radicals are transi-

(17) K. Dziewonski, *Chem. Ber.*, **53**, 142 (1920), and references cited therein.

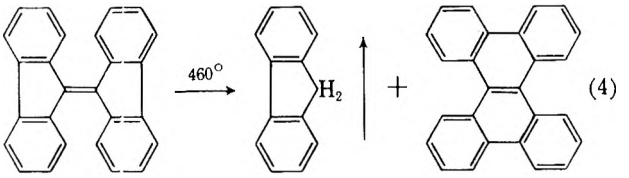
(18) K. Lang, H. Buffleb, and J. Kalowy, *ibid.*, **94**, 523 (1961).

TABLE IV

SUMMARY OF PROPERTIES OF RESIDUES FROM INTERRUPTED D.T.A. RUNS FOR ACENAPHTHYLENE AND 9,9′-BIFLUORENYLIDINE

	Starting material	Temp., °C.	Nature of residue	M.p., °C.[a]	% Residue	Molecular weight	Free radicals
1.	Acenaphthylene	25	Yellow solid	92	..	152	No
2.	Acenaphthylene	300	Orange crystalline solid	315	92	1890	No
3.	Acenaphthylene	360	Red crystalline solid	325–350	90	950	Yes
4.	Acenaphthylene	410	Brown amorphous solid	210, 340	42	1360	Yes
5.	Acenaphthylene	440	Brown amorphous solid	215, 325	37	2025[b]	Yes
6.	Acenaphthylene	750	Black carbonaceous solid	Infusible	21	..	Yes
7.	9,9′-Bifluorenylidene	25	Red solid	188	..	328	No
8.	9,9′-Bifluorenylidene	382	Red solid	110–115	94	396	Slight
9.	9,9′-Bifluorenylidene	400	Red solid	100, 170–184	88	565	Yes
10.	9,9′-Bifluorenylidene	450	Brown-red solid	115, 210–230	72	604	Yes
11.	9,9′-Bifluorenylidene	750	Black carbonaceous solid	Infusible	31	..	Yes

[a] In several residues, two melting points are reported as the material was heterogeneous. [b] Determined for benzene-soluble portion only.



9,9′-Bifluorenylidene Fluorene Tetrabenzonaphthalene
+ reactive condensed aromatic hydrocarbons and radicals

tory aromatic radicals formed by thermal dissociations of hydrogens at reactive ring sites, by cleavage of substituent groups, or by rearrangement. The formation of such stable radicals as well as the internal rearrangements of hydrogens appears to be intrinsic to the thermal condensation or carbonization process for many of the "reactive" aromatic hydrocarbons.

In summary, the thermal reactivities of the aromatic hydrocarbons in our system show a marked dependence on structure. Employing the spectral p-band measurement and the empirically derived ionization potential as a qualitative criterion of reactivity, it is evident that the aromatic hydrocarbons of high ionization potential are thermally "unreactive" whereas those of low ionization potential are thermally "reactive." Molecular size and concomittant physical stability criteria are seen to influence borderline cases in both categories. Additionally, hydrocarbons capable of undergoing vinyl-type polymerizations can produce thermal polymers which represent more reactive molecular entities capable of carbonizing.

Consistent patterns of hydrogen transfer and concurrent condensation to more reactive aromatic hydrocarbon molecules and radicals are found for many of the thermally "reactive" aromatics.

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Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes[1a]

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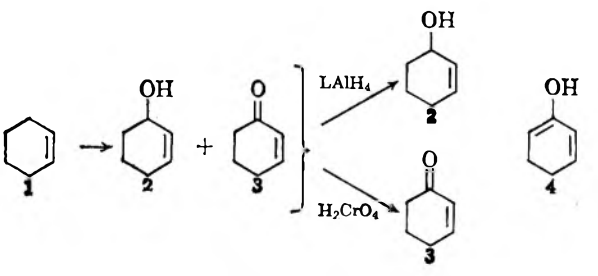
A re-examination of the oxidation of cyclohexene (**1**) with hydrogen peroxide–vanadium pentoxide (HP–VP, peroxyvanadic acid) revealed 2-cyclohexen-1-ol (**2**) to be a major reaction product. This contradicts an earlier report[2] claiming exclusive formation of 2-cyclohexen-1-one (**3**) as the volatile product. Similar oxidative experiments with the isomeric methylcyclohexenes (**7**, **13**, and **17**) demonstrate the reaction to be essentially nonselective as to site of oxidation and that both alcohols and ketones appear in the volatile products, these being a mixture of direct oxidation products and products derived from allylic shifts.

Treibs[2] and co-workers claimed 2-cyclohexen-1-ol (**2**) to be absent from the products of the oxidation of cyclohexene (**1**) with HP–VP and 2-cyclohexen-1-one (**3**) was reported to be the exclusive low boiling product (40% yield). *trans*-1,2-Cyclohexanediol (**6**) and adipic acid were reported as higher boiling products (9% yield for both). These authors considered 2-cyclohexen-1-one (**3**) to be present in part as the enol **4** to account for the formation of a borate ester.

We have demonstrated that 2-cyclohexen-1-ol (**2**)



(1)(a) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.; (b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.; (c) Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany.

(2) W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

is a major product of the oxidation of cyclohexene with HP–VP, and that it actually exceeds 2-cyclohexen-1-one (**3**) in the product mixture by a ratio of 2.3:1. The oxidation was repreated several times according to the published procedure,[2] and each experiment gave essentially the same product boiling at 61–63° (14 mm.) in reasonable agreement with the reported value. However, gas chromatographic studies show the presence of two sharply defined and completely separated peaks. The mixture of volatile products shows a maximum λ_{max}^{EtOH} 225 mμ (ε 3905) while the reported[3] maximum for **3** is 225 mμ (ε 11,270). Strong hydroxyl group absorption was noted in the infrared spectrum of the mixture. These data suggested the mixture to be **2** and **3**. Attempts to separate the mixture by fractional distillation through a spiral column and by preferential reaction with semicarbazide hydrochloride were ineffective. Accordingly, the products were directly interconverted and the identity of the components established through isolation of the individual pure compounds by oxidation to **3** and reduction to **2**.

A Jones' oxidation[4] with chromic acid in acetone solution readily converted the entire mixture to **3**. The course of the reaction was followed conveniently with gas chromatographic analyses at regular intervals. The peak of the gas chromatogram of the reaction product at termination of the oxidation coincides exactly with the smaller and second peak of the chromatogram of the original mixture. The oxidation product was identified as **3** through its ultraviolet spectrum, in agreement with Woodward's rules,[5] its ininfrared spectrum, and the melting point of its red 2,4-dinitrophenylhydrazone.[6] Other syntheses of **3**, each by a different procedure, have been reported.[7]

Reduction of the original volatile oxidation mixture with lithium aluminum hydride in ether solution gave a single product. This product shows no carbonyl band in its infrared spectrum but shows strong absorption in the hydroxyl and double bond regions. These data and the melting point of the phenylurethane derivative,[6] 107–109°, established the identity of the product as 2-cyclohexen-1-ol (**2**).

A reconstituted mixture (70% **2** and 30% **3**) prepared from pure **2** and **3** gives essentially identical spectra (ultraviolet and infrared) and gas chromatographic curve as those from the original mixture obtained by oxidizing cyclohexene with HP–VP.

Pure 2-cyclohexen-1-ol (**2**) was oxidized with HP–VP under the same conditions used for the oxidation of cyclohexene. The steam volatile products from this reaction were shown through gas chromatographic analyses to be a mixture of **2** and **3** in a ratio of 7.3:1. This experiment suggests **2** to be one of the precursors of **3**.

Several routes may exist for the formation of the various products obtained from the oxidation of cyclohexene with HP–VP. 2-Cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) may be rationalized as being formed from cyclohexene hydroperoxide by the indicated routes in Fig. 1. *trans*-1,2-Cyclohexanediol (**6**) may arise from cleavage of cyclohexene oxide which has been reported along with **2** as a product of the bimolecular epoxidation of cyclohexene by cyclohexene hydroperoxide.[8,9]

cis-1,2-Cyclohexanediol (**5**) and adipic acid are formed by direct oxidation of the double bond of cyclohexene. We suggest that peroxyvanadic acid, $H_3[V(O_2)O_3]$,[10] attacks the double bond of cyclohexene to form a cyclic ester of peroxyvanadic acid in a reaction reminiscent of the osmic ester formation of olefins.[11,12] The cyclic ester may then be hydrolyzed to *cis*-1,2-cyclohexanediol (**5**) or undergo cleavage to adipic aldehyde in the manner of periodate oxidation of 1,2-glycols.[13] The aldehyde is oxidized in turn to adipic acid. This rationalization suggested the possible presence of some *cis*-1,2-cyclohexanediol (**5**) in the reaction products. The diol **5** is not formed as a major product but we were able to establish its presence through gas chromatographic studies by enrichment of the crude reaction product with authentic *cis*-diol **5**. The diols **5** and **6** are present in the crude reaction product in the ratio of 1:15. The presence of the *trans*-diol **6** was established readily through gas chromatographic studies and direct isolation from the reaction products. Distillation and recrystallization afforded a pure sample of the diol **6** which shows no depression in melting point on admixture with authentic *trans*-1,2-cyclohexanediol (**6**). The proposed routes permit accumulation of *trans*-diol **6** with simultaneous formation of adipic acid.

Milas[14] reported that the HP–VP oxidation of cyclohexene in *t*-butyl alcohol gives a small amount of *cis*-1,2-cyclohexanediol (**5**), an unidentified aldehyde, and considerable quantities of adipic acid. This suggests that it may be possible to control selectively direct attack on the double bond over allylic attack by altering the reaction conditions.

An interesting parallel to the HP–VP oxidation of cyclohexene is provided by the work of Farmer and Moore.[15] These investigators demonstrated that both 2-cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) are formed (ratio 6:1) when cyclohexene (**1**) is oxidized with *t*-butyl hydroperoxide at 140°. These authors also demonstrated that oxidation of 1-methyl-1-cyclohexene (**7**) with *t*-butyl hydroperoxide yielded both ketones and alcohols among the products and that all possible allylic positions except on the methyl group were attacked. This is to be expected for a nonselective oxidation process and was rationalized through a free radical mechanism with a hydroperoxide and an olefin radical as intermediates.

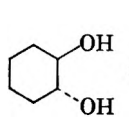
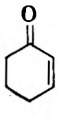
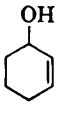
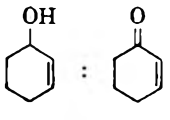
The effect of change in concentration of hydrogen peroxide on the composition of the products from the oxidation of cyclohexene was studied with gas chromatography. We found an increase of hydrogen peroxide

(3) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).
(4) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).
(5) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).
(6) F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941).
(7) For a reference list of other preparations of 2-cyclohexen-1-one, see K. I. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S. Johnson, *J. Org. Chem.*, **27**, 1612 (1962).
(8) R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).
(9) E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121 (1942).
(10) N. V. Sidgwick, "Chemical Elements and Their Compounds," Vol. 1, Oxford University Press, New York, N. Y., 1950, p. 810.
(11) R. Criegee, *Ann.*, **522**, 75 (1936).
(12) N. A. Milas and S. Sussmann, *J. Am. Chem. Soc.*, **58**, 1302 (1936).
(13) E. L. Jackson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 341.
(14) N. A. Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).
(15) E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1951).

concentration from 1/6 to 1/3 and 1/2 mole caused an increase in yield of **2** and **3**. However, additional increase of hydrogen peroxide failed to increase the yield, and not all the peroxide was consumed during the reaction. The results of these studies on 1/6, 1/3, and 1/2 mole of hydrogen peroxide per mole of cyclohexene are presented in Table I. Thus, the maximum yields of the mixture of **2** and **3** may be obtained with the 1/2 mole ratio.

TABLE I[a]

SUMMARY OF CYCLOHEXENE OXIDATIONS WITH HYDROGEN PEROXIDE

Moles of hydrogen peroxide per mole cyclohexene	Ratio of peak areas			Ratio
				
1/6	1	1.9	3.2	1.7
1/3	1	2.8	5.0	1.8
1/2	1	3.0	4.1	1.3

[a] These data are the average of two analyses.

To account for formation of a borate ester Treibs,[2] *et al.*, stated that 2-cyclohexen-1-one (**3**) exists in part as the enol **4**. In our hands, pure 2-cyclohexen-1-one (**3**) failed to give significant yields of borate ester since major portions of unchanged boric acid and 2-cyclohexen-1-one (**3**) were recovered (84 and 67%, respectively). We were, however, able to isolate a low yield (3.2%) of 2-cyclohexen-1-one (**3**) by steam distilling the pot residue after unchanged **3** had been distilled at 25–35° (0.05 mm.). To isolate **3** from the pot residue suggests that some **3** may have reacted with boric acid through the enol **4**. However, under identical conditions, 2-cyclohexene-1-ol reacted completely with boric acid, and a 78% yield of borate ester was isolated.

The HP–VP oxidations of each of the methylcyclohexenes (**7**, **13**, and **17**) in acetone were studied to determine whether the methyl substituent has any steric effect or directive influence on the site of the oxidation and, hence, the isomer composition. The gas chroma-

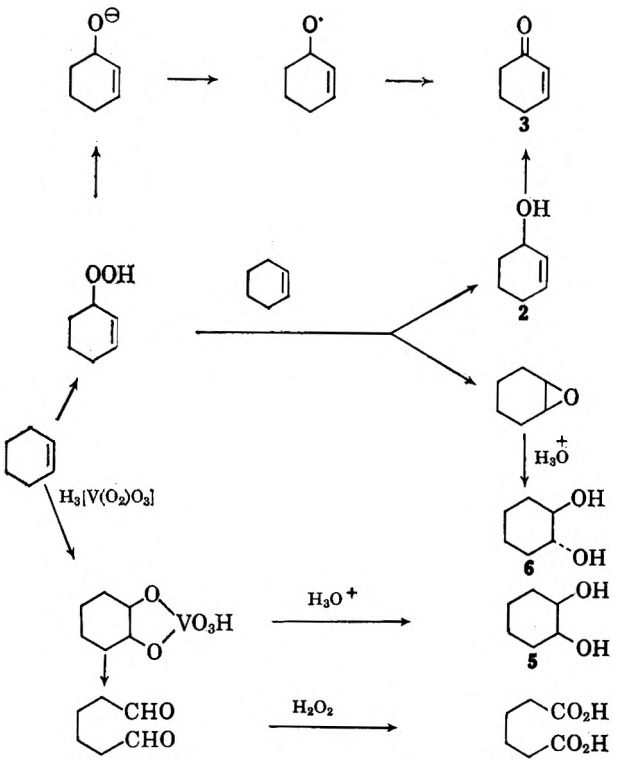
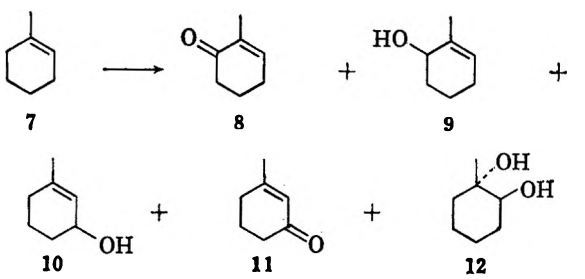


Figure 1

togram of the reaction products from 1-methyl-1-cyclohexene (**7**) showed seven *major* components of which five have been identified by successive enrichment with authentic products. The identified products from the oxidation of 1-methyl-1-cyclohexene (**7**) are **8**–**12** (see Table II).



Reduction of the reaction mixture containing **8**, **9**, **10**, **11**, and **12** with lithium aluminum hydride caused

TABLE II

GAS CHROMATOGRAPHIC ANALYSES OF HP–VP–METHYLCYCLOHEXENE OXIDATION PRODUCTS

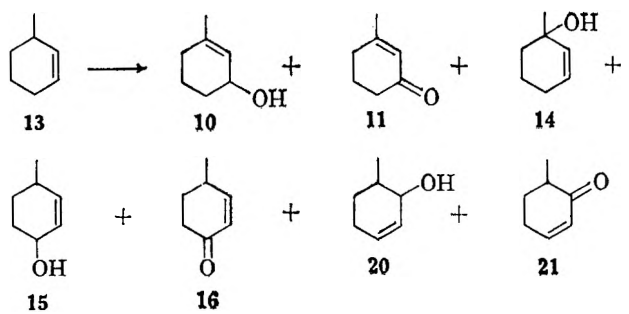
Starting material	Moles of hydrogen peroxide per mole of methylcyclohexene	Column	Oxidation products (time of emergence in min.; relative area)						
7	1/6	Carbowax[a]	Unknown alc. (2.8; 1.6)	Unknown ketone (5.9; 1)	**8** (8; 3.2)	**9** (8.8; shoulder)	**10** (12; 1.6)	**11** (22.2; 6.6)	**12**
7	1/6	PDEAS[b]	Unknown (2.1; 1.2)	**10** (3.2; 1)	**9** (4.5; 3.3)	**8** (5.4; 1.2)	**11** (12.2; 1.4)	**12** (24.8; 10.7)	
13	1/6	PDEAS[c]	Unknown alc. (1.0; 1.3)	**14** (2.1; 3.3)	**20** (3.2; 5.7)	**15** (5.0; 3.2)	**10** (6.2; 6.3)	**21** (6.5; shoulder)	**16** (8.0; 1.0)	**11** (15; 2.1)
17	1/6	PDEAS[d]	Unknown (5.5; 1.4)	**20** (6.1; 5.3)	Unknown (6.7; shoulder)	**18** (7.0; 2.9)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 2.8)	
17	1/3	PDEAS[d]	Unknown (5.5; 0.7)	**20** (6.1; 2.8)	Unknown (6.7; shoulder)	**18** (7.0; 1.2)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.0)	
17	1/2	PDEAS[d]	Unknown (5.5; 0.5)	**20** (6.1; 3.6)	Unknown (6.7; shoulder)	**18** (7.0; 1.5)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.2)	

[a] 10% Carbowax 20M on alkaline firebrick; 1/4 in. × 5 ft.; temperature programmed from 130–200°; helium flow, 80 ml./min. [b] 15% PDEAS on acid-washed firebrick; 1/4 in. × 5 ft.; 140°; [c] Same as *b*, except 135°. [d] 15% PDEAS on acid-washed firebrick; 1/4 in. × 4 m.; 160°; helium flow, 65 ml./min. [e] From PDEAS the alcohol **10** emerges with the ketone **21**; these can, however, be separated on Carbowax at 115°. A quantitative estimation is, however, difficult because **21** polymerizes on the alkaline support.

disappearance of **8** and **11**, and an increase of **9** and **10**; this latter compound is present as a minor component in the crude oxidation product. Oxidation of the mixture containing **8**, **9**, **10**, and **11** with Jones' reagent in acetone solution[4] caused disappearance of **9** and **10** with simultaneous increase of **8** and **11**.

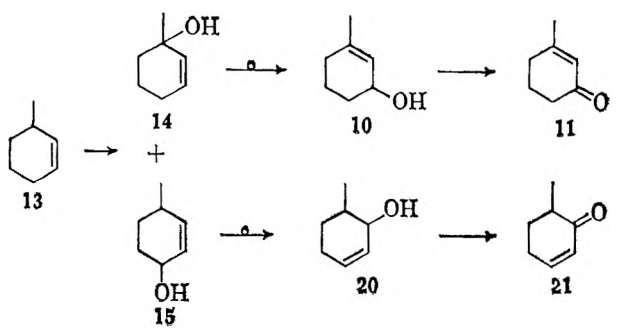
1-Methyl-1-cyclohexene (**7**) was oxidized with chromium trioxide in acetic acid, according to the method of Whitmore and Pedlow,[6] to determine whether this closely related reaction gives the reported mixture of 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) in the ratio of 1:9.6. We obtained a ratio of 1:7.8. Gas chromatographic analyses also showed the presence of five additional, minor products.

3-Methyl-1-cyclohexene (**13**) was oxidized with the HP–VP oxidant, and the crude product steam distilled to minimize high boiling products (presumed to be diols). These were observed as six minor peaks appearing late in the gas chromatogram. The gas chromatogram of the steam-distilled mixture showed eight peaks, of which seven have been identified (see Table II). The presence of the expected oxidation products **14**, **15**, and **16** from **13** was established by gas chromatographic studies of samples successively enriched with authentic materials.

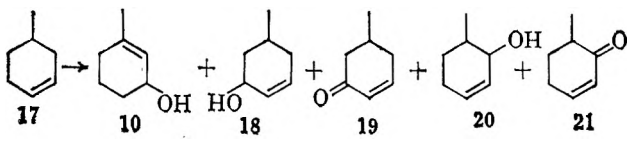


The identities of the remaining peaks were established in a circuitous manner. The total mixture was oxidized with Jones' reagent to a mixture of three ketones with gas chromatography peaks in the ratio 1.0:1.7:3.0. These peaks were shown to be due to ketones **21**, **16**, and **11** in this order, by collecting the ketones in a 2,4-dinitrophenylhydrazine solution as they emerged from the column. The 2,4-dinitrophenylhydrazones were recrystallized and melted at 147–151°, 164–165°, and 176–178°, respectively. An admixture with authentic 2,4-dinitrophenylhydrazones showed no depression in melting point. The presence of the alcohols **10** and **20** was then shown in the HP–VP oxidation mixture by enrichment with authentic materials.

The presence of the abnormal oxidation products **10**, **11**, **20**, and **21** among the expected allylic oxidation products suggested that allylic rearrangement takes place during the HP–VP oxidation of 3-methyl-1-cyclohexene (**13**). The products **10**, **11**, **20**, and **21** are presumed to form as shown (bottom, col. 1).



4-Methyl-1-cyclohexene (**17**) was oxidized similarly and five of the seven major steam-volatile products were identified by enrichment of the product mixture with authentic materials (see Table II). The presence of the unexpected alcohol **10** was confirmed by oxidizing the mixture with Jones' reagent, and showing the presence of **11** in the product by enrichment with authentic **11** in gas chromatographic studies, and by isolating the 2,4-dinitrophenylhydrazone of **11** as it emerged from the column.



While **13** yields both the normal oxidation products, **15** and **16**, and the products of the allylic shift, **20** and **21**, we were unable to detect **15** and **16**, the corresponding products produced by allylic shift accompanying **18** and **19** in the oxidation of **17**.

Experimental

Starting Materials.—The cyclohexene (**1**) used for the HP–VP oxidation was homogenous by gas chromatography (Ucon Polar column at 40°). 1-Methyl-1-cyclohexene (**7**), b.p. 110.3°, showed a single gas chromatographic peak (Ucon Polar column at 50°). 3-Methyl-1-cyclohexene (**13**), b.p. 102.5°, was obtained by fractional distillation from a mixture of 1-methyl-1-cyclohexene (**7**) and 3-methyl-1-cyclohexene (**13**). The gas chromatographic curve (200-ft. squalane capillary column at 26°, hydrogen flame detector) of the fractionated 3-methyl-1-cyclohexene showed 3-methyl-1-cyclohexene (**13**) to be 99% pure. Under these conditions 3-methyl-1-cyclohexene (**13**) and 4-methyl-1-cyclohexene (**17**) showed separation. 4-Methyl-1-cyclohexene (**17**), b.p. 102.7°, was shown to be 99% pure through the same gas chromatographic procedure as described for 3-methyl-1-cyclohexene.

Oxidations with HP–VP.[2] **(a) Cyclohexene, 1/6 Mole Hydrogen Peroxide.**—To an 8-l. vessel equipped with stirrer, condenser, and dropping funnel were added 500 g. (6.1 moles) of cyclohexene (**1**) and 5.0 l. of acetone. To the well stirred mixture was added the catalyst prepared by mixing 20 ml. of 30% hydrogen peroxide and 2.0 g. of vanadium pentoxide at 5–10° and diluting with 200 ml. of precooled (−10°) acetone. The catalyst mixture was filtered as rapidly as possible so that the temperature did not rise above −2° during preparation. The flask was cooled in a water bath and 100 ml. (*ca.* 1 mole total) of 30% hydrogen peroxide was added to the agitated mixture over about 30 min. The reaction was maintained at 30°. After about 10 ml. of hydrogen peroxide was added, the color changed from orange to green. If the color change did not take place, an additional 5.0 ml. of hydrogen peroxide was added. The mixture was stirred an additional hour and then allowed to stand overnight. The reaction mixture was then held at reflux for 1 hr. with stirring and checked for hydrogen peroxide with titanium sulfate solution (if hydrogen peroxide was present, more cyclohexene was added and the reaction held at reflux for an additional hour). If peroxide was absent, acetone and excess cyclohexene were distilled (4 to 4.5 l.), the distillate diluted with water, and about 100 g. of cyclohexene was recovered from the water-insoluble layer. The residue was dried over anhydrous sodium sulfate, filtered, and distilled at 61–63° (14 mm.) to give 42–45 g. of a mixture of 2-cyclohexen-ol (**2**) and 2-cyclohexen-1-one (**3**). Gas chromatographic studies on 15% phenyldiethanolamine succinate (PDEAS) substrate supported on a column of 60–80-mesh acid-washed firebrick (1/4 in. × 5 ft.) showed the presence of two sharply defined, completely separated peaks (2 min. at 140°; 80 ml. helium/min.; Wilkens Model A-90P, thermal conductivity detector). A cleaner product containing less impurities in the gas chromatogram was obtained if the crude product was steam

distilled before final distillation. The distilled product gave λ_{max}^{EtOH} 225 mμ (ε 3905)[16]; $\lambda_{max}^{CS_2}$ 3.0 and 5.95 μ.

(b) **Cyclohexene, 1/3 Mole Hydrogen Peroxide and (c) Cyclohexene, 1/2 Mole Hydrogen Peroxide.**—These oxidations were carried out essentially as described for part a. The yield of product boiling at 61–64° (14 mm.) was 63–65 g. for 1/3 mole and 78–80 g. for 1/2 mole. Gas chromatographic data on parts a, b, and c are summarized in Table I and described as part of the Jones' oxidation procedure.

(d) **1-Methyl-1-cyclohexene (7).**—The oxidation of **7** was similar to part a and was carried out in a 2-l., three-necked flask containing 1 l. of acetone and 96 g. (1 mole) of **7**. The catalyst was prepared from 0.4 g. of vanadium pentoxide and 2 ml. of cold 30% hydrogen peroxide and diluted with 30 ml. of acetone after 2–3 min.; see Table II for gas chromatographic data of the steam-distilled product mixture. 1-Methyl-*trans*-1,2-cyclohexanediol (12) crystallized directly from the reaction mixture and was also isolated as a high boiling fraction, b.p. 100° (12 mm.), m.p. 84–86°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.53; H, 10.83. Found: C, 64.51; H, 10.59.

(e) **3-Methyl-1-cyclohexene (13) and (f) 4-Methyl-1-cyclohexene (17).**—These olefins were oxidized in the same manner as described in part d, and the results are tabulated in Table II.

Oxidation of 1-Methyl-1-cyclohexene (7) with Chromic Acid.—1-Methyl-1-cyclohexene (**7**) (96 g. 1.0 mole), was oxidized according to the precedure of Whitmore and Pedlow[6] except that the reaction mixture was steam distilled rather than extracted. The steam distillate was saturated with salt, extracted with ether, the ether dried over anhydrous magnesium sulfate, filtered, and distilled. The distillation residue was directly injected onto a 1/4 in. × 5 ft. gas chromatographic column containing 15% PDEAS on 60–80-mesh acid-washed firebrick. Flow rate was 80 ml. helium/min. and column temperature was 140°. Two major peaks in the ratio of 1:7.8 were observed. These were established as 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexene-1-one (**11**) by successively enriching the reaction product with authentic ketones **8** and **11** and analyzing by gas chromatography.

Jones' Oxidations[4] of the Reaction Products from HP–VP Oxidations. (a) **Crude Mixture of 2-Cyclohexen-1-ol (2) and 3-Cyclohexen-1-one (3).**—The crude reaction product from the oxidation of cyclohexene with HP–VP[2] was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether layer dried over anhydrous magnesium sulfate, filtered, and the ether distilled slowly under water aspirator vacuum. The concentrate (424 g.) was dissolved in 5 l. of redistilled acetone and oxidized by dropwise addition of Jones' reagent[4] to the well stirred solution. The reagent is a mixture of 267 g. of chromium trioxide and 230 ml. of sulfuric acid (Spectro Grade 1.84) made up to 1.0 l. with distilled water.[4] The temperature of the reaction was maintained at 20–30° by cooling in a water bath. Progress of the oxidation (2 hr.) was followed by occasionally withdrawing a 1-ml. sample to which was added about 25 mg. of sodium bicarbonate and the pH checked to ensure neutrality. The sample was shaken; the solution decanted and dried over anhydrous magnesium sulfate. The supernatent liquid was directly injected onto the PDEAS column at 140°. Two peaks were observed before oxidation was begun. As the oxidation proceeded, the second peak grew at the expense of the first peak until at termination only the second peak remained. The orange-yellow end point was maintained for about 10 min. This end point is demonstrated easily with a drop of Jones' reagent in a few milliliters of acetone. A few drops of isopropyl alcohol will consume the excess reagent. The reaction product was decanted and the suspension of green salts rinsed with a few milliliters of acetone. Sodium bicarbonate (50 g.) was added to reaction mixture, suspension filtered, anhydrous magnesium sulfate (500 g.) added, the suspension filtered once more, and the acetone distilled through a Vigreux column. On occasion it was necessary once more to dry the product with anhydrous magnesium sulfate before final distillation. Distillation at 61° (14 mm.) gave 371 g. of 2-cyclohexen-1-one (**3**); λ_{max}^{EtOH} 224 mμ (ε 11,716) and $\lambda_{max}^{CS_2}$ 5.95 μ.[16] The red 2,4-dinitrophenylhydrazone was recrystallized from isopropyl alcohol and melts at 166–167°.[3,6]

(b) **Products from 1-Methyl-1-cyclohexene (7).**—The crude reaction product obtained from the HP–VP oxidation of 1-methyl-1-cyclohexene (**7**) was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether separated and concentrated by distillation. The concentrate was oxidized with Jones' reagent in a manner similar to part a but on a smaller scale. The oxidation product was isolated by steam distillation, extracted with ether, and the dried ether concentrate injected onto an alkaline Carbowax 20M gas chromatographic column, temperature programmed from 30–200°.

The peaks represented by 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) were identified by enriching the reaction product sample with authentic materials. The peaks due to the alcohols **9** and **10** were not present in the gas chromatogram.

(c) **Products from 3-Methyl-1-cyclohexene (13).**—The Jones' oxidation of the products from HP–VP oxidation of **13** was conducted in the same manner as for part b. The gas chromatogram (PDEAS column at 135°) showed three peaks in the ratio of 1.0:1.7:3.0. The ketones were collected from the PDEAS column in a 2,4-dinitrophenylhydrazine solution. The resulting red 2,4-dinitrophenylhydrazone derivatives were collected, recrystallized, and found to melt at 147–151°, 164–165°, and 176–178°. Admixtures of these red 2,4-dinitrophenylhydrazones with 2,4-dinitrophenylhydrazones derivatives of authentic 6-methyl-2-cyclohexen-1-one (**21**), 4-methyl-2-cyclohexen-1-one (**16**), and 3-methyl-2-cyclohexene-1-one (**11**), respectively, show no depression in melting point. The ketones from the individual peaks were collected in ether as they emerged from the column and used to identify peaks in the chromatogram of the crude reaction product and as a source for lithium aluminum hydride reduction to obtain the respective alcohols.

(d) **Products from 4-Methyl-1-cyclohexene (17).**—The Jones' oxidation of **17** was carried out as in part b. The presence of **11**, which emerged last on the PDEAS column, was shown by enrichment with authentic **11** and by the isolation of its red 2,4-dinitrophenylhydrazone derivative, m.p. 176–178°, which does not depress the melting point of the 2,4-dinitrophenylhydrazone of authentic 3-methyl-2-cyclohexen-1-one (**11**).

Lithium Aluminum Hydride Reductions. (a) **Mixture of 2-Cyclohexen-1-ol (2) and 2-Cyclohexen-1-one (3).**—To a 5-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel with pressure equalizing side arm, containing 42 g. lithium aluminum hydride dissolved in 3 l. of anhydrous ether, was added a 300-g. sample of a mixture comprised of 37% 2-cyclohexen-1-one (**3**) and 63% 2-cyclohexen-1-ol (**2**) at a rate to maintain gentle reflux. Two hours were required for addition. The reaction mixture was stirred an additional 4 hr. at reflux temperature and water was added dropwise until evolution of gases ceased. The suspension was allowed to settle; the ether solution was decanted and tested with water to ensure complete destruction of lithium aluminum hydride. The suspended salts were rinsed twice with 200-ml. portions of ether and the combined ether solution dried over anhydrous magnesium sulfate, filtered, and ether distilled. The concentrate was distilled at 64–65° (10.5 mm.) to give 240 g. of 2-cyclohexen-1-ol (**2**) whose infrared spectrum showed $\lambda_{max}^{CS_2}$ 3.0 and 6.08 μ. The gas chromatogram (PDEAS at 115°) showed a single major peak and no peak corresponding to 2-cyclohexen-1-one (**3**). The phenyl urethane melts at 107–109°.[6]

(b) **Crude Products from 1-Methyl-1-cyclohexene (7).**—The crude HP–VP products of 1-methyl-1-cyclohexene (**7**) were reduced with lithium aluminum hydride as described under part a. The products were isolated by steam distillation. The steam distillate was saturated with salt and extracted with ether; the ether layer was separated and washed with small portions of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 130°). The peaks corresponding to the ketones **8** and **11** were completely absent. The peaks corresponding to the alcohols **9** and **10** were found to have increased.

Borate Ester Preparation. (a) **From 2-Cyclohexen-1-ol (2).**—A mixture of 49.0 g. (0.5 mole) of 2-cyclohexene-1-ol (**2**), 8.4 g. (0.136 mole) boric acid, and 100 ml. of dry benzene was heated at reflux temperature for approximately 2 hr. until water–benzene azeotrope (7.0 ml. total) no longer collected in the Dean–Stark separator. The boric acid completely dissolved within a few minutes after reflux was attained. Most of the benzene (75 ml.) was distilled at atmospheric pressure and the product distilled through a short-path Vigreux column at 30–115° (0.04 mm.). The benzene forerun was discarded and the product fractionated

(16) D. Dusterhoft of Lakeside Laboratories kindly carried out these determinations.

through a spiral column to give 15.8 g. recovered **2** and 32.0 g. (0.133 mole, 78% yield based on boric acid) of colorless boric acid ester, b.p. 133–145° (0.2 mm.). A center cut, b.p. 142–145° (0.2 mm.), was used for analyses and infrared spectrum; λ_{max}^{neat} 2.95, 6.08, 7.05, 7.24, 7.60, 8.00, 9.60, 9.40, 9.56, 10.42, 10.76, 11.11, and 13.80 μ.

Anal. Calcd. for $C_{18}H_{27}BO_3$: B, 3.57. Found: B, 3.73.

A 14.9-g. (0.049 mole) sample of the borate ester of **2** was steam distilled, the distillate extracted with ether, the ether extract dried over anhydrous magnesium sulfate, filtered, and the ether distilled to give 12.3 g. (85% recovery) of regenerated 2-cyclohexen-1-ol (**2**). The infrared spectrum and gas chromatogram (PDEAS at 140°) were identical with those of original **2**. The contents of the steam distillation reaction flask were colorless.

(b) **From 2-Cyclohexen-1-one (3).**—Under conditions similar to part a, 2-cyclohexen-1-one (**3**) (0.5 mole) and boric acid (0.136 mole) in 100 ml. of benzene gave 2 ml. of water–benzene azeotrope. The dark-colored reaction product was filtered to yield 7.1 g. (84% recovery) of unchanged boric acid. The filtrate was distilled at 25–35° (0.05 mm.) to give 32.1 g. (66% recovery) of 2-cyclohexene-1-one whose gas chromatogram (PDEAS at 125°) and infrared spectrum were identical with those of original ketone **3**.

The dark-colored, viscous pot residue was steam distilled to give 1.6 g. (0.016 mole, 3.2%) of regenerated 2-cyclohexen-1-one (**3**) whose infrared spectrum, gas chromatogram (PDEAS at 125°) and gas chromatogram of an admixture with **3** were identical with 2-cyclohexene-1-one (**3**). A dark-colored tar remained in the steam distillation flask.

Preparation of Comparison Compounds. (a) ***cis*-1,2-Cyclohexanediol (5).**—A sample of a mixture of *cis*-1,2-cyclohexanediol (**5**) and *trans*-1,2-cyclohexanediol (**6**) was separated by gas chromatography on PDEAS at 162° and collected in ethyl acetate. The retention times were 11.5 and 12.4 min., respectively.

(b) **2-Methyl-2-cyclohexen-1-one (8).**—2-Methyl-2-cyclohexen-1-one (**8**) was obtained by dehydrohalogenation[17] of 2-chloro-2-methylcyclohexanone[18] with lithium bromide and lithium carbonate in dimethylformamide. The ketone **8**, $n^{23}D$ 1.4852, λ_{max}^{neat} 6.05 μ, gives a single peak on the PDEAS gas chromatographic column at 145°. Its red 2,4-dinitrophenylhydrazone crystallized from isopropyl alcohol melts at 207–209°.[19]

(c) **2-Methyl-2-cyclohexen-1-ol (9).**—The alcohol **9** was obtained from the ketone **8** *via* lithium aluminum hydride reduction in ether solution followed by steam distillation. The product shows a single gas chromatographic peak on the PDEAS column at 145°.

(d) **3-Methyl-2-cyclohexen-1-ol (10).**—A sample of 3-methyl-2-cyclohexen-1-one (**11**) was reduced with lithium aluminum hydride in ether to give 3-methyl-2-cyclohexen-1-ol (**10**), $n^{23}D$ 1.4835, b.p. 82–84° (15 mm.,) and λ_{max}^{neat} 3.07 and 6.08 μ. Gas chromatographic analysis on PDEAS at 140° shows a single peak.

(e) **3-Methyl-2-cyclohexen-1-one (11).**—A 182-g. (1.0 mole) sample of 4-carbethoxy-3-methyl-2-cyclohexen-1-one,[20] $n^{23}D$ 1.4842, was hydrolyzed by steam distilling from 1 l. of 15% sulfuric acid. The steam distillate was saturated with salt and extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and distilled to give 87 g. (0.79 mole, 79% yield) of 3-methyl-2-cyclohexene-1-one (**11**), b.p. 80–95° (9 mm.,) $n^{25}D$ 1.4910, and λ_{max}^{neat} 6.05 and 6.2 μ. The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate melts at 176–178°.

(f) **1-Methyl-2-cyclohexen-1-ol (14).**—A 24-g. sample (0.25 mole) of 2-cyclohexen-1-one was added to 2 equivalents of methylmagnesium iodide contained in a 1-l., three-necked flask equipped with stirrer, condenser protected with a calcium chloride tube, and dropping funnel. The 2-cyclohexene-1-one was added to the chilled (−5°) reaction flask over a 2-hr. period. The reaction mixture was allowed to come to room temperature and then heated at reflux temperature for 0.5 hr. The reaction mixture was then poured onto 500 g. of ice, and the product was directly steam distilled without addition of ammonium chloride or acid. [It was intentional that acid was avoided to minimize isomerization of 1-methyl-2-cyclohexen-1-ol (**14**) to 3-methyl-2-cyclohexen-1-ol (**10**).] The steam distillate (1 l.) was saturated with salt, extracted with 200 cc. of ether, and washed with two small portions of water; the ether layer separated, dried over anhydrous magnesium sulfate, filtered, and the ether distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 100°) and found to be a mixture of 36% 1-methyl-2-cyclohexen-1-ol (**14**),[6] 58% 3-methylcyclohexanone,[6] and 6% 3-methyl-2-cyclohexen-1-ol (**10**).[5] The 3-methylcyclohexanone and the alcohol **10** were identified by enriching the total reaction product with authentic materials and analyzing by gas chromatography. A pure sample of the alcohol **14** was obtained by collection from the PDEAS column at 125°.

(g) **4-Methyl-2-cyclohexen-1-ol (15).**—The ketone **16** was reduced with lithium aluminum hydride in ether to give 4-methyl-2-cyclohexen-1-ol (**15**) which shows essentially a single gas chromatographic peak; the yield of **15** was 71%.

(h) **4-Methyl-2-cyclohexen-1-one (16).**—A procedure similar to j was employed in the preparation of 4-methyl-2-cyclohexen-1-one (**16**) from 4-methylcyclohexanone. The ketone **16** gave a red 2,4-dinitrophenylhydrazone which melts at 168–169° on recrystallization from isopropyl alcohol.

(i) **5-Methyl-2-cyclohexen-1-ol (18).**—A sample of 5-methyl-2-cyclohexen-1-one (**19**) was purified by gas chromatography on PDEAS, reduced by lithium aluminum hydride, and the product isolated by steam distillation. The product, 5-methyl-2-cyclohexen-1-ol (**18**), shows a single peak on the PDEAS gas chromatographic column.

(j) **5-Methyl-2-cyclohexen-1-one (19).**—A 112-g. sample of *dl*-3-methylcyclohexanone was chlorinated with sulfuryl chloride in carbon tetrachloride solution.[19] The chlorocyclohexanone was distilled at 35–87° (0.1 mm.) and shown by gas chromatography on PDEAS at 170° to contain 3-methylcyclohexanone in the initial cut. Center cuts, b.p. 50–80° (0.1 mm.), were free of 3-methylcyclohexanone but appeared to be a mixture of 2-chloro-3-methylcyclohexanone and 2-chloro-5-methylcyclohexanone since double peaks were observed in the gas chromatogram on PDEAS at 170° column temperature.

Dehydrohalogenation[17] in the presence of lithium bromide and lithium carbonate in dimethylformamide solvent was carried out on a 50-g. sample of the mixture of chloro ketones. The product was isolated by steam distillation and extraction of the steam distillate with ether. Dimethylformamide was removed from the ether extract by washing with water. The product, b.p. 34–54° (0.1 mm.), was shown by gas chromatography on PDEAS at 170° to be a mixture containing the desired product, 5-methyl-2-cyclohexen-1-one (**19**) (3.5 min. retention time), as well as 3-methyl-2-cyclohexen-1-one (**11**) and 3-methylphenol (6.2 and 14 min., respectively). The latter compounds were identified by enriching the mixture with authentic materials. A pure sample of 5-methyl-2-cyclohexen-1-one (**19**) was obtained by collecting the ketone as it emerged from the column. An orange 2,4-dinitrophenylhydrazone was prepared from the collected sample and found to melt at 148–149°[21] after recrystallization from methanol.

(k) **6-Methyl-2-cyclohexen-1-ol (20).**—A sample of 6-methyl-2-cyclohexen-1-one (**21**) was purified through gas chromatography (PDEAS column at 150°) by collecting in ether solution. The ether solution was added dropwise to a stirred solution of lithium aluminum hydride in ether. The reaction was heated at reflux temperature for approximately 0.5 hr., cooled, and the excess lithium aluminum hydride cautiously destroyed by the dropwise addition of water. Additional water was added and the reaction product steam distilled. The alcohol **20** was isolated from the steam distillate by extraction with ether, the ether solution dried, concentrated, and analyzed by gas chromatography (PDEAS column at 120°) which showed essentially a single peak with a slight trailing shoulder. This shoulder was assumed to be due to the presence of *cis* isomer. The yield of **20** was 72%. The alcohol **20** was added to a sample of the HP–VP oxidation product of 4-methyl-1-cyclohexene (**17**) and this enrichment established the presence of **20** in the reaction mixture.

(l) **6-Methyl-2-cyclohexen-1-one (21)** was generously donated by D. R. Coulson and E. J. Warawa of Columbia University. Reduction with lithium aluminum hydride gave 6-methyl-2-cyclohexen-1-ol (**20**).

(17) R. Joly, J. Warnaut, G. Nomine, and D. Bertin, *Bull. soc. chim. France*, 360 (1958).

(18) Generously donated by J. Levy and H. L. Goering of the University of Wisconsin.

(19) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

(20) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893).

(21) H. L. Goering and J. P. Blanchard, *J. Am. Chem. Soc.*, **73**, 5863 (1951).

Further Hydrolytic Studies on Tetracyanocyclopropanes[1]

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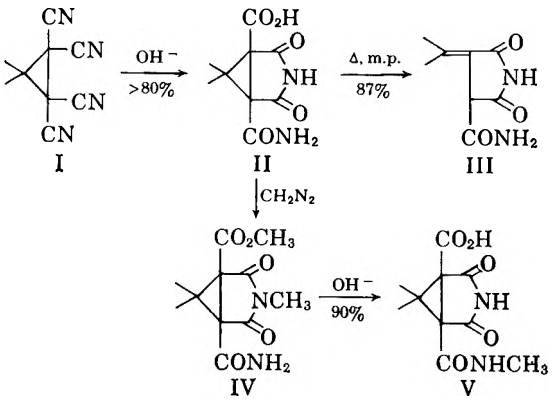
1,1,2,2-Tetracyanospiro[2.4]heptane has been subjected to a hydrolytic sequence leading ultimately to methyl spiro[2.4]heptane-1,1,2,2-tetracarboxylate. Two additional[2] examples of ring cleavage during the decarboxylation of cyclopropanecarboxylic acids are presented, as is another example of the reaction in which a five-membered imide ring between *cis* substituents is hydrolyzed on one side of a cyclopropane ring plane and formed on the opposite side. N.m.r. evidence for hydrogen bonding in VIII supports a previously proposed mechanism for the latter reaction. The rapid alkaline hydrolysis of 3,3-dialkyltetracyanocyclopropanes to acid amide imides is shown to be general, with three examples in the spiro series.

Several unusual reactions (Scheme 1) were encountered[2] in the hydrolysis of 3,3-dimethyl-1,1,2,2-tetracyanocyclopropane (I) to the corresponding acid. Conversion of I to the acid amide imide (II) was complete after a few minutes of reflux with dilute base, after which further hydrolysis was extremely slow. Prolonged reflux of II with alkali ultimately gave the diacid imide, which failed to hydrolyze further. At its melting point, II lost carbon dioxide with cleavage of

SCHEME 1



the three-membered ring, giving III. Finally, hydrolysis of IV, obtained from the reaction of II with diazomethane, proceeded smoothly to V by cleavage of the N-methylimide ring followed by ring closure to an imide by reaction of the *cis* amide and ester functions on the opposite plane of the cyclopropane ring.

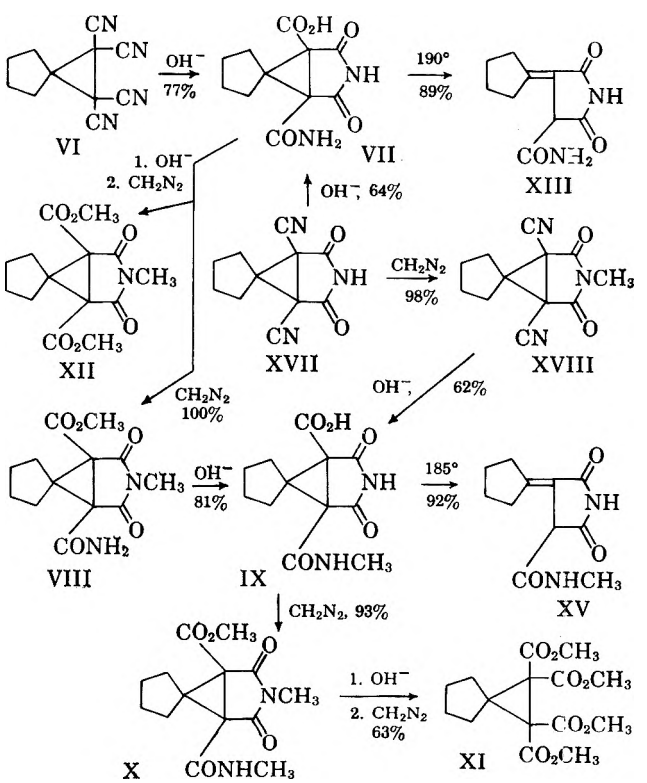
Cessation of the initial hydrolysis at II (and after lengthy reflux, at the diacid imide) can be rationalized in terms of the sluggishness with which hydroxide ion would attack the dianion of II (or the trianion of the diacid imide).[3] Compelling arguments were presented[2] to show that decarboxylation of II to III involves the *cis* amide carbonyl (and not the imide carbonyl) assisting in the proton removal. Finally, hydrogen bonding in IV between the amide nitrogen and the imide carbonyl oxygen closest to it was postulated as the principal reason why attack by base at that imide carbonyl was favored; the product V follows logically from attack by base at that point.

To determine whether these unusual reactions were general, the tetracyanocyclopropane VI, from cyclopentanone,[4] has been subjected in detail to a similar sequence of conversions, and the present paper describes the results. Limited hydrolytic experiments on tetracyanocyclopropanes from cyclohexanone and cyclobutanone are also described.

Results

The tetracyanocyclopropane VI[5] was prepared from cyclopentanone, bromomalononitrile, and iodide ion.[4] Its ultimate hydrolysis to the corresponding tetracarboxylic acid (methyl ester XI) and various intermediate reactions are shown in Scheme 2.

SCHEME 2



Reflux with potassium hydroxide in aqueous methanol converted VI to the acid amide imide VII. The structure of VII follows from its elemental analysis, neutralization equivalent (dibasic), and from its n.m.r. spectrum, which in dimethyl sulfoxide showed singlets at -1.12 τ (imide[2]) and 2.44 τ (amide) with relative areas 1:2. The same product was obtained by alkaline

(1) We are indebted to the Petroleum Research Fund, American Chemical Society (grant 488-C), and to the National Science Foundation (G 14289) for financial support.

(2) H. Hart and F. Freeman, *J. Am. Chem. Soc.*, **85**, 1161 (1963).

(3) This is, in fact, an oversimplification, but in the absence of mechanistic studies, further discussion seems at present unwarranted.

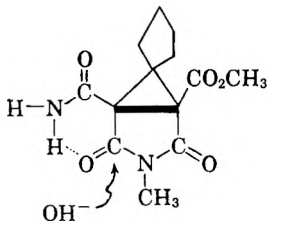
(4) H. Hart and F. Freeman, *J. Org. Chem.*, **28**, 1220 (1963).

(5) Because the systematic names of all compounds described in this paper are cumbersome, they will be given only in the experimental part; otherwise they shall be referred to by number or a trivial name.

hydrolysis of the known[6] dinitrile XVII. Prolonged hydrolysis of VII proceeded only as far as the diacid imide, which was converted by diazomethane to its trimethyl derivative XII, whose n.m.r. spectrum showed sharp singlets at 6.37 τ ($O-CH_3$) and 7.25 τ ($N-CH_3$), and a complex multiplet from 8.0–8.5 τ (CH_2), relative areas 6:3:8.

When heated at its melting point for a few minutes, VII lost carbon dioxide and gave XIII. Its n.m.r. spectrum (in dimethyl sulfoxide) showed imide N–H (−1.07 to −0.73 τ), amide N–H (2.43 to 3.53 τ), and a sharp singlet at 4.43 τ (C–H) with relative areas 1:2:1. XIII gave a positive Baeyer test for unsaturation, and with diazomethane gave an N-methyl derivative (XIV).

Reaction of VII with diazomethane afforded a dimethyl derivative VIII, whose n.m.r. spectrum in deuteriochloroform showed sharp singlets at 6.22 τ ($O-CH_3$) and 7.08 τ ($N-CH_3$) as well as a broad band in the 8.3-τ region, with relative areas 3:3:8. The n.m.r. also showed broad equal singlets at 2.48 and 3.35 τ, each corresponding to a single proton of the amide group. This supports the postulated[2] hydrogen bonding of one amide hydrogen to the imide carbonyl in such compounds, which should make that carbonyl the most vulnerable position for attack by hydroxide ion.



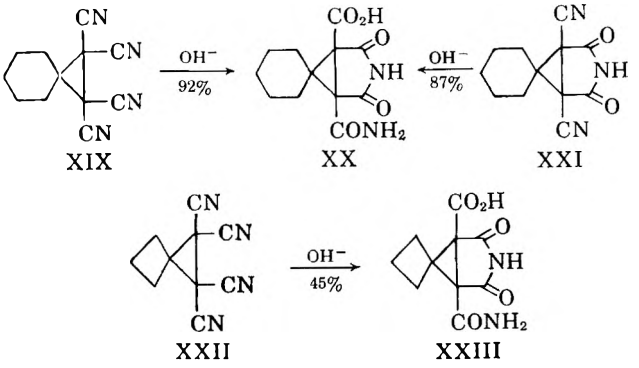
Hydrolysis of VIII by brief reflux with dilute aqueous methanolic alkali gave IX. Its structure follows from its analysis, neutralization equivalent, and additional conversions; its n.m.r. spectrum in dimethylsulfoxide showed one imide (singlet, −0.85 τ) and one amide (poorly resolved symmetrical multiplet, 2.32 τ) proton. Alkaline hydrolysis of XVIII (synthesized from known XVII and diazomethane) also gave IX.

IX was dibasic, and reacted with two moles of diazomethane to give the dimethyl derivative X, which still showed the N–H stretch at 2.95 μ in the infrared, due to the secondary amide group; its n.m.r. spectrum in carbon tetrachloride clearly established its structure as formulated. It showed a single amide proton (complex symmetrical multiplet centered at 2.78 τ), $O-CH_3$ (singlet, 6.40 τ), imide–$N-CH_3$ (singlet, 7.23 τ), amide–$N-CH_3$ (unequal doublet at 7.30 and 7.58 τ; J = 17 c.p.s.), and CH_2 (broad band, 8.13–8.58 τ) with the calculated relative areas. Hydrolysis of X gave the tetracarboxylic acid, which was converted to its tetramethyl ester XI. In contrast to previous intermediates in its synthesis, XI showed a single sharp carbonyl band, at 5.75 μ. Its n.m.r. spectrum in carbon tetrachloride had a single sharp peak at 6.45 τ (OCH_3), and a complex multiplet, 8.12–8.42 τ (CH_2), relative areas 3:2, as expected.

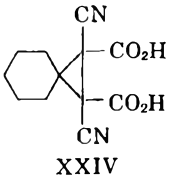
As with VII, IX lost one mole of carbon dioxide when heated just above its melting point and gave the cyclopentylidene derivative XV; the latter was monobasic and, with diazomethane, gave an N-methyl derivative XVI.

Reactions of tetracyanocyclopropanes from cyclohexanone and cyclobutanone are summarized in Scheme 3.

SCHEME 3



XIX[7] was hydrolyzed rapidly in excellent yield to the acid amide imide XX, which also was obtained from the previously known[8] dinitrile XXI. The imide and amide hydrogens of XX appeared at −1.14 and 2.47 τ, respectively, relative areas 1:2, in dimethyl sulfoxide. This compound previously had been assigned[8] the incorrect structure XXIV.



The structure XXIII is assigned to the hydrolysis product of XXII[4] on the basis of elemental analysis, infrared spectrum, analogy with the hydrolysis of I, VI, and XIX, and an n.m.r. spectrum in dimethyl sulfoxide which showed imide (−0.78 τ) and amide (2.72 τ) nitrogen, relative areas 1:2.

In summary, the rapid alkaline hydrolysis of tetracyanocyclopropanes derived from ketones leads to acid amide imides (I → II, VI → VII, XIX → XX, and XXII → XXIII).[9] The cyclopropane ring cleavage in the decarboxylation of a cyclopropanecarboxylic acid with a fused five-membered ring and a carbonyl group situated favorably for proton removal is also general (three examples previously given,[2] to which VII → XIII and IX → XV may be added). Finally another example (VIII → IX) is presented of the previously observed (IV → V[2]) ring opening and closing reactions on opposite sides of the cyclopropane plane. Studies of the mechanisms of these reactions are in progress.

Experimental[10]

2-Carboxamido-1,2-dicarboximidospiro[2.4]heptane-1-carboxylic Acid (VII). From 1,1,2,2-Tetracyanospiro[2.4]heptane (VI).—A solution of 3.14 g. (0.016 mole) of VI[4] in 30 ml. of methanol and 30 ml. of 25% aqueous potassium hydroxide was

(6) S. S. G. Sircar, *J. Chem. Soc.*, 1257 (1927).

(7) S. Wideqvist, *Arkiv Kemi, Mineral. Geol.*, 20B, 4, 8 (1945).

(8) S. F. Birch, W. H. Gough, and G. A. R. Kon, *J. Chem. Soc.*, 119, 1315 (1921).

(9) Preliminary experiments on the alkaline hydrolysis of tetracyanocyclopropanes from aldehydes shows that the reaction takes a different course and, with aromatic aldehydes, leads to dihydroxypyridine derivatives.

refluxed for 3 hr. The alcohol was removed on a rotary evaporator and the remaining liquid extracted continuously with ether for 4 hr. to remove nonacidic products. The aqueous solution was acidified (congo red) with dilute hydrochloric acid and once again extracted with ether for 24 hr. Filtration of the extract gave a solid which, on recrystallization from water, gave 3.1 g. (76.9%) of white crystals of VII, m.p. 187–188° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.37; H, 4.80; N, 11.10; neut. equiv., 126.1. Found: C, 52.17; H, 4.88; N, 11.08; neut. equiv., 124.6.

Its n.m.r. spectrum in dimethyl sulfoxide showed singlets at −1.12 and 2.44 τ, relative areas 1:2.

From 3,3-Pentamethylene-1,2-dicyanocyclopropane-1,2-dicarboximide (XVII).—A solution of 1.9 g. (0.01 mole) of XVII[6] in 15 ml. of 10% aqueous sodium hydroxide was refluxed for 30 min., made strongly acidic with dilute hydrochloric acid, and allowed to stand in the refrigerator for 2 days. The resulting crystals (1.62 g., 64%), m.p. 187–188°, were identical with those described previously.

VII was quantitatively converted to **methyl 2-carboxamido-1,2-(N-methyl)dicarboximidospiro[2.4]heptane-1-carboxylate (VIII)** by reaction with excess diazomethane in methanol, followed by recrystallization from methanol, m.p. 133–134°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.70; H, 5.75; N, 10.00. Found: C, 55.61; H, 5.77; N, 10.06.

The n.m.r. spectrum of VIII had broad singlets at 2.48 and 3.35 τ, sharp singlets at 6.22 and 7.08 τ, and a multiplet centering around 8.3 τ, relative areas 1:1:3:3:8, in deuteriochloroform.

1,2-Dicarboximidospiro[2.4]heptane-1,2-dicarboxylic Acid and Methyl 1,2-(N-Methyl)dicarboximidospiro[2.4]heptane-1,2-dicarboxylate (XII).—A solution of 1.26 g. (5 mmoles) of VII in 30 ml. of 10% sodium hydroxide was refluxed for 3.25 hr., acidified with dilute hydrochloric acid, and extracted continuously with ether for 36 hr. The resulting acid (0.99 g.) was recrystallized from ethyl acetate–pentane and had a m.p. 135–136.5° dec. It was not analyzed, but converted with diazomethane in methanol to XII, m.p. 101–102°, in 83.5% yield.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.73; H, 5.85; N, 4.78.

The n.m.r. spectrum (in carbon tetrachloride) had bands at 6.37 and 7.25 τ (sharp singlets) and 8.0–8.5 τ (multiplet), with relative areas 6:3:8.

Decarboxylation of VII.—Heating VII (2.52 g., 0.01 mole) just above its melting point (188–190°) for a few minutes in a nitrogen atmosphere gave, upon cooling and recrystallization from water, 1.85 g. (89%) of **4-carboxamido-3-cyclopentylidenesuccinimide (XIII)**, m.p. 137–138°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.79; H, 5.68; N, 13.38.

Its n.m.r. spectrum in dimethyl sulfoxide showed an unequal doublet (−0.97 and −0.80 τ), two unequal doublets centered at 2.77 and 3.07 τ (J = 32 c.p.s.), and a sharp singlet at 4.43 τ, with relative areas 1:2:1. XIII gave a positive permanganate test for unsaturation; with an excess of diazomethane in absolute methanol, it was converted to **4-carboxamido-3-cyclopentylidene-1-methylsuccinimide (XIV)**, m.p. 148.5–149°, from methanol.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.51; H, 6.26; N, 12.77.

2-(N-Methyl)carboxamido-1,2-dicarboximidospiro[2.4]heptane-1-carboxylic Acid (IX). From VIII.—A solution of 2.80 g. (0.01 mole) of VIII in 35 ml. of methanol and 25 ml. of 10% aqueous sodium hydroxide was refluxed for 30 min., cooled to room temperature, and the methanol removed on a rotary evaporator. The solution was made strongly acidic (hydrochloric acid) and refrigerated overnight. The resulting crystals, recrystallized from methanol, were obtained in 80.6% yield, m.p. 180–181° dec.

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52; neut. equiv., 133.1. Found: C, 54.43; H, 5.10; N, 10.54; neut. equiv., 133.3.

The n.m.r. spectrum in dimethyl sulfoxide showed equal peaks at −0.85 τ (singlet) and 2.32 τ (multiplet).

From XVIII. 3,3-Tetramethylene-1,2-dicyanocyclopropane-1,2-(N-methyl)carboximide (XVIII) was prepared (98%) by adding ethereal diazomethane to a methanolic solution of XVII.[6] Recrystallization from methanol gave white crystals, m.p. 247–248° (dec.).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.81; H, 4.90; N, 18.28.

When 2.29 g. (0.01 mole) of XVIII was refluxed in 15 ml. of 10% sodium hydroxide for 30 min., cooled, acidified with hydrochloric acid, and refrigerated overnight, there was obtained 1.65 g. (62%) of IX, recrystallized from water. Its m.p. and m.m.p. with a sample prepared from VIII was 180–181°.

Decarboxylation of IX.—When IX (2.66 g., 0.01 mole) was heated just above its melting point (185°) for a few minutes in a nitrogen atmosphere, there was obtained, on cooling and recrystallization from water, 2.05 g. (92.4%) of **4-(N-methyl)-carboxamido-3-cyclopentylidenesuccinimide (XV)**, m.p. 131–132°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.30; H, 6.28; N, 12.70.

XV gave the N-methyl derivative XVI on treatment with diazomethane, m.p. 93.3–94.0°, from methanol.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.08; H, 6.82; N 11.68. Found: C, 60.80; H, 6.80; N, 11.79.

Methyl Spiro[2.4]heptane-1,1,2,2-tetracarboxylate (XI).—A solution of 0.26 g. (1 mmole) of IX in 5 ml. of absolute methanol was treated with excess ethereal diazomethane, and the resulting product recrystallized from methanol, giving 0.27 g. (93.1%) of **methyl 2-(N-methyl)carboxamido-1,2-(N-methyl)dicarboximidospiro[2.4]heptane-1-carboxylate (X)**, m.p. 118–119°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.25; H, 6.02; N, 9.48.

Its n.m.r. spectrum in carbon tetrachloride showed bands at 2.78 τ (multiplet), 6.40 and 7.23 τ (equal singlets), 7.30 and 7.58 τ (together account for three protons), and a broad band at 8.13–8.58 τ, relative areas 1:3:3:3:8.

A solution of 1.47 g. (5 mmoles) of X in 13 ml. of 10% sodium hydroxide and 20 ml. of methanol was refluxed for 30 min., cooled, and the methanol removed using a rotary evaporator, after which the residue was extracted for 6 hr. with ether. The aqueous solution was acidified with hydrochloric acid and again continuously extracted with ether (36 hr.). Evaporation of the ether, Norit treatment of the residue in ethyl acetate solution, and reaction with diazomethane in ether, followed by recrystallization from methanol, gave 1.04 g. (63.1%) of XI, m.p. 103–104°, carbonyl absorption at 5.75 μ.

Anal. Calcd. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 55.01; H, 6.23.

Its n.m.r. spectrum in carbon tetrachloride showed a sharp singlet at 6.45 τ and a broad multiplet, 8.1–8.4 τ, with relative areas 3:2.

2-Carboxamido-1,2-dicarboximidospiro[2.5]octane-1-carboxylic Acid (XX). From 1,1,2,2-Tetracyanospiro[2.5]octane (XIX).—A solution of 3.36 g. (0.016 mole) of XIX[4] in 30 ml. of 25% aqueous potassium hydroxide and 40 ml. of methanol was refluxed for 3 hr., the alcohol removed with a rotary evaporator, and the remaining solution extracted for 4 hr. with ether to remove nonacidic products. After acidification to congo red with hydrochloric acid, the solution was extracted continuously with ether for 24 hr., the solid filtered from the extract and recrystallized from water, giving 3.92 g. (92.4%) of white crystals, m.p. 202.5–203° dec., with n.m.r. bands (dimethyl sulfoxide solvent) at −1.14 and 2.47 τ, relative areas 1:2.

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.24; H, 5.20; N, 10.50.

From XXI.—An identical product (XX), m.p. and m.m.p., was obtained in 87.2% yield by refluxing 2.29 g. (0.01 mole) of XXI[3] in 15 ml. of 10% sodium hydroxide for 30 min., followed by acidification, refrigeration, and recrystallization from water. With diazomethane, XX was converted in 97% yield to **methyl 2-carboxamido-1,2-(N-methyl)dicarboximidospiro[2.5]octane-1-carboxylate.** m.p. 147–148°, from methanol.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.21; H, 5.96; N, 9.50.

2-Carboxamido-1,2-dicarboximidospiro[2.3]hexane-1-carboxylic Acid (XXIII).—A solution of 2.82 g. (0.01 mole) of 1,1,2,2-tetracyanospiro[2.3]hexane (XXII)[4] in 40 ml. of 2 N aqueous potassium hydroxide was refluxed for 25 min., cooled, acidified to congo red with 4 N hydrochloric acid, and refrigerated for 2 days, during which time white crystals deposited. Recrystallization from methanol gave 1.14 g. (44.9%) of XXIII, m.p. 218–219° dec.

Anal. Calcd. for $C_{10}N_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.55; H, 4.34; N, 11.62.

(10) Melting points are uncorrected. Analyses are by Spang Microanalytical Laboratories, Ann Arbor, Mich. N.m.r. spectra were obtained on a Varian Model A-60 instrument.

Mechanisms of Elimination Reactions. XXV. Stereoconvergent Elimination from the Diastereoisomeric 2-*p*-Toluenesulfonyl-1,2-diphenyl-1-chloroethanes[1]

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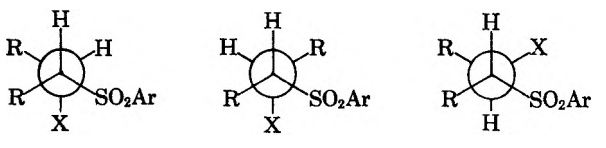
Received November 19, 1962

The diastereoisomeric 2-*p*-toluenesulfonyl-1,2-diphenyl-1-chloroethanes have been subjected to base-promoted dehydrochlorination. The *erythro* isomer eliminates cleanly *trans;* the *threo* isomer eliminates cleanly *cis;* thus both give α-*p*-toluenesulfonyl-*cis*-stilbene. This unsaturated sulfone and the corresponding *trans*-stilbene derivative have been prepared by straightforward syntheses; the latter rearranges to the former much more slowly than the former is produced in the elimination reactions. The results are consistent with a concerted elimination for the *erythro* isomer and a carbanion-intermediate process for the *threo* isomer.

In general it has been observed that bimolecular elimination from acyclic diastereoisomeric halides or sulfonate esters leads by *trans* elimination to isomeric olefins.[2] *trans*-Stereospecific elimination has even been observed in base-promoted elimination from *dl-erythro-* and *dl-threo*-3-*p*-toluenesulfonyl-2-butyl *p*-bromobenzenesulfonates[3] and the corresponding isomers of 3-benzenesulfonyl-2-butyl iodides,[4] where activation of the proton by the sulfonyl group might have been anticipated to lead to nonstereoselective carbanionic elimination.[5-8]

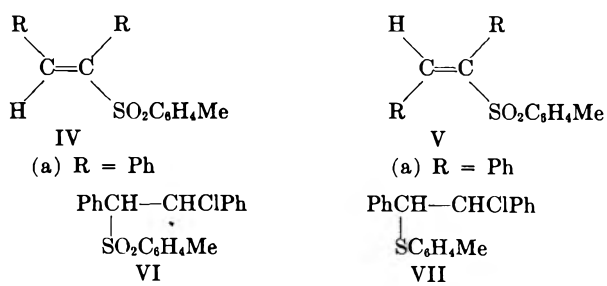
trans-Elimination from these *erythro* and *threo* chlorosulfones may be assumed to have transition states with conformations related to the structures I and II, respectively, which would lead (with loss of H and X) to the sulfonyl *cis* olefins IV and *trans* olefins V, respectively.



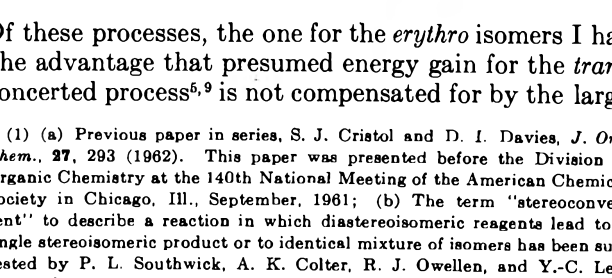
I (a) R = CH_3 (b) R = Ph

II (a) R = CH_3 (b) R = Ph

III (a) R = CH_3 (b) R = Ph



IV (a) R = Ph



V (a) R = Ph

Of these processes, the one for the *erythro* isomers I has the advantage that presumed energy gain for the *trans* concerted process[5,9] is not compensated for by the large increase in steric strain to be anticipated by the nonbonding interaction between the large arenesulfonyl group and the R group. This interaction occurs in the corresponding *trans* elimination from the *threo* isomers in conformation II. For this reason it was tempting to predict that increasing the size of the R groups and/or increasing their ability to stabilize a negative charge might lead to a carbanionic process with the *threo* isomers. These would then presumably react *via* the more stable conformation III, and thus result in the formation of the more stable arenesulfonyl *cis* olefin IV. We, therefore, decided to prepare and study the diastereoisomeric 2-*p*-toluenesulfonyl-1,2-diphenyl-1-chloroethanes (VI), anticipating that the extra delocalization energy in a carbanion stabilized by a phenyl group as compared with a methyl group as well as the extra steric interaction might suffice. This, in fact, resulted, as is discussed subsequently.

As the desired compounds were unknown, the preparations of the chlorosulfones and of the corresponding olefins were undertaken. Addition of *p*-toluenesulfenyl chloride to *trans*- and to *cis*-stilbene led to diastereoisomeric chlorothioethers. These are *erythro*- and *threo*-2-*p*-toluenethio-1,2-diphenyl-1-chloroethanes (VII), respectively, assuming *trans* addition[10] to each olefin. Both chlorides solvolyzed in acetic acid and in ethanol, with the *erythro* isomer reacting more rapidly than the *threo* isomer.[11] Oxidation of these thioethers led to the corresponding β-chloro sulfones VI. Both sulfones reacted very rapidly with ethanolic sodium hydroxide to give, in substantially quantitative yield, α-*p*-toluenesulfonyl-*cis*-stilbene (IVa), the product of *trans* elimination from *erythro*-VI, but of *cis* elimination from *threo*-VI. The elimination proceeded at a rate possible to measure using ordinary techniques with the *threo* isomer at 10°, but too fast to measure in this way even at 0° with the *erythro* isomer; the fact that the eliminations were base-promoted was shown by the fact that both isomers could be recrystallized from ethanol without difficulty.

Proof of structure of the resulting olefin IVa was essential; its preparation and that of its isomer V were, therefore, carried out by alternative syntheses. Treatment of the *erythro* and *threo* isomers of VII with potassium *t*-butoxide in dimethyl sulfoxide and *t*-butyl alcohol gave α-*p*-thiocresoxy-*cis*-stilbene (VIII) and α-*p*-thiocresoxy-*trans*-stilbene (IX), respectively, as-

(1) (a) Previous paper in series, S. J. Cristol and D. I. Davies, *J. Org. Chem.*, **27**, 293 (1962). This paper was presented before the Division of Organic Chemistry at the 140th National Meeting of the American Chemical Society in Chicago, Ill., September, 1961; (b) The term "stereoconvergent" to describe a reaction in which diastereoisomeric reagents lead to a single stereoisomeric product or to identical mixture of isomers has been suggested by P. L. Southwick, A. K. Colter, R. J. Owellen, and Y.-C. Lee, *J. Am. Chem. Soc.*, **84**, 4299 (1962).

(2) References to many such reactions have been given recently. See S. J. Cristol and R. S. Bly, Jr., *ibid.*, **82**, 142 (1960).

(3) F. G. Bordwell and P. S. Landis, *ibid.*, **79**, 1593 (1957).

(4) P. S. Skell and J. H. McNamara, *ibid.*, **79**, 85 (1957).

(5) S. J. Cristol, *ibid.*, **69**, 338 (1947).

(6) F. G. Bordwell and J. Kern, *ibid.*, **77**, 1141 (1955).

(7) H. L. Goering, D. I. Relyea, and K. L. Howe, *ibid.*, **79**, 2502 (1957).

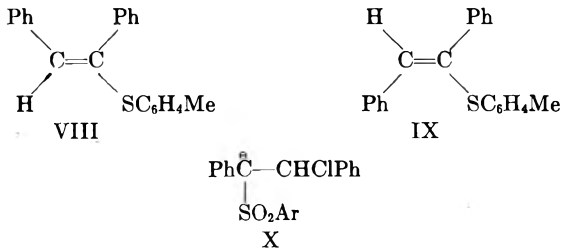
(8) S. J. Cristol and R. P. Arganbright, *ibid.*, **79**, 3441 (1957).

(9) S. J. Cristol, N. L. Hause, and J. S. Meek, *ibid.*, **73**, 674 (1951).

(10) (a) N. Kharasch, H. L. Wehrmeister, and H. Tigerman, *ibid.*, **69**, 1612 (1947); (b) D. J. Cram, *ibid.*, **71**, 3883 (1949); (c) N. Kharasch and A. J. Havlik, *ibid.*, **75**, 3734 (1953); (d) W. S. Orr and N. Kharasch, *ibid.*, **75**, 6030 (1953).

(11) P. G. Papathanassiou, Ph.D. thesis, University of Colorado, 1961.

suming that both eliminations are *trans*. Oxidation of VIII and IX with hydrogen peroxide in acetic acid gave isomeric unsaturated sulfones. Of these, that from VIII was identical with the sulfone IV obtained by the dehydrochlorination of *erythro*- and *threo*-VI; the other isomer was thus the *trans*-stilbene V. The structural assignments were confirmed by the preparation of the thioethers VIII and IX by treatment with *p*-toluenesulfenyl chloride of α-lithio-*cis*-stilbene[12] and α-lithio-*trans*-stilbene,[12] respectively. These reactions should be expected to go with retention[3,12] and, in fact, were stereospecific.



Before one may assume that both *erythro*- and *threo*-VI give IVa directly upon dehydrochlorination, it is, of course, necessary to show that Va is not an intermediate in one or both eliminations. The base-catalyzed rate of isomerization of Va to IVa was readily followed spectrophotometrically. The rate of isomerization of Va to IVa was shown to be very slow compared to the dehydrochlorination reaction, being approximately one-thirtieth that of elimination of the *threo* isomer at a temperature about 60° higher. Thus, IVa is the direct product from both isomers of VI.

The *trans* eliminations observed with *erythro*-VI, as well as with the *erythro* and *threo* butane derivatives,[3,4] Ia and IIa, are consistent with a concerted dehydrochlorination,[5,9] while the *cis* elimination observed with *threo*-VI may be readily rationalized by assuming a carbanion-intermediate mechanism.[13]

A transition state configurationally related to conformation Ib for elimination from *erythro*-VI is not in steric difficulty if one (or both) of the phenyl groups is rotated slightly out of the plane.[15] Such a conformation allows for the departing hydrogen and chlorine atoms to have the *trans* coplanarity required for concerted elimination. Conformation IIb is required for *threo*-VI in order to accommodate the proper geometry of hydrogen and chlorine for *trans* coplanar elimination. The steric overlap[16] between the *cisoid* phenyl group and the bulky elliptical *p*-toluenesulfonyl group is very substantial and cannot be removed completely in any orientation of the phenyl group when these groups are eclipsed. Thus steric strain may be expected to lower the reactivity of *threo*-VI compared with that of the *erythro* isomer by a concerted process.

The formation of carbanion X should not have a marked geometric requirement, and the most stable conformation IIIb for *threo*-VI should be suitable for reaction. Resonance stabilization of X by the conjugated phenyl and sulfone groups should enhance its rate of formation, and the decomposition of X into olefin IVb and chloride ion is unremarkable.[17]

The results observed then bear out the prediction that even with acyclic systems, when steric strains make the geometry required for *trans* coplanar elimination difficult to attain, resonance stabilization of a carbanion intermediate results in a fairly facile *cis* elimination.

Our results are related to those reported recently by Southwick and his co-workers[1b] in a carbonyl-activated system where a pair of diastereoisomeric halides gave largely one isomeric olefin. The term "stereoconvergent," which they have used to describe such a result, seems to us to be a particularly apt one.

Experimental[19]

***erythro*-2-*p*-Thiocresoxy-1,2-diphenyl-1-chloroethane** (*erythro*-VII).—*p*-Toluenesulfenyl chloride[20] (17.2 g., 0.11 mole) was added in the dark to a solution of 20.0 g. (0.11 mole) of *trans*-stilbene in 110 ml. of carbon tetrachloride; the reaction mixture was heated at reflux until the red color disappeared (about 8 hr.). The mixture was cooled to room temperature and allowed to stand overnight. The crystals which separated were recrystallized from ethyl ether to give 26.3 g. (72%) of *erythro*-VII, m.p. 129–130°.

Anal. Calcd. for $C_{21}H_{19}ClS$; C, 74.42; H, 5.60. Found: C, 74.69; H, 5.79.

***erythro*-2-*p*-Toluenesulfonyl-1,2-diphenyl-1-chloroethane** (*erythro*-VI).—A solution containing 2.0 g. (5.9 mmoles) of *erythro*-VII and a large excess of peroxyphthalic acid in 300 ml. of ethyl ether was placed in a refrigerator for 24 hr. The solvent was then removed by distillation, and the remaining solid was dissolved in a mixture of 100 ml. of chloroform and 200 ml. of water and heated at reflux for 2 hr. The insoluble phthalic acid was removed by filtration and the chloroform layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed by distillation after filtration of the desiccant. Recrystallization from ethanol gave 1.48 g. (66%) of *erythro*-VI, m.p. 182.5–184°.

Anal. Calcd. for $C_{21}H_{19}O_2ClS$: C, 68.00; H, 5.17. Found: C, 68.16; H, 5.15.

Preparation of α-*p*-Toluenesulfonyl-*cis*-stilbene (IVa) from *erythro*-VI.—Two grams (5.5 mmoles) of *erythro*-VI was dissolved in 50 ml. of ethanol and treated with 20 ml. of 0.3 *N* ethanolic sodium hydroxide. The reaction mixture stood for a few minutes at room temperature. The solvent was removed and the remaining precipitate was washed once with water and recrystallized from alcohol. The yield was 1.65 g. (92%) of IVa, m.p. 179–180°.

Anal. Calcd. for $C_{21}H_{18}O_2S$: C, 75.41; H, 5.38. Found: C, 75.43; H, 5.25.

Preparation of α-*p*-thiocresoxy-*cis*-stilbene (VIII) by Dehydrochlorination.—Three grams (8.9 mmoles) of *erythro*-VII was dissolved in 75 ml. of dimethyl sulfoxide, and then 45 ml. of 0.2 *M*

(12) D. Y. Curtin and E. E. Harris, *J. Am. Chem. Soc.*, **73**, 4519 (1951).

(13) Evidence and discussions regarding the existence of carbanion intermediates in bimolecular elimination reactions where the geometry is unfavorable to a concerted elimination mechanism have been given in a large number of the papers in this series, dating from 1947. For a recent discussion of *cis* elimination in sulfones, see ref. 14.

(14) J. Hine and O. B. Ramsay, *J. Am. Chem. Soc.*, **84**, 973 (1962).

(15) The transition state, if *trans* concerted elimination is involved, will have the phenyl–phenyl steric strain intermediate between that in Ib and that in the olefin IVa.

(16) The transition state, if *trans* concerted elimination is involved, will have the phenyl–arenesulfonyl steric strain intermediate between that in IIb and that in Va.

(17) An attempt to find evidence for the intermediacy of X by partial dehydrochlorination and deuterium exchange in O-deuterated ethanol was unsuccessful, within the limits of infrared analysis. As pointed out before,[18] such negative evidence is consistent with a carbanion mechanism in which the reverse rate of the carbanion formation (reprotonation of the carbanion) is much smaller than loss of halide ion and formation of olefin.

(18) Deuterium-exchange experiments in eliminations with relatively simple alkyl halides or arenesulfonates have been routinely unsuccessful, except for an experiment with β-benzene hexaachloride, where the rate of reaction of the carbanion with deuterioethanol was approximately 0.7% of that of loss of chloride ion. This value was too small to observe by infrared techniques. S. J. Cristol and D. D. Fix, *J. Am. Chem. Soc.*, **75**, 2647 (1953). Such results are also compatible with concerted *cis* eliminations. See C. H DePuy, R. D. Thurn, and G. F. Morris, *ibid.*, **84**, 1316 (1962), and ref. 14.

(19) Analyses are by Galbraith Laboratories.

(20) H. Lecher, R. Holschneider, K. Köberle, W. Speer, and P. Stöcklin *Ber.*, **58**, 423 (1925).

potassium *t*-butoxide in *t*-butyl alcohol was added. The reaction mixture was heated for 30 min. on a steam bath, at the end of which time the reaction mixture was neutral to pH paper. The solvent was then distilled under reduced pressure. The remaining precipitate was washed once with water and dissolved in pentane. The hydrocarbon solution was extracted twice with water and was then separated and dried over anhydrous magnesium sulfate. The solvent was evaporated; recrystallization from ethanol gave 2.37 g. (90%) of VIII, m.p. 83–84°.

Anal. Calcd. for $C_{21}H_{18}S$: 83.40; H, 6.00. Found: C, 83.19; H, 5.76.

Preparation of α-*p*-Toluenesulfonyl-*cis*-stilbene (IVa) from α-*p*-Thiocresoxy-*cis*-stilbene (VIII).—α-*p*-Thiocresoxy-*cis*-stilbene, 400 mg. (1.32 mmoles), was dissolved in 25 ml. of glacial acetic acid. The solution was brought to boiling and 3 ml. of 30% hydrogen peroxide was added. The solution was boiled for 1 min., was allowed to stand for 1 hr., and then poured over crushed ice. The product was separated by filtration and recrystallized from ethanol. There was obtained 320 mg. (73%) of IVa, m.p. 179–180°.

Preparation of α-*p*-Toluenesulfonyl-*cis*-stilbene (IVa) from α-Bromo-*cis*-stilbene.—In 40 ml. of a 40% benzene–ethyl ether mixture was dissolved 1.5 g. (5.8 mmoles) of α-bromo-*cis*-stilbene.[21] The solution was cooled to −30°, and to the cold solution was added 6.4 ml. of 1.1 *M* *n*-butyllithium in ethyl ether.[12] After 20 min. there was added 800 mg. (5.8 mmoles) of *p*-toluenesulfenyl chloride, and the whole reaction mixture was maintained for 1.5 hr. at −30°. The solution was filtered and the solvent was removed. The remaining precipitate was washed once with water and was then dissolved in glacial acetic acid where it was brought to boiling and treated with 10 ml. of 30% hydrogen peroxide. The reaction mixture was then poured over crushed ice and the product was separated. After several recrystallizations from ethanol, it melted at 177–179° and weighed 1.12 g. (57%). This material was identical (melting point, mixture melting point, and infrared spectra) with IVa prepared by the alternative procedures.

***threo*-2-*p*-Thiocresoxy-1,2-diphenyl-1-chloroethane (*threo*-VII).**—Eight grams (44 mmoles) of *cis*-stilbene[22] was dissolved in 120 ml. of glacial acetic acid, warmed over a steam bath, and to the warm solution was added 7.50 g. (44 mmole) of *p*-toluenesulfenyl chloride. The *p*-toluenesulfenyl chloride was added quite rapidly and, as soon as the solution was colorless, the reaction was poured over crushed ice. The product was separated by filtration and recrystallized from ethyl ether or ethanol. There was obtained 9.67 g. (69%) of *threo*-VII, m.p. 69–70°.

Anal. Calcd. for $C_{21}H_{19}ClS$: C, 74.42; H, 5.60. Found: C, 74.19; H, 5.60.

2-*p*-Toluenesulfonyl-1,2-diphenyl-1-chloroethane (*threo*-VI).—Nine grams (27 mmoles) of *threo*-VII was dissolved in 100 ml. of glacial acetic acid and the solution was brought to boiling quite rapidly. Fifteen milliliters of 30% hydrogen peroxide was added and the solution was brought to boiling for 1 min. The solution was cooled to room temperature and poured over crushed ice. The product was separated by filtration and recrystallized from ethanol. The yield of *threo*-VI was 4.8 g. (49%), m.p. 151–152°. If this experiment were repeated, it would seem advisable to conduct the oxidation at lower temperatures or in a nonprotonic solvent to minimize solvolysis.

Anal. Calcd. for $C_{21}H_{19}O_2ClS$: C, 68.00; H, 5.17. Found: C, 68.10; H, 5.27.

Elimination of Hydrogen Chloride from *threo*-VI.—Two grams (5.5 mmoles) of *threo*-VI was dissolved in 50 ml. of ethanol and treated with 20 ml. of 0.30 *N* ethanolic sodium hydroxide. The reaction mixture was heated at reflux for 1 hr. The precipitated sodium chloride was removed by filtration and the solvent was removed by evaporation. The precipitated compound was washed once with water and recrystallized from ethanol. There was obtained 1.50 g. (84%) of IVa, m.p. 179–180°, which had the same infrared spectrum in carbon disulfide solution as the olefin obtained from the *erythro* isomer. A mixture melting point showed no depression. Similar results obtained when the dehydrochlorination was conducted for 6 hr. at 10°.

Reaction-rate studies were carried out at 10.2° using sodium hydroxide in ordinary (92.6 wt. %) ethanol, following the reaction by titrating the chloride ion formed with silver nitrate. Duplicate runs with 0.005 *M* *threo*-VI and 0.015 *M* sodium hydroxide gave $k_2 = 6.9 \times 10^{-2}$ l./sec./mole; with 0.010 *M* sodium hydroxide $k_2 = 7.1 \times 10^{-2}$ l./sec./mole. Average $k_2 = 7.0 \times 10^{-2}$ l./sec./mole.

α-*p*-Thiocresoxy-*trans*-stilbene (IX).—This was prepared from 1.0 g. (3.0 mmoles) of *threo*-VII as described previously for the *erythro* isomer. There was obtained 0.78 g. (88%) of IX, m.p. 52–53°.

Anal. Calcd. for $C_{21}H_{18}S$: C, 83.40; H, 6.00. Found: C, 83.52; H, 6.08.

α-*p*-Toluenesulfonyl-*trans*-stilbene (Va).—This was prepared from 650 mg. (2.1 mmoles) of IX as described previously for the *cis*-stilbene isomer. The yield of Va was 450 mg. (72%), m.p. 148.5–149.5°.

Anal. Calcd. for $C_{21}H_{18}O_2S$: C, 75.41; H, 5.38. Found: C, 75.43; H, 5.52.

Preparation of α-*p*-Toluenesulfonyl-*trans*-stilbene Va from α-Bromo-*trans*-stilbene.—This preparation used 670 mg. (2.5 mmoles) of α-bromo-*trans*-stilbene.[21] Treatment with butyllithium[12] and with *p*-toluenesulfenyl chloride was conducted substantially as described before for the *cis* isomer. There was obtained 350 mg. (43%) of Va, m.p. 146–148°. This material was identical with the sample described in the preceding paragraph.

Isomerization of α-*p*-Toluenesulfonyl-*trans*-stilbene (Va) to α-*p*-Toluenesulfonyl-*cis*-stilbene (IVa).—In a 50-ml. flask containing 10 ml. of ethanol was dissolved 85 mg. of Va. The solution was treated with 5 ml. of 0.19 *M* ethanolic sodium hydroxide and heated at reflux over a steam bath for 6 hr. The solution was allowed to stand at room temperature for a few hours. Crystals separated whose melting point (179–180°) and infrared spectrum were identical with those of IVa.

The rate of this reaction was measured at 71.9° with 0.01 *M* Va and 0.05 *M* sodium hydroxide in ordinary ethanol, following the reaction by the change in extinction coefficient at 275 mμ. Va has ε 13,700 and IVa has ε 22,400 at this wave length. Duplicate runs gave $k_2 = 2.7 \times 10^{-3}$ l./sec./mole. Va has λ_{max} at 270 mμ (ε 13,800) while λ_{max} for IVa is 275 mμ.

Acknowledgment.—The authors are indebted to the National Science Foundation for generous support of this work.

(21) P. Pfeiffer, *Z. physik. Chem.*, **48**, 40 (1904).

(22) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p. 180.

Carbodiimides. IV. High Polymers Containing the Carbodiimide Repeat Unit

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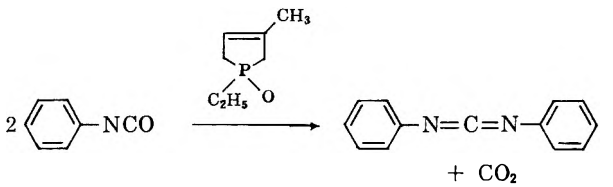
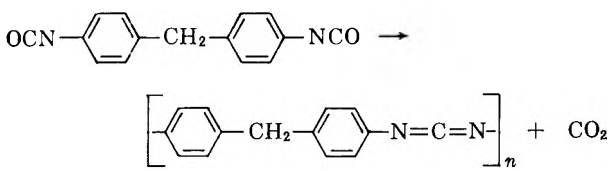
High molecular weight polymers containing the carbodiimide repeat unit have been synthesized by the catalytic action of 1-ethyl-3-methyl-3-phospholene oxide on diisocyanates in inert solvents. These polymers are tough, flexible, and can be molded into clear, tough films and other objects. Chemically they are quite inert when in the solid state. When swollen or in solution, however, they react with active hydrogen compounds to give new classes of polymers: for example, high molecular weight polyguanidines.

The number of chemical linkages which have been used to build high molecular weight condensation polymers is quite small, since there are very few condensation reactions which proceed in the near-quantitative yield necessary for achieving high molecular weight. Thus, polyesters, polyamides, polyethers, and polyurethanes are the major types now available. A recent discovery[1] of the catalytic activity of certain phospholenes and phospholene oxides, notably 1-ethyl-3-methyl-3-phospholene oxide, in converting isocyanates to carbodiimides prompted investigation of this catalyst for preparation of polymers containing carbodiimide linkages in the repeat unit.





The reaction proceeded quite well with a variety of diisocyanates, and the structurally very unusual polymeric carbodiimides were obtained, usually in quantitative yield. These polymers were unusual in that they were of quite high molecular weights, could be molded into *tough, clear, nylon-like films*, which in some cases were crystalline and orientable, and exhibited quite good tensile and electrical properties (Tables I and II).

TABLE I

PROPERTIES OF FILMS OF POLY(3,3′-DIMETHOXY-4,4′-BIPHENYLENE CARBODIIMIDE). FILM MOLDED AT 300°, AND DRAWN 4.5 TIMES AT 115°

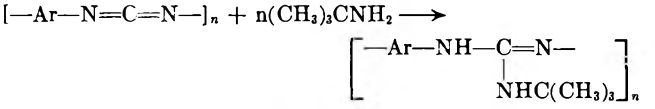
Initial modulus (p.s.i.)	1,183,500
% Elongation	6.2
Tenacity (p.s.i.)	39,800
Dielectric constant	3.4 (25°)
(10^2–10^5 c.p.s.)	3.8 (170°)
Dissipation factor	0.002–0.003 (25°)
(10^2–10^5) c.p.s.)	0.006–0.02 (170°)
Volume resistivity	$>1 \times 10^{14}$ (25°)
	2.2×10^{11} (200°)

TABLE II

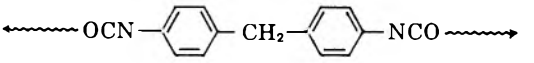
PHYSICAL TEST DATA ON POLY(TOLUENE CARBODIIMIDE) FILM STRIPS

Temp. °C.	Tenacity, g.p.d.	Elongation, %	Initial modulus, g.p.d.	Denier
25	3.2	52	38	467
110	0.3	121	0.19	449

The products were identified as polymeric carbodiimides by (1) method of preparation, (2) very characteristic infrared spectrum, (3) ultimate analyses, and (4) conversion to derivatives, such as polymeric guanidines. In the absence of solvents for the polymers, the polymers (in the form of thin films) were inert to boiling acid and alkali as well as to certain organic reagents. This is very surprising in view of the high degree of reactivity of the —N=C=N— linkage[2,3] in monomeric compounds. This probably reflects a lack of penetration of the reagent, rather than a lack of reactivity of the group, since addition of amines to metastable solutions such as are described brought about the rapid conversion of the carbodiimide linkages to guanidine groups.



Polymerization occurs by growth in both directions simultaneously and the products are of very high molecular weight, since a pure diisocyanate has a perfect material balance.



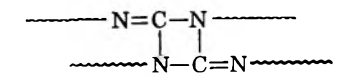
The end groups of the polymer chain must always be isocyanates, since no side reaction except that between isocyanate and carbodiimide can be visualized. Exchange of this type does occur, although no effect on molecular weight is possible, since such an exchange does not alter the number or nature of either the connecting links or the end groups.[4]

(1) T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Am. Chem. Soc.*, **84**, 3673 (1962).

(2) Monomeric carbodiimides have a reactivity similar to that of isocyanates towards organic reagents. Among the many examples of high reactivity, one of the most striking is the ability of diphenyl carbodiimide to dehydrate aromatic sulfonic acids to the corresponding sulfonic anhydride, $ArSO_2OSO_2Ar$ [H. G. Khorana, *Can. J. Chem.*, **31**, 585 (1953)].

(3) The reactions of carbodiimides are reviewed in a paper by H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(4) The very high molecular weight and intractable nature of the polymers may also reflect the presence of a few cross links of the following type.



If such cross links are present, they are not present in very high concentration, since they are not detectable in the infrared. See also ref. 7

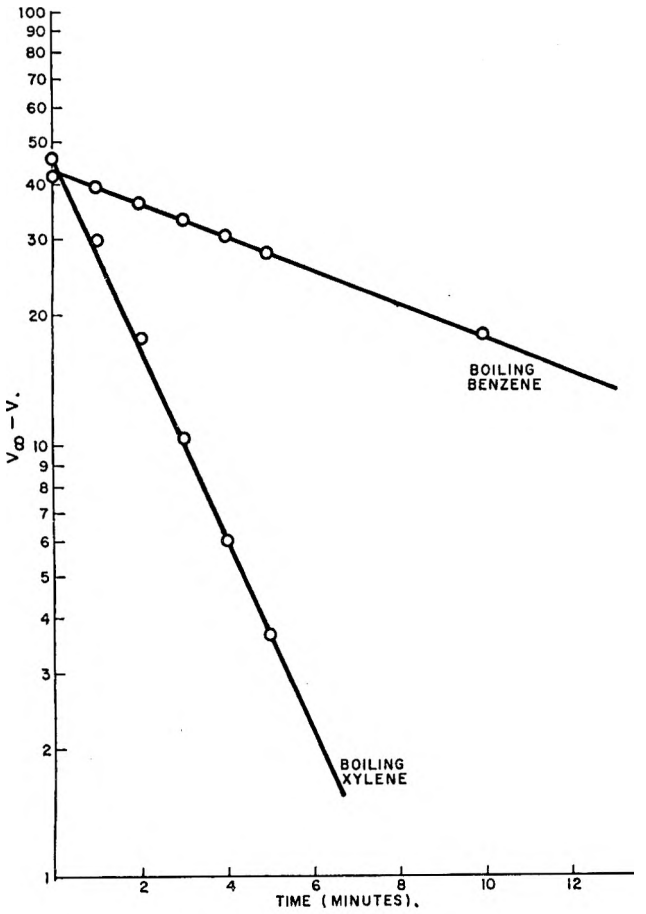
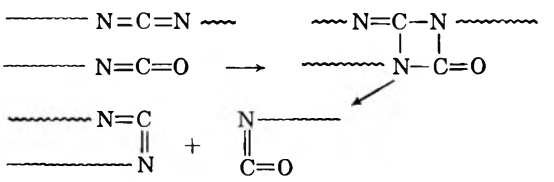
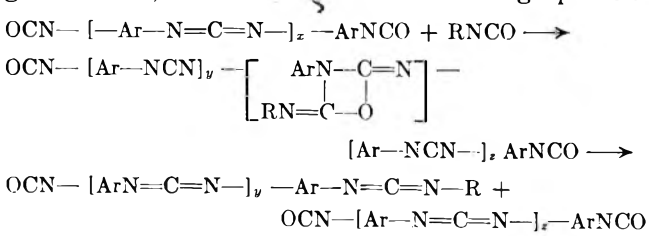


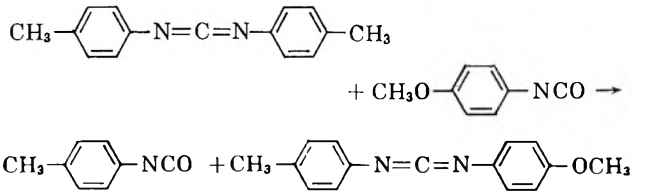
Figure 1



Proof that such an exchange occurs[5] can be found in two observations. Addition of a monoisocyanate to a viscous polycarbodiimide solution caused the viscosity to drop, indicating that reaction of the entering monoisocyanate was not exclusively with the end groups, but also took place randomly along the chain with cleavage at the point of attack. This could only occur if isocyanates and carbodiimides could exchange as suggested above, and as indicated in the following equation.



Existence of this exchange reaction was confirmed by heating a mixture of ditolyl carbodiimide and *p*-methoxyphenyl isocyanate.



The production of tolyl isocyanate was shown unequivocally by gas phase chromatography.

Scope of Polymerization.—A wide range of available diisocyanates was studied and a number of polymerization variables was examined. The results are summarized in the Experimental section. From the data, the following conclusions can be drawn.

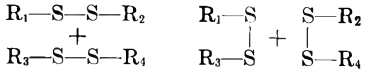
1. **Types of Monomers Which Will Polymerize.**—Since all diisocyanates examined could be polymerized, the reaction seems to be completely general. Aliphatic diisocyanates are slower than the aromatic derivatives, and the polymers obtained were in general of poorer quality. Steric hindrance in aromatic diisocyanates also slows the reaction; however, the resulting polymers are still attractively tough, although they may be slightly discolored by excessive reaction time.

2. **Nature of the Polymers.**—In general, the polymers separate from the polymerization medium as swollen lumps, which appear to be of extremely high molecular weight. In some cases, the polymer precipitates as a fine white powder with a high degree of crystallinity. With rare exceptions, it has not been possible to prepare a polymer, by the methods described in this paper, which could be redissolved in any solvent.[7] The polymers do not melt on the Dennis hot bar until about 350–400°, where they begin to leave a trail which is accompanied by decomposition. Certain of the polymers are crystalline (Fig. 3). Poly(3,3′-dimethoxy-4,4′-biphenylenecarbodiimide) showed a crystalline melting point of about 200°, although the melting point on the bar was in the 300–400° range, indicative of very high molecular weight. The polymeric carbodiimides were pressed at 250–300° to clear, usually somewhat yellowish film, again with difficulty because of high melt viscosity. These films, notably ones from poly(2,4-tolylenecarbodiimide), are characterized by their great toughness. The tensile properties of a few films decrease rapidly with increasing temperature. Thus, poly(2,4-tolylenecarbodiimide), which is quite stiff, and cold drawable at room temperature, becomes elastomeric at 100° (Table II).

3. **Stability.**—These polymers can be melt pressed in a Carver press at 250–300° repeatedly without change in properties. However, various samples maintained thirty minutes at 350° blackened and became brittle. Samples of finely divided polymer were refluxed for four hours with 10% sulfuric acid, 10% sodium hydroxide, 10% aqueous ethanol–amine, and distilled water. About 50% of the carbodiimide bonds were altered. However, poly(2,4-tolylenecarbodiimide) in film form (1-mil thickness) proved to be completely unaffected by the same series of reagents, after four hours' boiling. This would indicate that these polymers are not very permeable to the reagents used.

4. **Polymerization Conditions.**—Polymers are prepared from solutions containing 10–20% of monomer in refluxing solvent (hydrocarbon) with traces of cata-

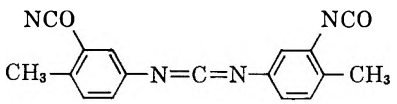
(5) Similar exchanges between polymer chains have been demonstrated for polysulfides.



M. D. Stern and A. V. Tobolsky, *J. Chem. Phys.*, **14**, 93 (1946); M. Mochulsky and A. V. Tobolsky, *Ind. Eng. Chem.*, **40**, 2155 (1948).

lyst. Polymerizations have been carried out at temperatures from 25° to 265°. The preferred range is 140° (boiling xylene) to 200° (boiling decahydronaphthalene). Yields of polymer were high, being best with more dilute solution, where they were essentially quantitative.[6]

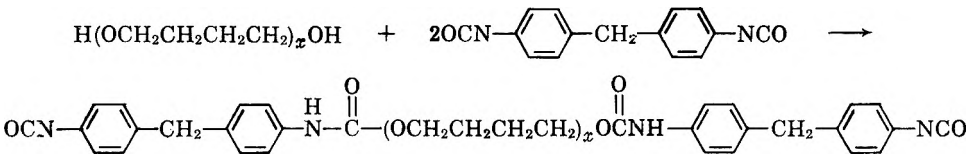
Rate of Polymerization.—It has been shown[6] that the conversion of monoisocyanates to carbodiimides is first order in isocyanate, and that the rate is affected by substituents and steric factors. Diisocyanates behave in the same fashion. The rate of evolution of carbon dioxide from some selected diisocyanates has been measured, and pseudo first-order rate constants have been calculated (Fig. 1 and Fig. 2 and Table V). In the case of toluene 2,4-diisocyanate, there are two nonequivalent isocyanate groups, so the k calculated from the half life is a weighted average. Examination of Fig. 2 indicates the difference in reactivity of the two isocyanate groups in toluene 2,4-diisocyanate. This difference in reactivity has made it possible to synthesize the unusual intermediate



by treating toluene 2,4-diisocyanate with catalyst under mild conditions.

Molecular Weight Control.—In most cases the polymers were insoluble in the usual polymer solvents and were of such high molecular weight as to prevent ready fabrication into films and fibers. Several methods for obviating the solubility and molecular weight problems were investigated. Promising results were obtained with all techniques.

In the first method, the carbodiimide linkages were separated by long polymeric segments. The most suitable monomer for doing this was a macro diisocyanate obtained by capping a hydroxyl-ended polytetramethylene ether of 1000 to 2000 molecular weight with a diisocyanate such as methylene bis(4-phenylisocyanate).



The macro diisocyanate was dissolved in xylene and polymerized at the boiling point. Very viscous solutions eventually were obtained. Precipitation of the polymer with alcohol gave an elastomer, which could be processed on a rubber mill to a tough rubbery slab. Elastomers of a similar type have been described in the literature[7]; however, the chain-extending step has ordinarily been the reaction of the macrodiisocyanate with water.

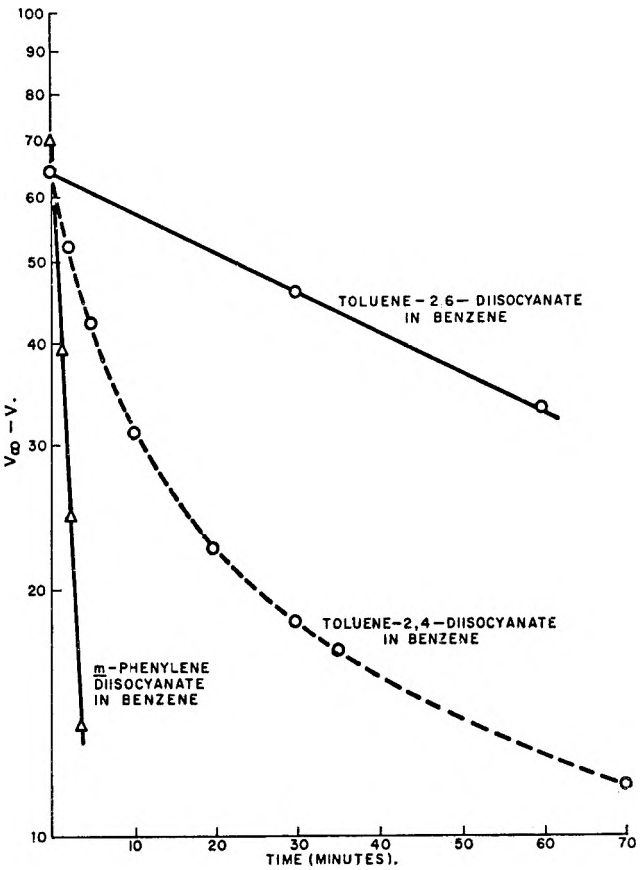
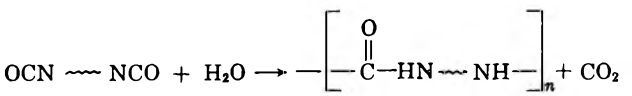
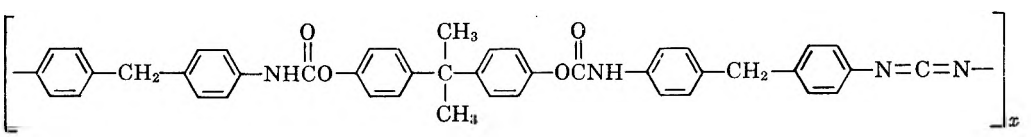


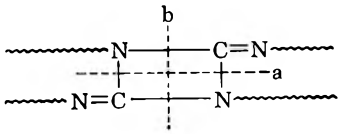
Figure 2



Other segments which were capped with isocyanates and polymerized included a hydroxyl-ended polyester, a polyethylene glycol, and diphenylolpropane. The latter polymer was not soluble in the usual solvents and had the following average structure.



The second method used for obtaining solutions involved the use of mixed solvents for the preparation of metastable solutions. As discussed previously, the carbodiimide groups are considered to interact strongly,[8]



(6) A study of the kinetics and mechanism of catalytic carbodiimide formation from isocyanates has confirmed the quantitative nature of the reaction; see J. J. Monagle, T. W. Campbell, and H. F. McShane, *J. Am. Chem. Soc.*, **84**, 4288 (1962).

(7) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 1 (1957). See p. 68 for references. See also E. O. Langerak, U. S. Patents 2,692,873-4, assigned to Du Pont.

(8) Interaction of carbodiimide groups in this way is substantiated by the fact that mesitylene diisocyanate (with hindrance around the functional groups) gives a soluble polymer which is lower melting and can be molded easily.

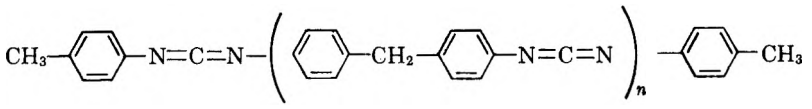
with a possible minor degree of cross linking through four-membered ring formation (p. 2071, bottom col. 2).

Reversion of the four-membered ring can take place by cleavage either *via* course a or b as indicated by the dotted lines. It was felt that, if this were so, addition of highly polar solvents to the polymerizing mixture would help maintain the polymer in solution, since they would be expected to associate with the —N=C=N— linkages, and shield them from interactions such as suggested previously.

The best solutions of carbodiimides obtained were metastable solutions prepared in mixtures of aromatic hydrocarbons with 10–20% of dimethyl sulfoxide, acetonitrile, or dimethylformamide. Most work was done with toluene 2,4-diisocyanate, methylenebis(4-phenyl isocyanate), and 3,3′-dimethoxy-4,4′-biphenylene diisocyanate as monomers. These metastable solutions could be cast to clear, colorless, tough films.

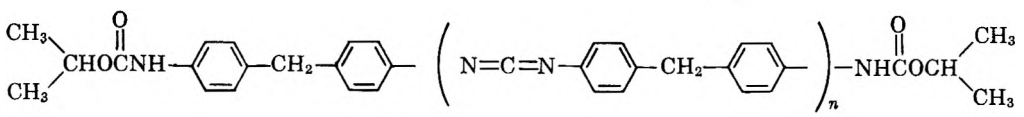
The third method used for molecular weight control was the incorporation of a chain-terminating species. The most promising agents were monomeric isocyanates, and hindered alcohols, such as isopropyl alcohol, which served as chain terminators for both ends of the growing polymer chain.

Since the rates of reaction of isocyanates vary depending upon substituents, it was necessary to take this into account. Thus when polymerizing methylenebis(4-phenyl isocyanate), a monoisocyanate such as *p*-tolyl was used.



A more reactive isocyanate would react preferentially with itself and be used up before it had performed its function. A less reactive isocyanate would react too slowly to act as an efficient terminator.

With alcohols, it was possible to obtain quite low molecular weight products, ranging from molecular weights of 600–700 on up. These products would have the following structure.



Experimental Part

The Catalyst.—Among the catalysts used, the most potent was 1-ethyl-3-methyl-3-phospholene oxide. It was used almost exclusively in our work, although occasionally the corresponding phospholene was used. These catalysts were prepared according to the method of McCormack.[9-11]

Synthesis of 4,4′-Ditolylcarbodiimide 3,3′-Diisocyanate.—Pure toluene 2,4-diisocyanate (1.0 mole) was added to 400 ml. of petroleum ether in a 1-l., seven-neck, round-bottom flask fitted with a stirrer, thermometer, four sintered glass nitrogen inlet (whose outlets were below the surface of the mixture) tubes and a spiral type condenser. The top of the condenser was connected to a Dry Ice–acetone cold trap which in turn was connected to a series of Ascarite towers set on a balance enclosed in a box with a movable plastic front.

The nitrogen flow was started through one of the inlet tubes and 0.4 ml. of 3-methyl-1-ethyl-3-phospholine 1-oxide was introduced into the reaction mixture from a hypodermic syringe at room temperature. The carbon dioxide began to evolve immediately. The amount which evolved was checked periodically by the increase in weight of the Ascarite towers. After 10 min. of reaction, a white solid precipitated from solution. During further reaction, the precipitate became so great that the extra nitrogen inlet tubes were used; otherwise, trouble was encountered with partial plugging of the end of the tube by the fine precipitate.

After 1 hr., 22 g. (0.5 mole) of carbon dioxide was evolved. At this point, 100 ml. of dry chloroform was added to the reaction mixture and the reaction was allowed to continue for 10 min. more. During this time, a small amount of carbon dioxide was evolved giving a total of 23.7 g. Boron trifluoride etherate (0.8 ml.) was introduced into the reaction mixture to inactivate the catalyst, and the mixture was stirred for an additional 15 min. during which time no more carbon dioxide was evolved. The mixture was then cooled in a Dry Ice–acetone cold bath. The mixture was filtered rapidly with the aid of vacuum.

The yellow colored residue was recrystallized from *n*-hexane giving a white powdery solid. At this stage, the product (53% yield) had a m.p. 54–101 with 21.4% NCO.

In order to obtain a purer product, the white solids were recrystallized three successive times from *o*-dichlorobenzene. During each recrystallization, the solution was allowed to cool slowly to room temperature and then filtered without further cooling.

In this way, approximately 7 g. of a white crystalline product was obtained with a m.p. of 113–115° and a isocyanate content of 26.7% or a purity of 97% (theoretical NCO, 27.6%).

Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.1; H, 3.95; N, 18.4; mol. wt., 304. Found: C, 67.1; H, 3.85; N, 18.8; mol. wt., 276.

The infrared spectra of a Nujol mull showed only the bands for isocyanate and carbodiimide.

In the isolation of toluene 2,4-diisocyanate-carbodiimide, it was found necessary to pump off absorbed solvents by vacuum in order to get a dry product. Toluene 2,4-diisocyanate-carbodiimide has a great tendency to hold on to solvents, especially hydrocarbons.

Bisethylurethane.—When toluene 2,4-diisocyanate-carbodiimide was refluxed for 2 hr. with a large excess of absolute ethanol, a white crystalline compound was obtained whose melting point was 125–132°.

Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.6; H, 6.1; N, 14.1. Found: C, 63.9; H, 6.0; N, 14.8.

The infrared spectra of a Nujol mull showed a peak at 3.07 μ (NH), a strong band at 4.7 μ (—N=C=N—), and a band at 5.82 μ (urethane, $\diagdown C{=}O \diagup$).

Polymerization of 2,4-Toluene Diisocyanate.—2,4-Toluene diisocyanate was distilled through a spinning band column. After a small forecut, distillation proceeded smoothly at 81° (1.3 mm.). Polymerization of a 10% solution in boiling decahydronaphthalene was carried out with catalytic quantities of 1-ethyl-3-methyl-3-phospholene oxide. The reaction was complete in less than an hour, and the polymer was obtained in small fluffy particles very reminiscent of puffed cereal in appearance and texture. These little particles were white and gave very tough, clear, nearly colorless film when pressed at 275°. Strips of this film could be cold drawn; however, the film strips relaxed in boiling water and exhibited no crystallinity and extremely low X-ray orientation.

Anal. Calcd. for $(C_8H_6N_2)_x$: C, 73.8; H, 4.61; N, 21.4. Found: C, 73.4, 73.5; H, 4.4, 4.2; N, 21.0, 21.0.

Polymerization of Methylenebis(4-phenyl Isocyanate).—In a three-neck, 500-ml. flask equipped with stirrer, condenser, and nitrogen inlet was placed 150 ml. of xylene, 20 g. of diisocyanate, and 0.03 g. of 1-ethyl-3-methyl-3-phospholene, and the mixture was heated to reflux. First the solution became milky, then a second liquid phase began to separate. This liquid phase became

(9) W. McCormack, U. S. Patents 2,663,736 to 2,663,739, assigned to Du Pont.

(10) Other catalysts have been studied. See J. Monagle, in press.

(11) The P-phenyl derivative is also effective. See W. McCormack, *Org. Syn.*, in press.

more and more viscous and eventually yielded high molecular weight fibrous material. The fibrous nature of the product resulted from the shearing action of the stirrer blade on the rapidly thickening prepolymer which separated initially. After the polymer had been separated and air dried, these short filaments could be separated manually from the bulk of the polymer and could be cold drawn. The drawn filaments were slightly cream colored and quite tough. Physical test data[12] were obtained on various of these filaments. The average values for T/E/M were 3.9/20/35 with a filament denier ranging from 51 to 630. It should be noted that these values are minimum values since the shape of these filaments was nonuniform, being rather that of a highly elongated, truncated cone. X-ray examination of the boiled fibers showed approximately 30% lateral crystallinity, and 5% longitudinal crystallinity, coupled with a high degree of orientation (Fig. 3).

Anal. Calcd. for $(C_{14}H_{10}N_2)_x$: C, 81.52; H, 4.89; N, 13.6. Found: C, 81.71, 81.86; H, 4.86, 5.04; N, 13.0, 13.2.

Preparation of Poly(3,3′-dimethoxy-4,4′-biphenylenecarbodiimide).—Ten grams of diisocyanate was dissolved in 100 ml. of hot xylene. The solution was filtered free of a small amount of undissolved foreign matter and polymerized with 0.04 g. of 1-ethyl-3-methyl-3-phospholene oxide in a three-necked flask with refluxing and stirring. After 5 hr. the white, finely divided polymer was filtered, washed with benzene, and dried. The yield was 8.5 g. It had a high X-ray crystallinity. It could be melt-pressed at 250° to a film with a slight yellow color. The film, cut in strips, could be stretched 3–4 times at 160°. The film exhibited typical necking phenomena on stretching, characteristic of high polymers such as nylon 6–6, polyethylene, etc., and showed strong birefringence when examined with a polarizing microscope. The birefringence disappeared at about 190°. X-ray examination of the drawn polymeric material indicated that the product was crystalline with good longitudinal order and a fairly high degree of orientation.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.76; N, 11.1. Found: C, 71.0, 70.6; H, 4.6, 4.6; N, 10.7, 10.8.

Polymerization of 3,3′-Dimethyl-4,4′-biphenylene Diisocyanate.—A sample of this diisocyanate weighing 20 g. was dissolved in 200 ml. of hot xylene. The solution was filtered free of insoluble matter and was polymerized with 1 drop of 1-ethyl-3-methyl-3-phospholene oxide at the boiling point of xylene. Carbon dioxide was evolved rapidly. The mixture was allowed to stir and reflux overnight. Next day the polymer had precipitated and had been sheared by the reaction of the stirrer blade to short filaments which were quite tough. Film could be pressed from the polymer at 250–275° and held at that temperature for 0.5 hr. without signs of decomposition. Short hand-drawn fibrils were quite tough but showed essentially no crystallinity and only a modest degree of orientation.

Polymerization of Propane-2,2-bis(4-phenyl Isocyanate).—A solution of 10 g. of diisocyanate in 75 ml. of hot xylene was filtered free of a trace of insoluble matter. One drop of the preferred phospholene oxide catalyst was then added and the mixture was allowed to polymerize in the usual way at the reflux temperature. Contrary to the usual polycarbodiimide formation, the solution thickened without immediate precipitation of the polymer. The viscous solution was poured into a hypodermic syringe and wet spun into hexane. The fibers so obtained could be cold-drawn and showed moderate toughness. This polymer showed the best as-prepared solubility in pure xylene of any polycarbodiimide studied.

In another experiment, the same diisocyanate was polymerized in the presence of a chain terminator. A mixture of 7.5 g. of isocyanate, 45 ml. of toluene, 5 ml. of tetrachloroethane, 0.04 g. of *p*-chlorophenyl isocyanate, and 1 drop of catalyst was refluxed. After about 3 hr., the mixture became quite viscous and some polymer precipitated around the edges. Contrary to any previous observation, this precipitated polymer returned to solution on stirring. A portion of this viscous solution was cast to a tough film. The remainder of the polymer was precipitated with acetone and could be pressed into clear film at 200°. The precipitated polymer was dried in a high vacuum at 100° for 3 hr. before pressing.

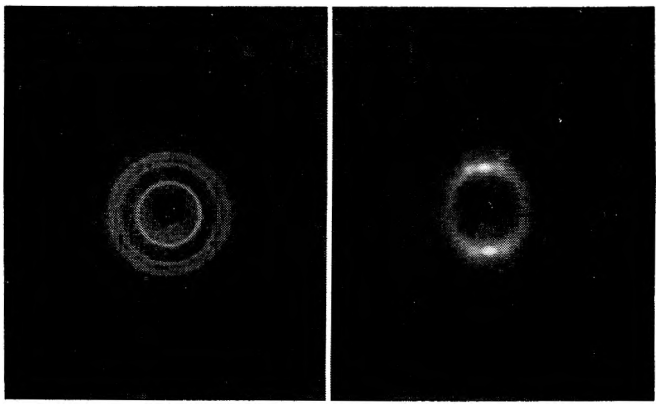
Polymerization of *m*-Phenylene Diisocyanate.—Eight grams of monomer was dissolved in 75 ml. of xylene, and the mixture was heated to reflux, and 0.03 g. of the preferred phospholene oxide catalyst was added. The polymerization was carried out at the boiling point for about 3 hr. The resulting polymer, which was obtained in the form of very tough lumps, was washed with benzene and dried in a vacuum. The yield was about 6.5 g., with considerable loss occurring because of the tendency of the polymer to adhere to the glass flask. The polymer was amorphous and could be pressed at about 250° into clear, colorless, very tough film. A combustion analysis of the dried polymer showed the following results.

Anal. Calcd. for $(C_7H_4N_2)_x$: C, 72.4; H, 3.45; N, 24.1. Found: C, 72.2, 72.4; H, 3.4, 3.5; N, 23.1, 23.3.

Polymerization of 4,4′-Biphenylene Diisocyanate.—A 15-g. sample of the diisocyanate was dissolved in 150 ml. of xylene, and the mixture was heated to the boiling point. The preferred phospholene oxide catalyst (0.03 g.) was added, and the mixture was refluxed for 4 hr. The polymer was isolated as a finite white powder by filtration. It had a high degree of crystallinity as formed (Fig. 3) and a crystalline melting point above 300°. It could be molded to very stiff, tough film at temperatures over 300°.

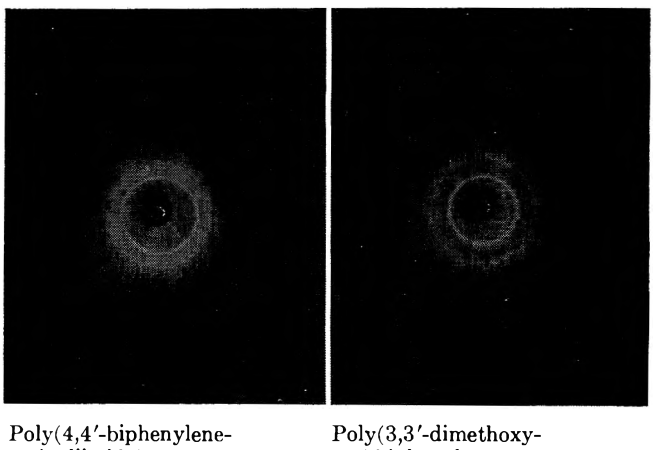
Polymerization of Mesitylene Diisocyanate.—Fifteen grams of mesitylene diisocyanate was dissolved in 150 ml. of xylene, and 0.15 g. of the preferred phospholene oxide catalyst was added to the refluxing solution. After 24 hr., a moderately viscous solution resulted from which could be obtained a tough film by evaporation of the solvent. The polymer was precipitated by the addition of isopropyl alcohol and then was dried. The polymer had a melting point of 130°. A clear, tough film was easily melt pressed at 100°. This film could be stretched 8 times at 100°. X-Ray examination of the stretched polymer showed a low degree of crystallinity and orientation.

Polymerization of Hexamethylene Diisocyanate.—Fifteen grams of the diisocyanate was mixed with 25 ml. of xylene and held at 140° in the presence of 0.15 g. of the phospholene oxide catalyst for 6 hr. The polymer precipitated as a lump of gel



Poly(1,5-naphthalene-carbodiimide) as formed

Poly[methylene-bis(*p*-phenylene)-carbodiimide] stretched filaments



Poly(4,4′-biphenylene-carbodiimide) as formed

Poly(3,3′-dimethoxy-4,4′-biphenylene-carbodiimide) as formed

Fig. 3.—X-ray patterns of polycarbodiimides.

(12) R. G. Beaman and F. B. Cramer, *J. Polymer Sci.*, **21**, 223 (1956).

which was cut up in a Waring Blendor in acetone. The resulting polymer could be pressed to rather weak film. The infrared spectrum of the polymer films showed conclusively that the material contained no isocyanate and the calculated amount of carbodiimide linkages.

Polymerization of a Triisocyanate.—2,4,4′-Triisocyanatodiphenyl ether was prepared according to the literature.[13] A solution of 10 g. of this triisocyanate in 68 ml. of xylene was treated with 0.03 g. of 1-ethyl-3-methyl-3-phospholene-1-oxide. After about 2 hr. at the reflux temperature, the hard cream-colored solid which had precipitated was filtered and extracted with benzene. The polymeric product was completely infusible and insoluble and could not be molded to a film. These properties are those of a typical three-dimensional polymer.

Preparation of an Elastomer Based on a Polyester Glycol.—A polyester with hydroxyl end groups and a molecular weight of about 2000 was prepared by heating sebacic acid with excess 2,2-diethylpropanediol. Water and excess glycol were removed at reduced pressure. A mixture of 23 g. of this polyester was heated for 1.5 hr. on a steam bath with 5.8 g. of methylenebis(4-phenyl isocyanate). The reaction mixture was then diluted with 100 ml. of xylene containing 0.1 g. of the catalyst. After about 1 hr. at reflux, a very viscous solution resulted which could be converted into a sheet of tough elastomeric material similar to that in the following experiment.

Preparation of an Elastomer Based on Polytetramethylene Ether Glycol.—A mixture of 33.7 g. of polytetramethylene ether glycol having an average molecular weight of about 2000 was heated on a steam bath for 90 min. with 8.7 g. of methylenebis-(*p*-phenyl isocyanate). The reaction product was diluted with 200 ml. of xylene containing 0.1 g. of the preferred phospholene oxide catalyst. The mixture was refluxed for 1 hr. to give a very viscous solution. This viscous solution was cast onto a glass plate, and the solvent was evaporated. A clear, very tough, snappy sheet of an elastomer was obtained. This material could be elongated 600% and showed good recovery.

In a similar experiment, 145 g. of polytetramethylene ether glycol with an average molecular weight of 3400 was heated on the steam bath for 2 hr. with 171 g. of 2,4-toluene diisocyanate. The cooled product was transferred to a Werner–Pfleiderer mixer, where the mass was blended at 80–100° for 4 hr. with 0.8 g. of the phospholene oxide catalyst. The tough, rubbery mass which resulted was milled on a rubber roll mill to give a rough sheet, a portion of which was molded under pressure for 1 hr. at 232°. This slab of elastomer had the following properties at room temperature: tensile strength, 2400 p.s.i.; elongation, 500%; modulus at 300% elongation, 486 p.s.i.

Preparation of an Elastomer from Polyethylene Glycol.—A mixture of 50 g. of polyethylene glycol of a molecular weight about 1000 and 26.1 g. of toluene 2,4-diisocyanate was heated at 90–95° for about 1 hr. To the polyether now bearing isocyanate end groups was added 0.1 g. of the preferred phospholene oxide catalyst. The mixture was mixed in a Werner–Pfleiderer mixer at 70–100° for 2 hr. During this period, carbon dioxide was evolved, and the mass became quite thick. After 2 hr., the mixture was milled on a rubber mold for 1 hr. at 70° and then for 0.5 hr. at 100°. The resulting product was molded under pressure at 120° to give a clear slab of synthetic elastomer which had good snap and elasticity.

Polymerization of the Reaction Product from 4,4′-Isopropylidenediphenol and Methylenebis(4-phenyl Isocyanate).—A mixture of 11.4 g. of 4,4′-isopropylidenediphenol and 25 g. of methylene bis(4-phenyl isocyanate) was refluxed with 85 ml. of xylene for 2 hr. to yield a diurethane with terminal isocyanate groups. Three-tenths gram of the preferred phospholene oxide catalyst was then added and refluxing was continued for about 30 min. Polymerization occurred rapidly with the production of an insoluble, very tough polymer.

Anal. Calcd. for $(C_{44}H_{36}N_4O_4)_x$: C, 77.2; H, 5.3; N, 8.2. Found: C, 77.5; H, 5.2; N, 7.6.

Polymerization of Toluene Diisocyanate in Mixtures Containing Dimethyl Sulfoxide.—A mixture of 40 ml. of xylene and 10 ml. of dimethyl sulfoxide was heated to boiling and 10 ml. of toluene diisocyanate was added, followed by 1 drop of the preferred phospholene oxide catalyst. Evolution of carbon dioxide was brisk. After about 1.5 hr., the polymer was still in solution. Continued heating eventually caused the solution to gel. The polymer was isolated in a Waring Blendor, washed repeatedly with acetone, and pressed to film. This film stuck to a Dennis hot bar at 340° and could be pulled out to long filaments.

In another experiment, polymerization was carried out in a mixture of 45 ml. of xylene and 5 ml. of dimethyl sulfoxide. Again, the mixture became quite viscous but the polymer did not precipitate out of solution. The solution was cast after about 1.5 hr. to a film which was dried at 110° for 3 hr. in a forced draft oven. The film was quite tough and stiff. Strips of this film could be drawn 5 times at 100°. However, the film strips could not be heat-set. The film strips proved to be elastomeric above 110°.

Use of Phenyl Isocyanate as a Chain Terminator.—Three identical polymerizing mixtures were prepared by mixing 47 ml. of xylene, 3 ml. of dimethyl sulfoxide, 10 ml. of toluene diisocyanate, and 1 drop of catalyst at the boiling point. To one was added 0.1 g. of phenyl isocyanate, to the second 0.2 g., and to the third 0.5 g. Qualitatively, the rate at which the solutions thickened decreases with increasing phenyl isocyanate. When an appropriate viscosity was reached, each solution was cast on a plate and dried. Qualitatively, the toughness decreased with increasing phenyl isocyanate content.

Polymerization of 2,4-Toluene Diisocyanate in the Presence of *p*-Chlorophenyl Isocyanate.—A stock solution of *p*-chlorophenyl isocyanate was prepared by diluting 1.0 g. of isocyanate to 50 ml. with xylene. Two polymerizations then were carried out. In the first, 90 ml. of xylene, 10 ml. of dimethyl sulfoxide, 10 ml. of toluene diisocyanate, and 1 drop of the phospholene oxide catalyst were mixed and refluxed until the mixture began to get viscous. At this point, 5 ml (0.1 g.) of the stock solution (0.1 g. *p*-chlorophenyl isocyanate) was added. The viscosity of the solution dropped rapidly, indicating that depolymerization was taking place. In the second experiment, the *p*-chlorophenyl isocyanate (0.18 g.) was added before the catalyst. Polymerization of this mixture gave a solution which attained only a moderate viscosity. The polymer was precipitated with acetone and converted into a tough film at 250°. The precipitated, washed, polymer contained 0.4% by weight of chlorine, indicating that all of the capping agent had been incorporated.

Preparation of the Polycarbodiimide Derived from Toluene 2,4-Diisocyanate and Chain Terminated with Ethanol.—A 500-ml., four-necked, round-bottom flask was fitted with a stirrer, thermometer, a sintered glass tipped nitrogen inlet tube, and a spiral type condenser which was connected at the top to a Dry

(13) Werth and Krahler, U. S. Patents 2,765,341 and 2,786,864, to Du Pont.

TABLE III

EQUIVALENTS N=C=N PER MOLE FOR POLYCARBODIIMIDES DERIVED FROM TOLUENE 2,4-DIISOCYANATE

Alcohol used	Total wt. CO_2, g.	Mol. wt. calcd. from CO_2 data	Equiv. N=C=N/mole
Ethanol	7.3	902	4.89
Ethanol	6.7	670	3.11
Isopropyl alcohol	7.0	794	3.85
Isopropyl alcohol	7.8	1334	8.00
Benzyl alcohol	6.9	855	3.58
Ethanol	8.2	2114	14.22
Ethanol	7.3	1332	4.87[a]

[a] Polycarbodiimide derived from methylenebis(4-phenyl isocyanate).

TABLE IV

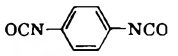
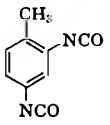
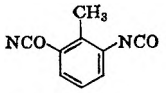
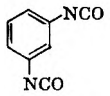
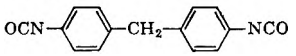
COMPARISON OF MOLECULAR WEIGHT FOR STABILIZED POLYCARBODIIMIDES USING TITRATION DATA AND CO_2 DATA

Diisocyanate used	Alcohol used	Total wt., CO_2, g.	Mol. wt. calcd. from CO_2 data	Mol. wt. from titration data
2,4-TDI[a]	Ethanol	6.7	670	664
2,4-TDI	Isopropyl alcohol	7.0	794	803
MDI[b]	Ethanol	7.3	1332	3700
2,6-TDI[c]	Ethanol	6.6	642	1176
MDI	Ethanol	8.1	2752	2771

[a] Toluene 2,4-diisocyanate. [b] Methylenebis(4-phenyl isocyanate). [c] Toluene 2,6-diisocyanate.

TABLE V

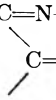
EVOLUTION OF CO_2 FROM SELECTED DIISOCYANATES IN AN OPEN SYSTEM CALCULATION OF PSEUDO FIRST-ORDER CONSTANTS

Diisocyanate	$t_{1/2}$ (80°), sec.	$t_{1/2}$ (110°), sec.	$t_{1/2}$ (140°), sec.	k (80°)	k (110°)	k (140°)
	204	—	—	3.4×10^{-3}	—	—
	570	168	—	1.2×10^{-3}	4.1×10^{-3}	—
	4080	—	552	1.7×10^{-4}	—	1.3×10^{-3}
	150	65	—	4.6×10^{-3}	9.4×10^{-2}	—
	480	—	84	1.4×10^{-3}	—	8.3×10^{-3}

Ice–acetone cold trap and then to an Ascarite tower fitted on a balance inside a box containing a movable plastic front panel. To the flask was added 34.8 g. of toluene 2,4-diisocyanate (0.2 mole) and 200 ml. of dry benzene. This mixture was heated in an oil bath to 50 ± 1° under a stream of dry nitrogen bubbling through the solution. To the heated mixture was added 0.2 ml. of 3-methyl-1-ethyl-3-phospholene 1-oxide from a calibrated hypodermic syringe.

Carbon dioxide evolution measurements were taken periodically by the increase in weight of the Ascarite tower. During 37 min., 6.0 g. (0.136 mole) of carbon dioxide had evolved; 12 ml. (0.2 mole) of absolute ethanol was introduced into the reaction mixture. During the next 23 min., a total of 6.7 g. (0.152 mole) of carbon dioxide was measured. The reaction mixture was then heated for an additional 45 min. during which time no more carbon dioxide had evolved.

The benzene and excess alcohol were distilled from the reaction mixture using high vacuum and a bath temperature of 40–50°.

The product was a light yellow solid which was soluble in chloroform, benzene, and tetrahydrofuran. The infrared spectra of an evaporated film from chloroform solution showed an —NH band at 3.02 μ, an —N=C=N— band at 4.70 μ, and a band at 5.77 μ for the urethane,  . All other urethane-terminated polycarbodiimides were prepared in a similar fashion.

The equivalents of carbodiimide groups per mole for a number of polycarbodiimides derived from toluene 2,4-diisocyanates are given in Table III.

Another series of polymers was prepared in similar manner, and the molecular weights checked by a titration method. This method consists of the reaction of excess ethylamine with the carbodiimide, elimination of the excess amine, and titration of the guanidine with 0.1 N hydrochloric acid. This procedure was found to be applicable to stabilize polycarbodiimides as well as to the simple compounds.

The per cent —N=C=N— present in the molecule is calculated as follows

$$\% \text{ N=C=N} = \frac{\text{ml. HCl} \times N \text{ of HCl} \times 4.0}{\text{weight of sample}}$$

where 4.0 is the equivalent weight of N=C=N × 100/1000. The data are shown in Table IV.

Hydrolytic Stability of Polycarbodiimides.—Both poly(3,3-dimethoxy-4,4-biphenylenecarbodiimide) and poly(4,4-biphenylenecarbodiimide) were boiled as fine powders with 10% sulfuric acid, 10% sodium hydroxide, distilled water, and 10% aqueous aminoethanol. After 24 hr. approximately half of the carbodiimide bonds had been altered, as shown by infrared measurements. These figures could not be obtained accurately since potassium bromide pellet formation for infrared analyses was poor.

In another experiment, five samples of poly(2,4-toluenecarbodiimide) film of 1-mil thickness were prepared. These samples were boiled with, respectively, 10% sulfuric acid, 3 N sodium hydroxide, water, and 10% ethanolamine. The fifth sample was retained as a control. No change could be detected in the spectra of the various film samples indicating that no chemical reaction had taken place between the polymer and the hydrolyzing medium.

Infrared Study of Carbodiimide Formation.—The infrared spectrum of a polymerizing mixture of 50 g. of methylenebis(4-phenyl isocyanate) in 200 ml. of boiling xylene was taken several times during the polymerization. The appearance of the carbodiimide band was matched quite closely by the disappearance of the isocyanate band. After about half an hour, the isocyanate band intensity had dropped to about one-half of its original intensity, and the carbodiimide band had built up to about one-half of its final intensity. After 3 hr., no isocyanate could be detected, only carbodiimide with a band at about 4.76 μ.[14] The intensity of the band was such that within the limits of accuracy of the infrared measurements, all of the isocyanate could be accounted for as carbodiimide.

Reaction of *p*-Methoxyphenyl Isocyanate with Ditolylcarbodiimide.—A mixture of approximately equal weights of ditolylcarbodiimide and *p*-methoxyphenyl isocyanate and a trace of phospholene oxide catalyst was heated at 150° for 5 min. and then swept out with a stream of argon gas. The effluent gases were run through a gas chromatographic column which gave a clear, well defined band indicative of the presence of substantial quantities of tolyl isocyanate.

Kinetic Measurements.—Rates of evolution of carbon dioxide were measured exactly as in paper II of this series.[6] Data are shown in Fig. 1 and 2 and Table V.

(14) (a) G. D. Meakins and R. J. Moss, *J. Chem. Soc.*, 993 (1957); (b) H. G. Khorana, unpublished work quoted in ref. 3.

Pyrolysis of N-*t*-Butyl-N-alkylcarbamoyl Chlorides. A New Synthesis of Isocyanates

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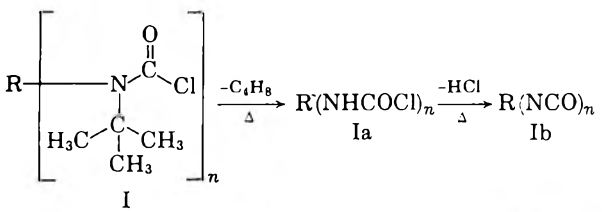
The Carwin Company, Division of the Upjohn Company, North Haven, Connecticut

Received December 27, 1962

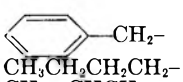
A number of N-*t*-butyl-N-alkyl carbamoyl chlorides have been synthesized by known methods. These compounds decompose readily at low temperature with or without catalysis to the corresponding alkyl isocyanates in high yield.

The pyrolysis of an N-*t*-Butyl-N-alkyl carbamoyl chloride (I) to the primary carbamoyl chloride (Ia) or even to the corresponding alkyl isocyanate (Ib) provides a synthetic approach to mono- and diisocyanates, some of which are not readily accessible by known synthetic methods.

Accordingly, a number of *t*-butylalkylamines were synthesized in high yield from *t*-butylamine and the corresponding alkyl chlorides using a modification of Bortnick's[1] method. The *t*-butylalkylamines were then phosgenated under a variety of conditions to the N-*t*-butyl alkyl carbamoyl chlorides which, in certain cases, were isolated, purified, and characterized; the yields depending both on the nature of the alkyl group and the method of phosgenation.



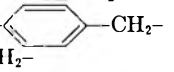
I

I, n = 1, R =  —CH_2–

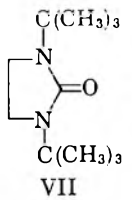
II, n = 1, R = $CH_3CH_2CH_2CH_2$–

III, n = 1, R = CH_2=$CHCH_2$–

IV, n = 2, R = –CH_2CH=$CHCH_2$–

V, n = 2, R = –CH_2–  –CH_2–

VI, n = 2, R = –CH_2CH_2–



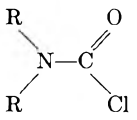
VII

Attempts to prepare VI from N,N′-bis-*t*-butylethylenediamine gave 1,3-bis-*t*-butyl-2-imidazolidinone (VII) instead.

The initial model selected, *t*-butylbenzylamine-N-carbonyl chloride (I), demonstrated the relative ease with which the decompositions to isocyanate may take place. Even during its formation in toluene (110°) traces of isocyanate were detectable. The pure material (I), a solid, in the melt at 130 to 160°, decomposed with vigorous gas evolution, to give hydrogen chloride, isobutylene, *t*-butyl chloride, and benzyl isocyanate in over 84% yield. The generality of the reaction has been established by similarly converting the *n*-butyl (II) and allyl (III) derivatives to the corresponding monoisocyanates, and the *p*-xylylene (IV) and 1,4-disubstituted butene-2 (V) derivatives to the corresponding diisocyanates in good yield.

Operational difficulties attendant with the more volatile II and III and with the more reactive IV and V when decomposed as the undiluted materials prompted a study, of the reaction in a variety of solvents. This study, using II as a model, revealed that the reaction proceeds with utmost ease in polar solvents[2] such as nitrobenzene at mild (100°) temperatures, while being slow in toluene. Moreover, the addition of catalytic amounts of ferric chloride, known to aid reaction of carbamoyl chlorides,[3] accelerated the reaction even to the extent that the reaction proceeded as well as with catalyst at 83° in ethylene dichloride as it had at 100° without catalyst in nitrobenzene. These results are shown in Fig. 1 and in Table I.

Synthesis of disubstituted carbamoyl chlorides (VIII) by phosgenation of secondary amines under various conditions is well known[4]; however, the formation of isocyanates from such carbamoyl chlorides or even during their synthesis has not been reported previously. Actually, compounds VIII appear to exhibit considerable thermal stability, especially the mono- and diaryl derivatives, but even straight-chain dialkyl derivatives are quite stable. This is demonstrated strikingly by the work of Slocombe[4i] who has obtained the dibutyl and diamyl derivatives in 80% yield by vapor phase phosgenation of the secondary amines at 200–275°. No isocyanate formation from these amines was mentioned.



VIII

From this work, it is evident that introduction of branching in the α-carbon reduces the thermal stability markedly. The highly stable examples cited are either aryl[5,6] or primary alkyl[4i] substituted. There are only a few secondary alkyl[4f,m,5] substituted carbamoyl chlorides reported. Isocyanate formation from these has not been observed, although Boon[4f] has de-

(1) N. Bortnick, *et al.*, *J. Am. Chem. Soc.*, **78**, 4039 (1956).

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw Hill Book Co., New York, N. Y., 1940, pp. 214, 215, 322, 323.

(3) F. Weygand and R. Mitgau, *Chem. Ber.*, **88**, 301 (1955); *Chem. Abstr.* **50**, 1663 (1956).

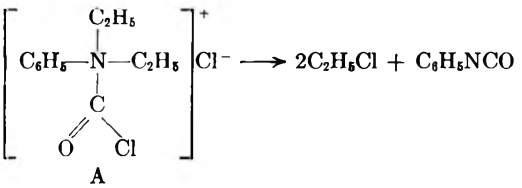
(4) (a) A. B. Boese, Jr., and R. T. Major, *J. Am. Chem. Soc.*, **57**, 175 (1935); *Chem. Abstr.*, **29**, 1412 (1935). (b) G. Lob, *Rec. trav. chim.*, **55**, 859–873 (1936); *Chem. Abstr.*, **31**, 1385 (1937). (c) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1954, (1937); *Chem. Abstr.*, **32**, 1666 (1938). (d) L. Raiford and K. Alexander, *J. Org. Chem.*, **5**, 300 (1940); *Chem. Abstr.*, **34**, 5065 (1940). (e) L. Orthner, U. S. Patent 2,251,892 (1941); *Chem. Abstr.*, **35**, 7586 (1941). (f) W. R. Boon, *J. Chem. Soc.*, 307–318 (1947); *Chem. Abstr.*, **41**, 5448–5451 (1947); British Patent 560,700 (1944); *Chem. Abstr.*, **40**, 3857 (1946); U. S. Patent 2,398,283 (1946); *Chem. Abstr.*, **40**, 4178 (1946). (g) O. Ya. Fedetova, *et al.*, *ibid.*, **53**, 1141 (1959). (h) P. E. Wilcox and W. A. Schroeder, *J. Org. Chem.*, **15**, 944 (1950); *Chem. Abstr.*, **45**, 2889 (1951). (i) R. J. Slocombe, *et al.*, *J. Am. Chem. Soc.*, **72**, 1888 (1950). (j) W. Siefken, *Ann.*, **562**, 75–136 (1949); *Chem. Abstr.*, **44**, 115 (1950). (k) S. Kushner and L. Brancone, U. S. Patent 2,467,895 (1949); *Chem. Abstr.*, **43**, 6245a (1949). (l) J. Weijlard and M. Tishler, U. S. Patent 2,642,450 (1953); British Patent 688,726 (1953); *Chem. Abstr.*, **48**, 2091 (1954). (m) A. Sekera, *et al.*, *Chem. Listy*, **46**, 762 (1952); *Chem. Abstr.*, **47**, 12302 (1953).

(5) T. W. Price, *J. Chem. Soc.*, 3230 (1926).

(6) R. Stolle, *J. prakt. Chem.*, **117**, 185–210 (1927); *Chem. Abstr.*, **22**, 422 (1928).

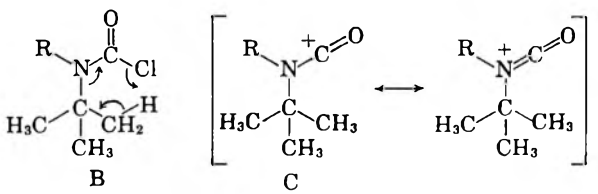
scribed some of them as undistillable liquids.[7] *t*-Alkyl substituted carbamoyl chlorides were not reported previously in the literature.

While the phosgene–tertiary amine reaction is a well known[8] reaction for synthesis of disubstituted carbamoyl chlorides, again, frequently under drastic (190°) conditions, there is only an isolated instance in which Wahl[8a] reports that the use of a large excess of phosgene at high temperature on di-*n*-alkylanilines afforded traces of phenyl isocyanate. This reaction could proceed *via* an intermediate such as A.



A

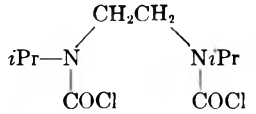
The decomposition of the *t*-butylcarbamoyl chlorides occurs more readily in polar than in nonpolar solvents and is catalyzed by Lewis acids such as ferric chloride. These effects of solvent and catalysis are demonstrated in Fig. 1, whereby the rate of decomposition in the polar solvent nitrobenzene or with ferric chloride in ethylene dichloride solvent is considerably enhanced over that in the nonpolar solvent toluene. These facts are consistent with a cyclic concerted process similar to the Cope and Chugaev reactions,[9,10] and illustrated by B. An alternative mechanism involving the initial ionization of chloride ion to give the resonance stabilized carbonium ion (C), a step facilitated both by polar solvent and Lewis acid, is perhaps more attractive.



B C

Analogous to this reaction are the observations of Mukaiyama, *et al.*,[11] who have obtained isocyanates among other formed products from acetoacetamides and α-chloroacetanilides, albeit only at 350° and above in the vapor phase. Very significantly, the yields were greatly improved when the N–H was replaced by N–*t*-Bu in the latter types.

(7) Among these were, however, compounds of the ethylenediamine type which have a structure predisposed to the elimination of phosgene with concomittant cyclization to ethyleneureas,[4b,4f] which we have rather similarly observed on attempted synthesis of VI (*cf.* Experimental section 6)



(8) (a) A. Wahl, *Bull. soc. chim.*, [5] **1**, 244–246 (1934); *Chem. Abstr.*, **28**, 5430 (1934). (b) C. Scholtissek, *Chem. Ber.*, **89**, 2562 (1956); *Chem. Abstr.*, **51**, 14712 (1957). (c) V. A. Rudenko, *et al.*, *J. Gen. Chem., USSR*, **17**, 2256–2258 (1947); *Chem. Abstr.*, **42**, 4918 (1948). (d) E. Stein and O. Bayer, U. S. Patent 2,698,343 (1954).

(9) D. J. Cram, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 310.

(10) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(11) T. Mukaiyama, *et al*, *J. Org. Chem.*, **26**, 4381 (1961); **27**, 803 (1962).

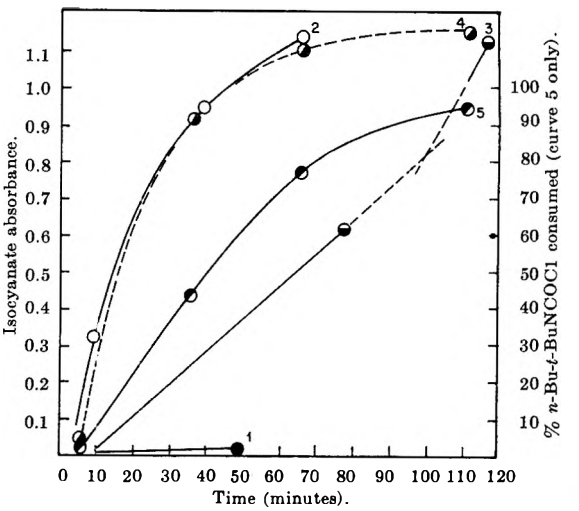
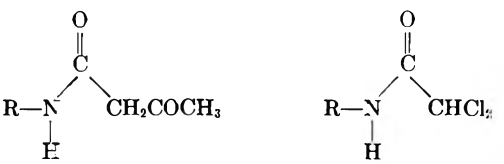


Fig. 1.—Formation of *n*-butyl isocyanate from *n*-butyl-*t*-butylcarbamoyl chloride. Curves 1 through 4 represent isocyanate absorbance (λ_{max} 4.45 μ, left ordinate) *vs.* time: (1) ●, in toluene at 100°; (2) ○, in nitrobenzene at 100°; (3) ◒, in 1,1,2-trichloroethane at 100° with a trace of ferric chloride catalyst introduced at a reaction time of 97 minutes; (4) ◕, in 1,2-dichloroethane with ferric chloride catalyst at 83°. Curve 5, ◔ indicates the per cent *n*-butyl-*t*-butylcarbamoyl chloride consumed in 4 as determined by the carbonyl absorption at λ_{max} 5.75 μ (right ordinate).



Experimental

Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer.

1. General Procedure for *t*-Butylamines

The procedure is a modification of Bortnick's method,[1] and is illustrated for *t*-butylbenzylamine. A solution of 75.9 g. (0.6 mole) of benzylchloride and 87.6 g. (1.2 moles) of *t*-butylamine in 150 ml. of dimethylformamide was heated at a gentle boil for 3 hr. during which the temperature rose from 80° to 140° with some crystals forming and redissolving. Thereafter, excess (78% recovery) *t*-butylamine was slowly (3 hr.) distilled. From the cooled mixture 112 g. (93% theory) of crude amine hydrochloride was obtained dry, m.p. 249–253°. Treatment with 15% caustic (no exotherm) afforded 76.1 g. of an oil which was dried over potassium hydroxide pellets and distilled *in vacuo*; b.p. 100° (17 mm.), b.p. 107° (20 mm.), b.p. 99° (14 mm.); $n^{22.7}$D 1.4951 [reported b.p. 91° (12 mm.), n^{25}D 1.4941].

Because the reaction of the allylic halides with *t*-butylamine was very exothermic, these halides were added dropwise to the preheated amine solution at 65–75° without additional heating until the addition was complete; by contrast, complete reaction with *n*-butyl chloride or ethylene dichloride required nearly 2 days.

2. Phosgenation of *t*-Butylamines

Method A. (a) ***t*-Butylbenzylamine-N-carbonyl Chloride** (I).—A solution of 48.6 g. (0.3 mole) of *t*-butylbenzylamine in 100 m. of toluene was added (25 min.) to a stirred, ice-cooled solution of 30 g. (0.3 mole) of phosgene in 500 ml. of toluene while passing excess phosgene at a rate of 0.1–0.2 mole/hr. The resulting thick suspension was refluxed until clear (100°, 16 hr.) while continuing to add phosgene. Evaporation *in vacuo* afforded a crystalline residue, pale brown to yellow, with a sweet and pungent odor, 66 g. (96%), m.p. 85–89°.

Spectrum: $\lambda_{max}^{CHCl_3}$ 3.42, 5.75, 6.85, 7.14, 7.34–7.45, 8.50, 8.95, 10.40 μ.

(b) *n*-Butyl-*t*-butylamine-N-carbonyl Chloride (II).—This procedure on *n*-butyl-*t*-butylamine in benzene gave a solution containing much unchanged suspended amine hydrochloride even after 24 hr. at 80°, but this filtered hydrochloride was completely phosgenated in 5.5 hr. in toluene at 110°. The carbonyl chloride was not isolated, but rather pyrolyzed on concentration.

(c) Bis-*t*-butylamino-*p*-xylylene-N,N′-dicarbonyl Chloride (V).—The procedure of method A using chlorobenzene solvent at reflux (130°) during 3 days still had 22% unchanged dihydrochloride present, which was insoluble and identical with original hydrochloride. The filtrate, on concentration, afforded a bright yellow solid which became colorless on standing in the air, crude V.

Method B. (a) 1,4-Bis-*t*-Butylaminobutene-2-N,N′-dicarbonyl Chloride (IV).—A solution of 19.8 g. (0.1 mole) of 1,4-bis-*t*-butylaminobutene-2 and 20.2 g. (0.2 mole) of triethylamine in 100 ml. of benzene was added to an ice-cooled (3–8°) solution of *ca.* 19.8 g. (0.2 mole) of phosgene in 150 ml. of benzene (40 min., 3–8°). After 1-hr. stirring at 20–30°, the mixture was purged and heated to 65°. The solid triethylamine hydrochloride was filtered off and triturated once with hot benzene (100 ml., 60°). The combined filtrates afforded 25.8 g. of fine crystals, m.p. 132–134°; and another 3.6 g., m.p. 132–133°, from the mother liquor (total 91%).

Anal. Calcd. for $C_{14}H_{24}N_2O_2Cl_2$: C, 52.01; H, 7.48; N, 8.67. Found: C, 52.14; H, 7.35; N, 8.72.

Spectrum: $\lambda_{max}^{CHCl_3}$ 3.40, 5.75, 6.80, 7.16, 7.3–7.5, 8.50, 8.90, 9.33, 10.45 μ.

(b) *n*-Butyl-*t*-butylamine-N-carbonyl Chloride (II).—This was also prepared by method B; however, filtering and triturating the triethylamine hydrochloride was done in the cold (20–30°). The filtrate, on concentration, afforded an oil which, on centrifuging free of trace impurities, weighed 16.6 g. (86% from 12.9 g., 0.1 mole, amine), m.p. −23 to −25°.

Spectrum: λ_{max}^{neat} 3.42, 5.75, 6.80, 7.3, 7.45, 7.75, 8.43, 9.25, 10.65, 11.83, 13.3, 13.65, 14.0, 14.8 μ.

Method C. Combined Phosgenation and Pyrolysis to Isocyanate. (a) Allyl Isocyanate.—Into an ice-cold, stirred solution of 100 ml. of *o*-dichlorobenzene and 27.8 g. (0.15 mole) of tributylamine was condensed *ca.* 15 g. (0.15 mole) of phosgene and then was added 17.0 g. (0.15 mole) of *t*-butylallylamine during 10 min. III was not isolated; rather 1.15 hr. later, the mixture was heated to 115–125° while adding another 0.15 mole of tributylamine. With a short distilling column attached, a receiver at room temperature, and a Dry Ice-cooled trap in series, the reaction mixture was heated to 175° (1 hr.) and then to 200° (1 hr.). During the latter period 9.3 g. (75%) of slightly impure allyl isocyanate distilled, b.p. 80–85° (760 mm.) [reported[12] b.p. 82° (760 mm.)]. Isocyanate equivalent, 83.9; theory, 83.1.

Infrared spectrum: λ_{max}^{neat} 2.75, 3.27, 4.42, 6.05, 6.92, 7.05, 7.4, 7.5, 10.07, 10.75–10.9 μ. The Dry Ice trap contained 7.6 g. of volatile material, b.p. mostly −10 to +1° (760 mm.) (reported for isobutylene −6°) with a strong olefinic odor; $\lambda_{max}^{CHCl_3}$ (5–15%) 4.42 μ for traces of isocyanate; traces *t*-butyl chloride, λ_{max} 6.84, 7.29, 8.07, 8.65 μ; and much isobutylene, λ_{max} 3.28, 3.45, 6.04, 11.30 μ. On overnight standing at room temperature the trap contents evaporated to a few drops of residue; λ_{max}^{neat} 4.45, 7.29, 8.65 μ were strong, while 6.04 μ was much decreased, and 11.30 μ entirely absent, consistent with a residue of *t*-butyl chloride and allyl isocyanate.

(b) *n*-Butyl Isocyanate.—Method C was used on *t*-butyl-*n*-butylamine with the variation that the reaction mixture was heated at 120–145° for 1 hr. and then cooled to 90° before adding the second 0.15 mole of tributylamine. During the initial period 9 g. of volatiles consisting of isobutylene and *t*-butyl chloride was collected. The distillation that followed provided a mid-cut, b.p. 114–117° (760 mm.) (reported 115°), 12.9 g. of butyl isocyanate (87%). The spectrum (neat) was identical with that of authentic material prepared from *n*-butylamine and phosgene. Since no λ_{max}^{neat} 7.77, 13.75, 15.32 μ, characteristic of *n*-butyl chloride were present, this material had not been formed.

3. Decomposition of Pure (Isolated) N-Carbonyl Chloride

(a) Benzyl Isocyanate.—The crude *t*-butylbenzyl-N-carbonyl (I) (66 g., 0.292 mole previously described) was melted and heated further, darkening from yellow to brown to greenish black at 120–160° while sweeping out volatile products with nitrogen into a Dry Ice-cooled flask. This distillate, 21 g. (77%), proved to be virtually pure *t*-butyl chloride by spectral comparison with purchased (Eastman) material. On cessation of gas evolution the residue was distilled; b.p. 104–110° (31–36 mm.); $n^{22}D$ 1.5242; 33.5 g. (86%) of benzyl isocyanate. The spectrum was identical with that of authentic material prepared from benzylamine and phosgene, having $n^{21.5}D$ 1.5242; $\lambda_{max}^{CHCl_3}$ 2.75, 4.45, 6.65, 6.85, 7.47, 11.5, 14.4 μ. The absence of any 7.89 μ absorption indicated that no benzyl chloride was produced.

(b) *p*-Xylylene Diisocyanate.—Eight grams (0.0215 mole) of crude V was pyrolyzed similarly and distilled; b.p. 138–147° (4–6 mm.); 2.5 g. (62%), m.p. 37–39°. Calcd. for isocyanate equivalent: 94.09. Found: 98.2. Spectrum (10% in chloroform) identical with authentic material having m.p. 37°, prepared by phosgenation of *p*-xylylenediamine.

4. Decomposition of (Pure) N-Carbonyl Chloride in Solution. Semiquantitative Kinetic Study

(a).—The oily II obtained [*cf.* method B (b)] was used. Solvent, 38 g., and 2.0 g. of II were heated quickly by insertion of the containing flask into a preheated oil bath. The well stirred solution was sampled at intervals by pipetting through a short reflux condeneer. The cooled samples were examined in the infrared usually from 4 to 6 μ *vs.* pure solvent in sodium chloride cells (0.095 mm.). Catalyst (5 to 30 mg.), when used, was added just prior to heating. In several cases hydrogen chloride evolution was detectable. Solvents nitrobenzene, toluene, ethylene dichloride, and trichloroethane were used (see Fig. 1, Table I).[13]

(b).—Because the method (undiluted) used for decomposing I and V caused much tar formation with IV, the solvent study

TABLE I

FERRIC CHLORIDE[a]-CATALYZED DECOMPOSITION OF II AND IV IN ETHYLENE DICHLORIDE

Compound, initial concn.	Sample point	Time, min.	Temp., °C.	% CC[b,c]	% NCO[d]	ANCO[e]
II, 5% by weight[a]	1	0	25	100	0	0.00
	2	5	83	98	2	0.055
	3	35	83	56	44	0.910
	4	65	83	23	(77)	1.1[b]
	5	115	83	6	(94)	1.1[b]
IV, 2.5% by weight	1	0	25	100	0	0.0
	2	5	83	98	2	0.01
	3	35	83	73	~30	0.245
	4	65	83	63	~40	0.357
	5	330	83	28	~70	0.63

[a] About 10–30 mg. of catalyst in a total 40 g. of reactant–solvent solution. [b] Per cent of unchanged carbonyl chloride, estimated from λ_{max} 5.75, this being the only carbonyl (and very sharp) absorption found in the ethylene dichloride systems. [c] A plot of % CC *vs.* time for II fits first-order kinetics quite well [log (% CC) *vs.* *t* is fairly linear]. With IV, however the plot is better described by % CC = 2 (A) + (B) for a system[14] $A \xrightarrow{k_1} B \xrightarrow{k_2} C$ in which $k_1/k_2 \approx 7$, and A is biscarbonyl chloride, B is monocarbonyl chloride monoisocyanate, and C is diisocyanate. [d] With II the yield of isocyanate formed is by difference only; with IV the values are rough averages of values obtained both by difference and by ANCO, the values agreeing to within 4% of theoretical (*e.g.*, let % NCO = ANCO/0.63 × 72) in point 5 for IV. [e] Isocyanate absorbance in the reaction solution at λ_{max} 4.45. [f] The discrepancy here probably is due to volatility of butyl isocyanate.

(12) Beilstein, Vol. 4, p. 214.

(13) Only in ethylene dichloride and toluene was there unambiguously a single carbonyl absorption at 5.75 μ assignable to pure II or IV throughout the entire reaction, whereas in the other solvent systems, shoulders at 5.8–5.9 and 5.67 μ eventually appeared, attributable to R–NHCOCl and perhaps urea formation.

(14) F. Daniels and R. Alberty, "Physical Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 337–338.

was initiated on II. Thereafter, the butene-2 derivative IV was decomposed in ethylene dichloride and trichloroethane, 1 g. of IV in 39 g. of solvent with added ferric chloride catalyst (see Table I).

5. (*trans*[15]?)-1,4-Diisocyanatobutene-2

A solution of 10.0 g. (0.031 mole) of IV, 30 mg. of ferric chloride (hexahydrate), and 90 g. of ethylene dichloride was refluxed (83°), while passing a gentle stream of nitrogen to entrain volatiles, for 25 hr., then cooled, filtered, and concentrated to a brownish oil. The oil was distilled *in vacuo*, b.p. 106–111° (13–19 mm.), affording 2.8 g. (65%) of a clear oil, $n^{23}D$ 1.4728, m.p. −2 to 0°; $\lambda_{max}^{CHCl_3}$ 2.75, 3.24, 4.45, 6.92, 7.10, 7.45, 10.3, 11.6 μ. The bismethylurethane (glistening flakes from methanol) had m.p. 143–144° (reported[8] m.p. 137°). The isocyanate turned brown on standing several days.

6. 1,3-Bis-*t*-butyl-2-imidazolidinone (VII)

When 17.2 g. (0.1 mole) of N,N′-bis-*t*-butylethylenediamine was added to 0.2 mole of a phosgene (20 g.)–triethylamine (20.2 g.) complex in cold benzene, followed by stirring and gentle warming, the reddish brown mixture gave a 67% yield of triethylamine hydrochloride and a filtrate which, on evaporation, gave a semicrystalline oil, 22.2 g. Crystallization (hexane) or distillation afforded solid, soft needles, m.p. 73–74°, b.p. 127° (16.5 mm.), b.p. 245° (760 mm.); $\lambda_{max}^{CHCl_3}$ 5.98, also 6.75, 6.85, 7.13, 7.35, and 7.8–8.3 μ.

Anal. Calcd. for $C_{11}H_{22}N_2O$: C, 66.60; H, 11.18; N, 14.13. Found: C, 66.73; H, 11.14; N, 14.27.

(15) The starting 1,4-dichlorobutene-2 (Eastman) was labeled *trans*.

The distillation yielded a considerable forecut, b.p. 80° (16 mm.), b.p. 180–185° (760 mm.), identified additionally as diethylcarbamoyl chloride [reported[4i] b.p. 81–85° (20 mm.)] by isolation of diethylamine (spectrum identical with authentic material) by mild alkaline hydrolysis.

7. Properties of the Intermediate Amines (See Table II)

TABLE II

t-BUTYLAMINES R—NH—C(CH$_3$)$_3$

Compound (R–)	M.p., °C.	B.p., °C (mm.)	Ref. index
CH$_2$=CH—CH$_2$—	...	112 (760 mm.)	$n^{22.5}D$ 1.4160
CH$_3$CH$_2$CH$_2$CH$_2$—	...	83 (140 mm.)	$n^{22.7}D$ 1.4086
—CH$_2$—C$_6$H$_4$—CH$_2$—	68–70	91 (177 mm.)	...
—CH$_2$CH$_2$—[b]	(42)[a]	99 (32 mm.)[c]	...
—CH$_2$CH=CH—CH$_2$—	(40–50)[a]	95–100 (6 mm.)	$n^{22}D$ 1.4494

[a] Hydrates. [b] Base equivalent, 85.8 (theory 86.15). [c] Lit. b.p. 198° (760 mm.).[4f]

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Direct Syntheses of Some Cyano and Nitro Derivatives of Carbohydrates by Nucleophilic Displacement[1]

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Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (I) and 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-diiodo-D-mannitol (II) reacted with sodium cyanide and with sodium nitrite in *N*,*N*-dimethylformamide to give the cyano and nitro derivatives expected following nucleophilic displacement of iodide. 6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (III) was appreciably less reactive toward sodium cyanide. *O*-Benzylidenepentaerythritol dibenzenesulfonate (IX) reacted with sodium nitrite in *N*,*N*-dimethylformamide at the reflux temperature to form *O*-benzylidenepentaerythritol benzenesulfonate (XII).

In previous investigations,[3] 1,2-*O*-isopropylidene-D-glucofuranose 6-*p*-toluenesulfonate and 1,3-*O*-benzylidene-L-arabinitol 5-*p*-toluenesulfonate reacted with potassium cyanide to afford the corresponding cyano derivatives. In these reactions, the carbon undergoing displacement is removed from the rings by an intervening carbon bearing a hydroxyl group, which was proposed[3] to form an intermediate epoxide that then added hydrogen cyanide to give product. Success realized in effecting nucleophilic displacement reactions of neopentyl-type sulfonate esters with cyanide ion[4] prompted an investigation in which carbohydrate derivatives with functional groups without hydroxyls on the adjacent carbon were subjected to similar reaction conditions with the objective of achieving direct displacement, which was previously reported[3] to have failed. Iodides were selected over sulfonate esters since the former tend to be more reactive[5] than the latter in reactions with SN2-type character and moreover are readily preparable from the latter.[6] Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (I),[7] 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-diiodo-D-mannitol (II),[8] and 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (III)[9] were selected as substrates for displacement reactions with sodium cyanide in *N*,*N*-dimethylformamide (DMF). Both I and II reacted readily to give the expected products of displacement, methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-*gluco*-heptopyranurononitrile (IV) and 3,4,5,6-di-*O*-benzylidene-2,7-dideoxy-D-*manno*-octaronitrile (V), respectively, in yields of 54 and 51%.

(1) Abstracted from portions of the Ph.D. theses of W. J. T. and S. M. D.

(2) Members of the "Research Participation for Teacher Training" Program at the University of Utah, 1962, sponsored by the National Science Foundation.

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(7) B. Helferich and E. Himmen, *Ber.*, **61**, 1825 (1928).

(8) R. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 1419 (1943).

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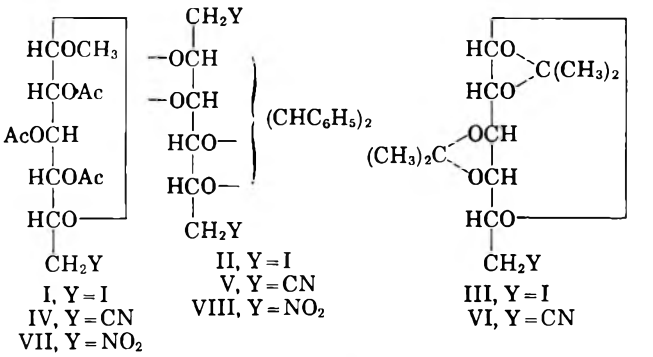
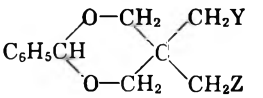
III was appreciably less reactive and gave 6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*galacto*-heptopyranurononitrile (VI) in 28% yield. Each of the products obtained exhibited absorption peaks in the infrared spectra at 4.43 μ, characteristic of aliphatic nitriles, and reacted with moist alcoholic base to release ammonia.

The marked difference in reactivity of III as compared to I may be rationalized by considering field effects influencing the approach of the nucleophilic reagent.[10] Placing the iodine atom away from neighboring oxygens, the backside of the primary carbon atom undergoing displacement is relatively accessible to cyanide ion in I. In III the axial oxygen at C-4 might be expected to impede the approach of the charged nucleophilic reagent. Rationalization of reactivity of II does not appear to be possible since the location of the benzylidene groups in this compound has not been established.

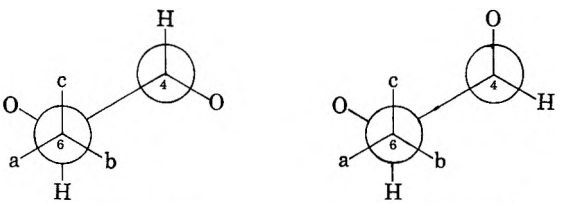
This direct method of increasing the length of the carbon skeleton presents the possibility of synthesis of a wide variety of novel or previously synthesized carbohydrate derivatives with deoxy carbons at the α-, α'-, or α,α'-positions. In all probability the nitriles obtained may undergo the same types of reactions described for the cyanohydrins derived in the classical Kiliani-Fischer method.[11] Another synthetic possibility afforded with these compounds is condensation reactions of β-carbons *via* both intramolecular and intermolecular processes.

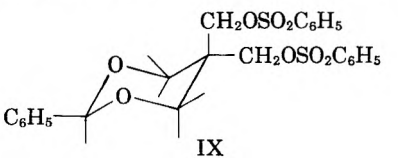
The nucleophilic displacement reactions have been extended to those using nitrite ion as the nucleophilic reagent. Kornblum and co-workers[12] have demonstrated that alkyl halides react with sodium nitrite in dimethylformamide to give good yields of nitro compounds. There are complications attending this reaction since any nitrite esters formed competitively may react with aliphatic nitro compounds.[13] The presence of phloroglucinol in the reaction mixture was very effective in scavenging nitrite esters and allowed synthesis of α-nitro esters in high yields.[14] Another side reaction is the interaction of alkyl halides with dimethylformamide to give products of dehydrohalogenation and salts.[15] Compounds I and II reacted smoothly with sodium nitrite in the presence of phloroglucinol in a dimethylformamide solution at low temperatures (30–40°) to form the corresponding nitro compounds, methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-nitro-α-D-glucopyranoside (VII) and 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-dinitro-D-mannitol (VIII), in yields of 64 and 44%. Infrared spectra of each compound showed absorbance at 6.43 and 7.29–7.33 μ, indicative of aliphatic nitro compounds, and no peaks suggestive of nitrite esters. Moreover, the presence of the nitrite ester scavenger, phloroglucinol,[14] precludes these products. This method of synthesis constitutes an independent path to primary nitro derivatives available by the well established nitromethane method.[16] Displacement with nitrite ion is likely to be influenced by field effects in the same manner as found with cyanide ion.





IX, Y = Z = $OSO_2C_6H_5$
X, Y = $OSO_2C_6H_5$, Z = I
XI, Y = Z = I
XII, Y = $OSO_2C_6H_5$, Z = OH





IX

1,2,3,4 - Tetra - *O* - acetyl - 6 - deoxy - 6 - iodo - β-D-glucopyranose,[17] mixed with sodium cyanide or sodium nitrite in a dimethylformamide solution, gave water-soluble products with a portion of the starting material as the sole isolable compound when reaction was effected at low temperature. Apparently, reaction occurred at the anomeric carbon, suggesting that all substrates with acyloxy functions at C-1 may be unsatisfactory for these displacement reactions.

When the foregoing reaction conditions for displacement by nitrite ion were applied to derivatives of *O*-benzylidenepentaerythritol, the dibenzenesulfonate (IX), the benzenesulfonate iodide (X), and the diiodide (XI), considerable starting material was recovered as the only isolable product except in one instance in which a small amount of *O*-benzylidenepentaerythritol benzenesulfonate (XII) was obtained. On the other hand, the reaction of *O*-benzylidenepentaerythritol dibenzenesulfonate with sodium nitrite in boiling dimethylformamide for brief periods with or without phloroglucinol gave 42% of XII, resulting from the over-all substitution of one benzenesulfonyloxy with a hydroxyl group. The nature of the compound was established by converting it into the known[4] dibenzenesulfonate (IX) by reaction with benzenesulfonyl chloride. The

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(17) B. Helferich, H. Dressler, and R. Griebel, *J. prakt. Chem.*, **153**, 285 (1939).

infrared spectrum indicated the absence of intramolecular hydrogen bonding[18]; thus a *trans* relationship of hydroxyl to phenyl appeared likely since the *cis* isomer should allow the hydroxyl group to hydrogen bond to the ring oxygens. The reaction of *O*-benzylidenepentaerythritol with limited amounts of benzenesulfonyl chloride gave IX, XII, and a third substance, intermediate in mobility on an alumina column between IX and XII. This material has not been obtained in a homogeneous form but in all probability is the isomer of XII.

The relative inertness of the *O*-benzylidenepentaerythritol derivatives is undoubtedly a consequence of steric factors. Since the nitrite ion appears to have greater steric requirement in the formation of a C–N bond than in the formation of a C–O bond,[19] the predominant reaction may lead to nitrite ester, which is then hydrolytically cleaved or which reacts with phloroglucinol when introduced. As an alternative explanation, some type of salt may be formed initially[19]; it is then hydrolytically cleaved.

Experimental[20]

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-α-D-*gluco*-heptopyranurononitrile (IV).—A mixture of 10.0 g. of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (I),[21] 4.0 g. of sodium cyanide, and 100 ml. of redistilled *N,N*-dimethylformamide was stirred mechanically for 4 hr. at 45°. The resulting red-brown reaction mixture was poured into 500 ml. of ice and water and allowed to stand overnight in a refrigerator. The following day the light brown solid which had precipitated was filtered, washed with water, and dried to yield 3.93 g. (51%) of crude methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-*gluco*-heptopyranurononitrile, m.p. 134–136°. Recrystallization first from ten parts methanol and then from chloroform–ligroin (b.p. 60–90°) gave fine white needles, m.p. 135–135.5°, $[\alpha]^{23}D$ +139° (*c* 1.88, chloroform).

Anal. Calcd. for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.66; H, 5.67; N, 4.25.

3,4,5,6-Di-*O*-benzylidene-2,7-dideoxy-D-*manno*-octaronitrile (V).—A mixture of 10.0 g. of 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-diiodo-D-mannitol (II),[22] 10.0 g. of sodium cyanide, and 150 ml. of redistilled *N,N*-dimethylformamide was stirred mechanically for 4 hr. at 50–55°. The resulting amber-colored reaction mixture was processed in the same manner as described for IV. The solid obtained was extracted with 40 ml. of boiling acetone and the extract concentrated to half its original volume. Upon adding 20 ml. of hot ethanol to the extract and cooling, 3.5 g. (54%) of fine white needles crystallized, m.p. 196–201° dec. After two recrystallizations from chloroform–ligroin (b.p. 60–90°), 3,4,5,6-di-*O*-benzylidene-2,7-dideoxy-D-*manno*-octaronitrile, m.p. 204–206° dec., $[\alpha]^{23}D$ +82.0° (*c* 0.45, chloroform), was obtained.

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 69.81; H, 5.28; N, 7.39.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-D-*galacto*-heptopyranurononitrile (VI).—A mixture of 8.00 g. of 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (III),[23] 3.2 g. of sodium cyanide, and 80 ml. of redistilled *N,N*-dimethylformamide was stirred mechanically for 4 hr. at 105°. The resulting dark brown reaction mixture was poured with stirring into 500 ml. of ice and water. After standing 2 hr., the aqueous solution was extracted with six 100-ml. portions of chloroform and the combined chloroform extracts were washed with six 100-ml. portions of water, dried over anhydrous sodium sulfate, and evaporated first under reduced pressure (aspirator) on a steam bath and then at 2 mm. The resulting sirup was dissolved in 15 ml. of absolute ethanol and cooled to −15°. Crystallization occurred after several hr. to yield 0.81 g. of impure III, m.p. 57–60°. Resulting filtrate was evaporated to a thick sirup, dissolved in 7 ml. of absolute ethanol and 7 ml. of ligroin (b.p. 40–48°), and the resulting solution cooled to −15°. Crystallization occurred slowly following seeding to yield 1.65 g. (28%) of 6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*galacto*-heptopyranurononitrile, m.p. 61–63°. Seed crystals were first obtained by allowing an ethanol solution of the sirup to stand on the shelf for a period of 6 months, during which time solvent slowly evaporated. Several recrystallizations from absolute ethanol–ligroin (b.p. 40–48°) (1:2, by volume) gave rods, m.p. 65.5–66.5°, $[\alpha]^{23}D$ −67.7° (*c* 0.83, chloroform).

Anal. Calcd. for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.10; H, 7.02; N, 5.38.

The infrared spectra of potassium bromide disks of IV, V, and VI showed peaks at 4.43 μ characteristic of the carbon–nitrogen stretching frequency of aliphatic nitriles. The three compounds liberated ammonia when refluxed in moist alcoholic sodium hydroxide.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-nitro-α-D-glucopyranoside (VII).—A mixture of 5.00 g. (0.0116 mole) of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (I),[21] 1.50 g. (0.0218 mole) of sodium nitrite, 3.00 g. (0.0185 mole) of phloroglucinol dihydrate, and 150 ml. of redistilled *N,N*-dimethylformamide was maintained at 30–40° for 18 hr. The reaction solution was poured into 700 ml. of ice and water to precipitate a white solid, which was filtered. After a single recrystallization from ethanol, 2.61 g. (64.4%) of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-nitro-α-D-glucopyranoside, m.p. 175–177°, was obtained. An analytical sample, m.p. 181–182°, $[\alpha]^{25}D$ +143° (*c* 1.82, chloroform), was prepared by recrystallization once from benzene–ligroin (b.p. 90–120°) and twice more from ethanol.

Anal. Calcd. for $C_{13}H_{19}NO_{10}$: C, 44.70; H, 5.48. Found: C, 44.79; H, 5.44.

2,3,4,5-Di-*O*-benzylidene-1,6-dideoxy-1,6-dinitro-D-mannitol (VIII).—A mixture of 5.78 g. (0.010 mole) of 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-diiodo-D-mannitol (II),[22] 2.8 g. (0.041 mole) of sodium nitrite, 5.5 g. (0.034 mole) of phloroglucinol dihydrate, and 150 ml. of redistilled *N,N*-dimethylformamide was maintained at 35–40° for 16 hr. The resulting reaction mixture was poured into 800 ml. of ice and water, and the resulting suspension was allowed to stand at 0° for 18 hr. The solid was filtered and recrystallized three times from ethanol, three times from chloroform–ligroin (90–120°), and once from toluene–ligroin to provide 1.82 g. (44%) of 2,3,4,5-di-*O*-benzylidene-1,6-dideoxy-1,6-dinitro-D-mannitol, m.p. 162.5–164°. An analytical sample, m.p. 164.4–164.8°, $[\alpha]^{25}D$ +41.7° (*c* 0.64, chloroform), was prepared by two additional recrystallizations from chloroform–ligroin.

Anal. Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.58; H, 4.95; N, 6.74.

The infrared spectra of chloroform solutions of VII and VIII showed peaks at 6.43 and 7.33 μ and 6.43 and 7.29 μ, respectively.

Reactions of 1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose with Sodium Cyanide and Sodium Nitrite.—1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose[24] was mixed with sodium cyanide in *N,N*-dimethylformamide at room temperature and at 0°. Considerable heat evolution was observed with immediate coloration of the mixture. Pouring the reaction mixture into ice and water after varying periods of time produced water-soluble materials only. A mixture of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose and sodium nitrite in *N,N*-dimethylformamide darkened considerably after 24 hr. at room temperature. Approximately 40% of the organic substrate was recovered after pouring the reaction mixture into ice and water, collecting the insoluble portion, extracting the aqueous phase with chloroform, and combining the crystalline material.

***O*-Benzylidenepentaerythritol Benzenesulfonate (XII).**—A mixture of 30.0 g. (0.0596 mole) of *O*-benzylidenepentaerythritol dibenzenesulfonate,[4] 30 g. (0.43 mole) of sodium nitrite, and 300 ml. of *N,N*-dimethylformamide was brought to the reflux point in about 5 min. and then refluxed for 10 min. During this time brown vapors of nitrogen dioxide were visible above the reaction mixture. (Addition of phloroglucinol to the original reaction

(18) B. Dobinson and A. B. Foster, *J. Chem. Soc.*, 2338 (1961).

(19) N. Kornblum, R. A. Smiley, R. K. Blackwood, and C. D. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(20) Melting points are corrected. Microanalyses by K. W. Zimmerman, Australian Microanalytical Service, University of Melbourne.

(21) Prepared by the procedure of J. Compton, *J. Am. Chem. Soc.*, **60**, 395 (1938).

(22) Prepared by the procedure of G. S. Skinner, L. A. Anderson, and C. G. Gustafson, Jr., *ibid.*, **80**, 3788 (1958).

(23) Prepared by the procedure of A. L. Raymond and E. F. Schroeder, *ibid.*, **70**, 2785 (1948).

(24) Prepared by the procedure of E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

mixture prevented nitrogen dioxide formation, but the same recovery of reaction product was observed.) After cooling the mixture, 500 ml. of water was added and the resulting suspension was placed in a refrigerator overnight. Filtration gave 9.2 g. (42%) of crude *O*-benzylidenepentaerythritol benzenesulfonate, m.p. 112–115.5°. Repeated recrystallizations from ethanol gave an analytical sample, m.p. 115.5–116°. The infrared spectrum in a chloroform (ethanol-free) solution showed an absorption at 2.74 μ, indicative of nonhydrogen-bonded hydroxyl stretching.

Anal. Calcd. for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53; S, 8.80. Found: C, 59.16; H, 5.61; S, 8.84.

Reaction of *O*-benzylidenepentaerythritol dibenzenesulfonate (IX), *O*-benzylidene-*O*-benzenesulfonylpentaerythritol iodide (X)[4], or *O*-benzylidenepentaerythritol diiodide (XI)[4] with sodium nitrite in *N*,*N*-dimethylformamide with or without phloroglucinol gave the starting compound as the main product when reaction was effected at 40–50°. With X, a very small amount of XII was also recovered. At higher temperatures, X and XI gave oily reaction products and the starting materials.

***O*-Benzylidenepentaerythritol Dibenzenesulfonate (IX) from *O*-Benzylidenepentaerythritol Benzenesulfonate (XII).**—To a solution of 0.91 g. (0.0025 mole) *O*-benzylidenepentaerythritol benzenesulfonate in 1.8 ml. of anhydrous pyridine cooled to 0°, 0.53 g. (0.0030 mole) of redistilled benzenesulfonyl chloride was added dropwise. The reaction mixture was maintained at 0° for 4 hr. during which time a large mass of crystals appeared. Then 0.5 ml. of ethanol was added and the resulting mixture allowed to stand for 0.5 hr. at room temperature. Cold water was added and the solid was filtered. After one recrystallization from ethanol–acetone, *O*-benzylidenepentaerythritol dibenzenesulfonate was obtained in 1.09 g. (87%) yield, m.p. and m.p. upon admixing with an authentic sample, 148.5–150°.

Reaction of *O*-Benzylidenepentaerythritol with Benzenesulfonyl Chloride.—A variety of reaction mixtures of benzenesulfonyl chloride and *O*-benzylidenepentaerythritol, in molar ratios of slightly less than one to more than two, in anhydrous pyridine at −10 to 0° for varying lengths of time gave *O*-benzylidenepentaerythritol dibenzenesulfonate in yields of less than 5 to some 86%. Separation was accomplished readily by suspending reaction mixture in acetone–water (40:60, by volume), in which the fully substituted compound has but slight solubility. Filtrates were evaporated and residues obtained dissolved in benzene and chromatographed on alumina. Very small amounts of the dibenzenesulfonate appeared in the first fractions followed by materials with melting points in the range 60–80°. Then the monobenzenesulfonate, m.p. 112–115°, obtained by the reaction of *O*-benzylidenepentaerythritol dibenzenesulfonate and sodium nitrite in *N*,*N*-dimethylformamide, was eluted in relatively small yields, up to 30%. Attempts to prepare a homogeneous sample of the lower melting fraction have not been successful.

Chemistry of Isocyanic Acid. II. Reactions with α,β-Unsaturated Ethers

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The addition of isocyanic acid to such α,β-unsaturated ethers as butyl vinyl ether, vinyloxyethyl methacrylate, and butyl isopropenyl ether proceeds readily to form α-alkoxy isocyanates.

In a previous paper[1] it was reported that hydroxy isocyanates can be obtained by the addition of isocyanic acid to certain carbonyl compounds. This paper describes a new route to the little-studied α-alkoxy isocyanates through the addition of isocyanic acid to α,β-unsaturated ethers.

$$C_4H_9OCH{=}CH_2 + HNCO \longrightarrow C_4H_9OCH(CH_3)NCO$$

This is apparently the first reported addition of isocyanic acid to a carbon–carbon double bond.

TABLE I

NEW ISOCYANATES FROM ISOCYANIC ACID AND α,β-UNSATURATED ETHERS

α,β-Unsaturated ether	Isocyanate
$C_2H_5OCH{=}CH_2$	$C_2H_5OCH(CH_3)NCO$
$C_4H_9OCH{=}CH_2$	$C_4H_9OCH(CH_3)NCO$
$C_4H_9OC(CH_3){=}CH_2$	$C_4H_9OC(CH_3)_2NCO$
$C_6H_5OCH{=}CH_2$	$C_6H_5OCH(CH_3)NCO$
$(CH_2OCH{=}CH_2)_2$	$(CH_2OCH(CH_3)NCO)_2$
$CH_3OCH_2CH_2OCH{=}CH_2$	$CH_3OCH_2CH_2OCH(CH_3)NCO$
$CH_2{=}C(CH_3)CO_2CH_2CH_2OCH{=}CH_2$	$CH_2{=}C(CH_3)CO_2CH_2CH_2OCH(CH_3)NCO$
$CH_2CH_2CH_2CH{=}CH$ (O)	$CH_2CH_2CH_2CH_2CHNCO$ (O)

The reaction of α,β-unsaturated ethers and isocyanic acid is strongly exothermic and proceeds rapidly, especially in the presence of *p*-toluenesulfonic acid or other strong acids. Solvents, such as diethyl ether or benzene, are desirable to moderate the reaction and to stabilize the isocyanic acid against trimerization. Polymerization of the unsaturated ether is the principal competitive reaction and is minimized by using an excess of isocyanic acid. It is usually desirable to add the unsaturated ether to the solution of isocyanic acid. With the divinyl ether of ethylene glycol, a severalfold excess of isocyanic acid is necessary to obtain a good yield of the diisocyanate. The addition of isocyanic acid to α,β-unsaturated ethers is apparently quite general as indicated by the variety of structures (see Table I) that undergo this reaction.

The structures of these new isocyanates are confirmed by hydrolysis, infrared, and proton magnetic resonance data. For example, hydrolysis of the isocyanates from vinyl ethers gives acetaldehyde in good yields, showing that the NCO group and ether oxygen are attached to the same carbon atom. Moreover, the proton n.m.r. spectra (see Fig. 1) of these compounds show a single hydrogen split into a quadruplet and methyl hydrogens split into a doublet as required for the $RCH_2OCH(CH_3)NCO$ structure. Interestingly, the n.m.r. spectra also show that the hydrogens of the methylene group next to the oxygen are nonequivalent even though this group is not attached directly to the asymmetric carbon atom. Thus, with $CH_3CH_2OCH(CH_3)NCO$, these hydrogens appear as four quadruplets.

Isocyanates of the structure $ROCH(CH_3)NCO$, containing a hydrogen on the same carbon as the NCO group, are moderately reactive, forming ureas and carbamates with amines and alcohols, respectively. The second-order rate constant for the reaction of

(1) F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963).

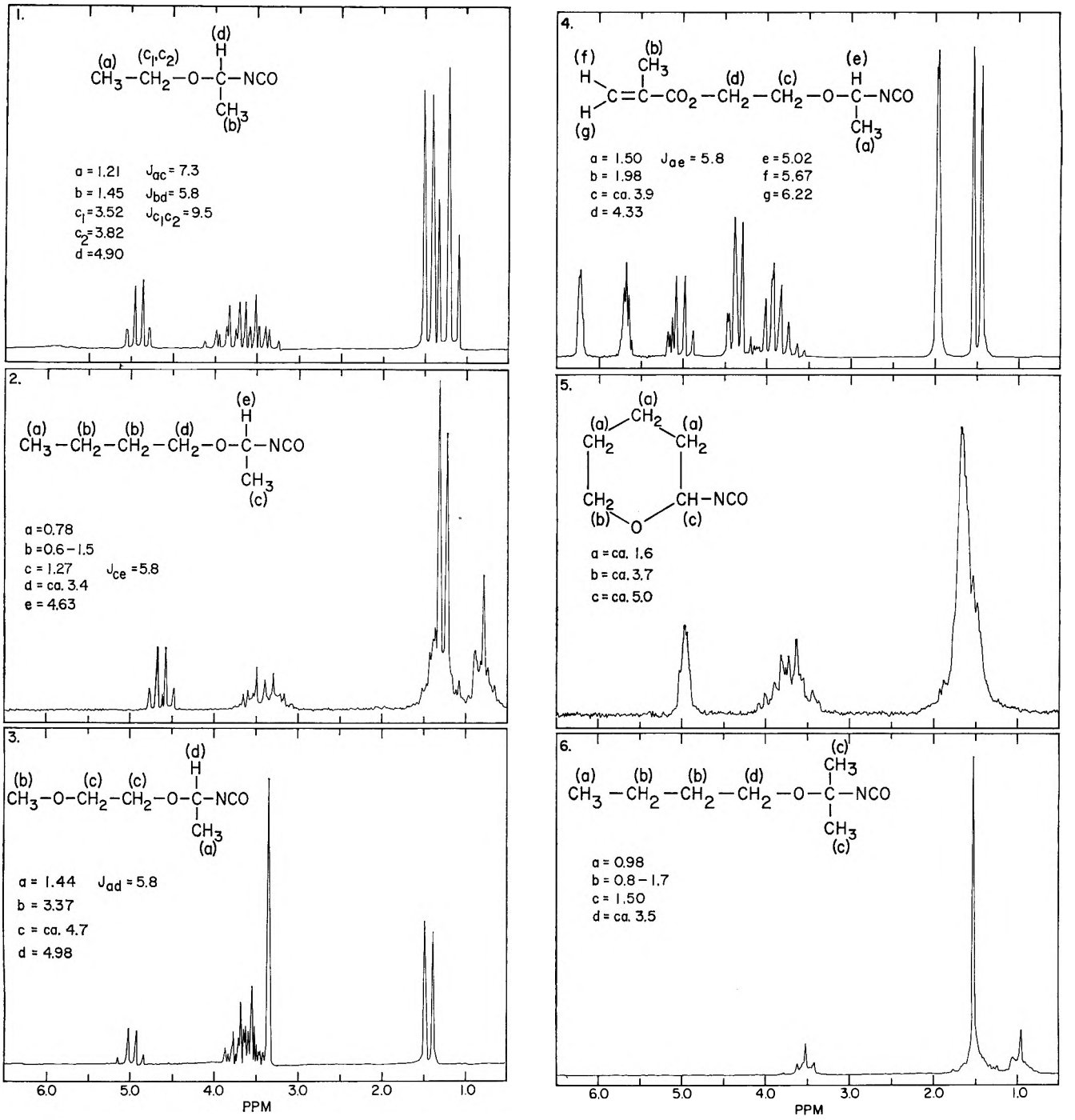

Fig. 1.—N.m.r. spectra of certain isocyanates using tetramethylsilane as an internal standard at 0.0. For spectrum 3, c = *ca.* 3.7 instead of the 4.7 given.

$C_4H_9OCH(CH_3)NCO$ with ethanol at 24° is 8×10^{-5} l. mole^{-1} sec.$^{-1}$, compared with $K_{28°}$ 2.5×10^{-4} for phenyl isocyanate.[2] Re[illegible]cer ent of the α hydrogen with an alkyl group results in much lower reactivity, apparently because of greater steric hindrance. Thus, $C_4H_9OC(CH_3)_2NCO$ reacts very slowly with ethanol in a complex manner to give several products, including ethyl allophanate and ethyl carbamate.

Polymers were obtained by the reaction of the diisocyanate from the divinyl ether of ethylene glycol with glycols or amines. The urea $C_4H_9OCH(CH_3)NHCONHC_6H_5$, obtained from aniline and 1-butoxyethyl isocyanate, underwent a disproportionation reaction on heating in acetone to give the bisurea $(C_6H_5NHCONH)_2CHCH_3$.

(2) I. C. Kogon, *J. Org. Chem.*, **24**, 438 (1959).

In the course of this study, it was found that isocyanic acid and diethyl ether form a maximum boiling point azeotrope (b.p. 48°) containing about 27 mole % isocyanic acid.

Experimental[3]

The following examples illustrate the procedures employed in this study for preparing α-alkoxy isocyanates.

1-Butoxyethyl Isocyanate. Method A.—To a stirred mixture of 100 ml. of benzene, 52.8 g. (1.2 moles) of isocyanic acid, and 0.1 g. of *p*-toluenesulfonic acid was added 110 g. (1.1 moles) of butyl vinyl ether over a period of 11 min.; the temperature rose to 56°. As soon as the temperature dropped to about 30°, the product was distilled rapidly at 1 mm. Redistillation gave

(3) All melting points (Fisher-Johns apparatus) and boiling points are uncorrected. Proton n.m.r. spectra were obtained with a Varian A60 spectrometer on neat samples.

100 g. (64%) of 1-butoxyethyl isocyanate, b.p. 62° (24 mm.), $n^{25}D$ 1.4080.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.75; H, 9.09; N, 9.80. Found: C, 59.17; H, 9.07; N, 10.27.

The infrared spectrum of this product showed strong absorption at 3.38 μ and 3.47 μ (saturated CH); 4.45 μ (NCO); 7.25 μ (C—CH_3); and 8.87 μ (C—O—C).

When a dioxane solution of this compound was treated with a drop of concentrated hydrochloric acid and then added to a solution of 2,4-dinitrophenylhydrazine, the hydrazone of acetaldehyde (m.p. 163–165°, no depression with an authentic sample) was obtained.

Method B.—1-Butoxyethyl isocyanate also was obtained by adding a mixture of 50 g. of vinyl butyl ether and 14.9 ml. of isocyanic acid dropwise to a stirred mixture of 50 ml. of diethyl ether and 0.1 g. of *p*-toluenesulfonic acid. The rate of addition was adjusted so that a temperature of 38–40° was maintained. On distillation, there was obtained 53 g. (90% yield) of 1-butoxyethyl isocyanate.

A mixture of 4.5 g. (0.03 mole) of 1-butoxyethyl isocyanate and 8.0 g. (0.17 mole) of ethanol was allowed to stand for 20 hr. Distillation gave 4.7 g. (79%) of ethyl N-(1-butoxyethyl)carbamate, b.p. 53° (0.04 mm.), $n^{25}D$ 1.4177.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 57.11; H, 10.02; N, 7.38. Found: C, 57.38; H, 10.02; N, 7.38.

When 0.36 g. of 1-butoxyethyl isocyanate was added to a solution of 0.28 g. of aniline and 2 ml. of acetone, a precipitate formed which, after recrystallization from acetone, melted at 102–103°. The infrared spectrum and elemental analyses were in agreement with the structure $C_6H_5NHCONHCH(CH_3)OC_4H_9$.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.10; H, 8.50. Found: C, 66.22; H, 8.60.

Some disproportionation of the product occurred when this reaction was carried out on a larger scale. Thus, from 14.3 g. of 1-butoxyethyl isocyanate, 10 g. of aniline, and 40 ml. of acetone, there was obtained 21.3 g. of slightly off-color product, m.p. 95–100°. On recrystallization of this product from acetone there was obtained 5 g. of a product, m.p. 218°, that was not soluble in acetone, chloroform, carbon tetrachloride, ethanol, 1,2-dimethoxyethane, or benzene. It was readily soluble in dimethylformamide and was recrystallized from a mixture of dimethylformamide and ethanol. Its infrared spectrum and elemental analyses were consistent with the structure $(C_6H_5NHCONH)_2CHCH_3$.

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.40; H, 6.05; N, 17.77. Found: C, 64.40; H, 6.08; N, 17.70.

A solution of 7.2 g. of 1-butoxyethyl isocyanate, 16.4 g. of *p*-chloroaniline, and 45 ml. of acetone was prepared at 10° and allowed to stand at 4° for 2 days during which time a precipitate formed. Collection of the product by filtration gave 8.2 g. (60%) of N-(1-butoxyethyl)-N′-*p*-chlorophenylurea, m.p. 108–109°.

Anal. Calcd. for $C_{13}H_{19}N_2O_2Cl$: N, 10.35; Cl, 13.10. Found: N, 10.57; Cl, 13.46.

The rate of the reaction of 1-butoxyethyl isocyanate with ethanol in carbon tetrachloride at 24 ± 1° was determined using near-infrared spectrophotometry[2] to follow the formation of carbamate (NH, 1.48 μ) and disappearance of ethanol (OH, 1.43 μ). Solutions (0.25 *M*) of the reactants were mixed in equal amounts, and the concentration of carbamate and ethanol were determined from time to time. The plot of

$$\frac{x}{a(a-x)} \text{ vs. } t$$

where x is concentration of carbamate and a is initial isocyanate or ethanol concentration gave a nearly straight line over a 90-hr. reaction period. The value of k, the second-order rate constant, was 8×10^{-6} l. mole^{-1} sec.$^{-1}$.

The following monoisocyanates were prepared in ether by the procedure (method B) used for preparing 1-butoxyethyl isocyanate.

1-Ethoxyethyl Isocyanate.—B.p. 58° (114 mm.); $n^{25}D$ 1.3975; yield 50%.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.76; H, 7.91; N, 11.88.

Infrared: 3.35 μ and 3.45 μ (saturated CH); 4.44 μ (NCO); 7.24 μ (C—CH_3); and 8.85 μ (C—O—C).

1-(2-Methacryloxyethoxy)ethyl Isocyanate.—B.p. 70° (0.3 mm.); $n^{25}D$ 1.4436; yield 83%.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.46; H, 6.40; N, 7.01.

Infrared: 3.23 μ shoulder (=CH); 3.35 μ and 3.41 μ (saturated CH); 4.44 μ (NCO); 5.80 μ (ester >C=O); 6.08 μ (—C=C—); 7.24 μ (C—CH_3); 8.55 μ and 8.85 μ (C—O—C); and 10.59 μ (CH_2=C(CH_3)—C(=O)—).

1-(2-Methoxyethoxy)ethyl Isocyanate.—B.p. 47° (4.5 mm.); $n^{25}D$ 1.4150; yield 48%.

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.70; H, 7.65; N, 9.36.

1-Phenoxyethyl Isocyanate.—B.p. 42° (0.4 mm.); $n^{25}D$ 1.5057; yield, 80%.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.30; H, 5.52; N, 8.60. Found: C, 66.04; H, 5.57; N, 8.23.

Infrared: 3.25 μ and 3.27 μ (=CH); 3.32 μ and 3.39 μ (saturated CH); 4.42 μ (NCO); 6.25 μ and 6.68 μ (aromatic —C=C—); 7.23 μ (C—CH_3); 8.17 μ (C_6H_5—O—C); and 13.27 μ and 14.47 μ (monosubstituted aromatic bands).

The proton n.m.r. showed five aromatic hydrogens, three methyl hydrogens, and a tertiary hydrogen in accordance with this structure.

2-Tetrahydropyranyl Isocyanate.—B.p. 72° (25 mm.); $n^{25}D$ 1.4500; yield 80%.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.82; H, 7.65; N, 11.06.

Infrared: 3.4 μ and 3.5 μ (saturated CH); 4.46 μ (NCO); and bands in 9–10-μ region (C—O—C).

The n.m.r. spectrum is shown in Fig. 1 (see spectrum 5). In decoupling experiments, c could be decoupled from a to give a singlet. Also, b could be decoupled from a to give a wssw pattern, but b would not decouple from c. These data are in agreement with the assigned structure.

1,1′-(Ethylenedioxy)diethyl Diisocyanate.—The divinyl ether of ethylene glycol (22.8 g., 0.2 mole) was added with stirring to a mixture of 36 g. (0.84 mole) of isocyanic acid, 100 ml. of benzene, and 0.1 g. of *p*-toluenesulfonic acid over a period of 20 min., during which time the temperature rose to 55°. The reaction mixture was stirred for 20 additional min. and the product distilled under reduced pressure. After removal of the solvent and excess isocyanic acid, the residue was distilled through a short-pass still at 0.3 mm. to separate the distillable products from the polymeric products. The distillate was then redistilled through a short Vigreux column to give 31.8 g. (80% yield) of 1,1′-(ethylenedioxy)diethyl diisocyanate, b.p. 65° (0.6 mm.), $n^{25}D$ 1.4360.

Anal. Calcd. for $C_8H_{12}N_2O_4$: N, 14.00. Found: N, 13.93.

The infrared spectrum showed absorption at 3.35 μ, 3.42 μ, and 3.46 μ (saturated CH); 4.44 μ (NCO); 7.24 μ (C—CH_3); and 8.94 μ (C—O—C).

1,1′-(Ethylenedioxy)diethyl diisocyanate reacted with ethylene glycol at room temperature to form a clear, viscous polymer and with hexamethylenediamine to form a white polymer that melted at about 150°.

The divinyl ether of ethylene glycol used in this experiment was prepared[4] in about 65% yield by heating a mixture of 220 g. of ethylene glycol, 12 g. of potassium hydroxide pellets, and acetylene in an autoclave at 150° for 22 hr.

When a mixture of 2.04 g. of 1,1′-(ethylenedioxy)diethyl diisocyanate and 99 g. of ethanol was allowed to stand for 4 days at room temperature, the dicarbamate (0.78 g.), m.p. 120–122°, precipitated. This dicarbamate was insoluble in water but was hydrolyzed by boiling water to give acetaldehyde as one of the products.

Anal. Calcd. for $C_{12}H_{24}N_2O_4$: C, 49.30; H, 8.27; N, 9.58. Found: C, 49.33; H, 7.67; N, 9.45.

1-Butoxy-1-methylethyl Isocyanate.—2,2-Dibutoxypropane, prepared[5] in 56% yield from 1-butanol and isopropenyl acetate, was converted to butyl isopropenyl ether by the following procedure adapted from the literature.[6] A mixture of 105 g. of 2,2-dibutoxypropane, 80 g. of quinoline, and 87 g. of potassium

(4) A. E. Favorskii and M. F. Shostakovskii, *J. Gen. Chem. USSR* (Eng. Transl.), **13**, 1 (1943).

(5) W. J. Croxall, F. S. Glavis, and H. T. Neher, *J. Am. Chem. Soc.*, **70**, 2805 (1948).

(6) H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, 2052 (1955).

hydroxide was heated to 190° and 56 g. of distillate was collected. A foam-producing reaction set in near the end of the run. After treatment with 10 g. of sodium hydride (in oil) to remove the alcohol, the crude product was distilled. There was obtained 22 g. (35%) of butyl isopropenyl ether, b.p. 111–114°, $n^{25}D$ 1.4076.

Anal. Calcd. for $C_7H_{14}O$: C, 73.64; H, 12.36. Found: C, 73.19; H, 12.26.

To a stirred mixture of 12.6 g. (0.29 mole) of isocyanic acid, 25 ml. of benzene, and 0.05 g. of *p*-toluenesulfonic acid was added 22 g. (0.19 mole) of butyl isopropenyl ether over a period of 24 min. with a temperature rise to 44°. On distillation, there was obtained 22.2 g. (71%) of 1-butoxy-1-methylethyl isocyanate, b.p. 58° (18 mm.), $n^{25}D$ 1.4104.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.56; H, 9.60; N, 9.08.

The infrared spectrum showed absorption at 3.33 μ and 3.38 μ and 3.47 μ (saturated CH); 4.45 μ (NCO); 7.23 μ and 7.32 μ ($C(CH_3)_2$); and 8–10-μ region (C—O—C).

In an attempt to obtain the carbamate by reaction of this isocyanate with ethanol, a slow complex reaction occurred with the formation of ethyl carbamate and ethyl allophanate. The stoichiometry corresponded to about 2.3 moles of ethanol consumed per mole of isocyanate. Apparently, the initial reaction involved displacement of NCO with OC_2H_5 to give HNCO, which underwent further reaction with ethanol to form ethyl carbamate and ethyl allophanate.

On the Nature of the Catalytic Agent in Friedel–Crafts Isomerization

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Infrared spectra of solutions containing aluminum bromide, 1,2,4-trichlorobenzene, and small quantities of water suggest that Al_2Br_5OH is a possible catalytic species in the "homogeneous" isomerization of *n*-hexane in these systems.

The "homogeneous" isomerization of *n*-hexane was studied recently using 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene as solvents and aluminum bromide promoted with small amounts of water as the co-catalyst.[1] Water is known to be a good promoter of Friedel–Crafts catalysts, and several reasons have been advanced for this phenomenon.[2] Typical arguments are that water reacts with aluminum bromide: to form hydrogen bromide which adds to trace quantities of olefins to form alkyl bromides which serve as carbonium ion initiators, to form a protonic acid which converts trace olefins to carbonium ions, or to form a protonic acid which interacts directly with and causes the rearrangement of a paraffin without carbonium ion formation.

The object of the present study was to obtain a better understanding of this co-catalyst system by determining the infrared absorption of solutions of aluminum bromide, trichlorobenzene, and small amounts of water.

Results and Discussion

It was observed that, when a small quantity of water is gradually added to a solution of aluminum bromide in 1,2,4-trichlorobenzene, some of it reacts at the surface to form a precipitate, possibly a hydrated aluminum oxide or very basic aluminum bromide, while the major portion dissolves to form a "homogeneous" solution. The precipitate would account only for a small portion of the added water and it was not further characterized, but the clear solution was examined by infrared. It was found that an OH band in the 2.9-μ (3450-cm.$^{-1}$) region of the spectrum developed in intensity as the nominal water–aluminum bromide mole ratio increased from 0 to 0.5. Adding more water resulted in a *decrease* in the 2.9-μ band (Fig. 1). This behavior suggests that the species in solution possessing an OH group is altered or removed by further reaction with excess water.

Also, in the spectra of these solutions no bands were observed at ~6.1 μ. A band in this spectral region is indicative of an H–O–H bending vibration, and its absence indicates that the added water did not simply form a hydrate with aluminum bromide, $Al_2Br_6 \cdot xH_2O$. For example, typical hydrates such as $LiClO_4 \cdot H_2O$ have a sharp band at 6.1 μ.[3] These spectra indicate that water reacts with aluminum bromide in 1,2,4-trichlorobenzene and forms a soluble complex containing a hydroxyl group.

While infrared absorption at 2.9 μ thus went through a maximum at a water–aluminum bromide mole ratio of 0.5, an exactly parallel behavior occurred in the 14.5–15-μ spectral region. Infrared bands in this region are due to the C–Cl vibrations of 1,2,4-trichlorobenzene.[4] This parallel behavior in the two spectral regions suggests that the soluble aluminum bromide complex interacts with trichlorobenzene to form a species which has infrared bands both at 14.5–15 and 2.9 μ. The interaction between 1,2,4-trichlorobenzene and the soluble aluminum bromide complex is weak, since the addition of excess water permitted the original spectrum of the solvent to be recovered (Fig. 2).

The result that water and aluminum bromide interact in 1,2,4-trichlorobenzene to form a species whose concentration is a maximum at a water–aluminum bromide mole ratio of 0.5 is supported by *n*-hexane isomerization rate measurements. In general, it was found previously that the *n*-hexane isomerization and cracking rates increased as the water–aluminum bromide mole ratio varied from 0 to 0.5,[1] but the solutions containing excess water, water–aluminum bromide >1, had no catalytic activity. Also, a slow evolution of hydrogen bromide from these solutions was detected during all of the *n*-hexane isomerization experiments. While hydrogen bromide may serve as a co-catalyst with aluminum bromide, hydrogen bromide adding to trace quantities of olefins to form alkyl bromides which serve as carbonium ion initiators, its contribution must be small since previous work[1] has shown that even in the presence

(1) G. M. Kramer, R. M. Skomoroski, and J. A. Hinlicky, *J. Org. Chem.*, **28**, 1029 (1963).

(2) H. Pines, "Advances in Catalysis," Vol. I, Academic Press, New York, N. Y., 1948, p. 201.

(3) F. A. Miller and C. H. Wilkins, *Anal. Chem.*, **24**, 1253 (1952).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

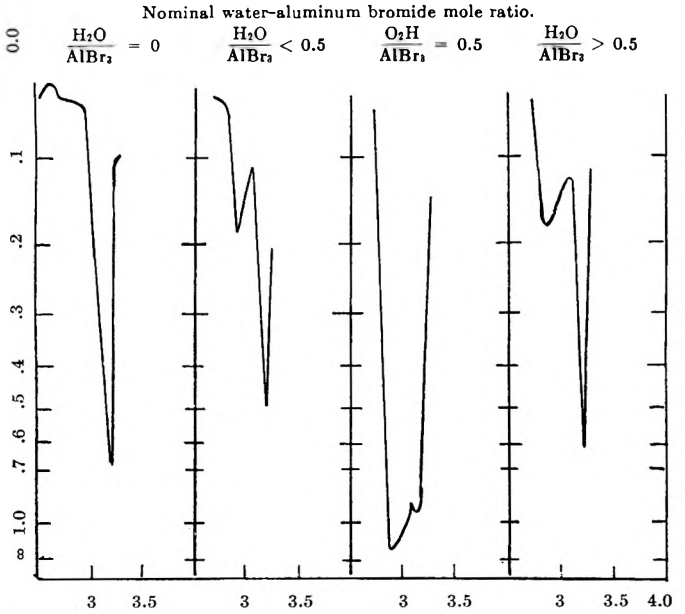


Fig. 1.—An OH band at 2.9 μ increases, and then decreases as the nominal water–aluminum bromide mole ratio passes through 0.5. Ordinate is wave length, μ; abcissa is absorbance.

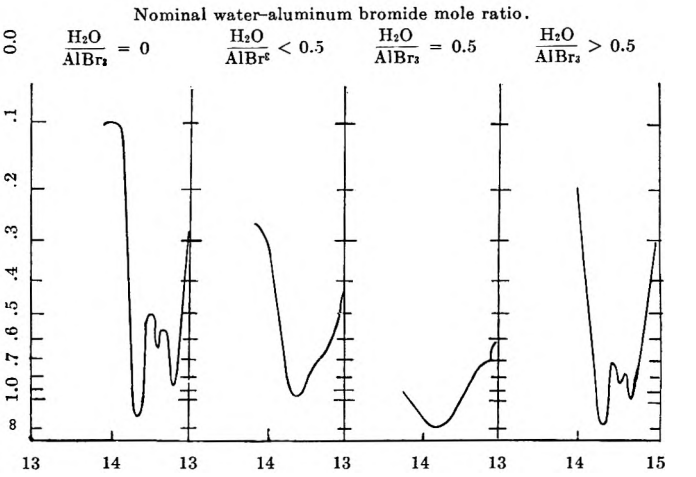


Fig. 2.—An interaction with C–Cl stretching vibration passes through a maximum at a nominal water–aluminum bromide mole ratio of 0.5. Ordinate is wave length, μ; abcissa is absorbance.

of small amounts of added olefin much less activity is obtained.

These infrared studies of the water–aluminum bromide system and the isomerization rate measurements suggest that the active catalytic agent is a soluble aluminum bromide complex. It is postulated that its probable composition is Al_2Br_5OH or $AlBr_3 \cdot AlOHBr_2$. The reactions which are thought to occur in the water–aluminum bromide system are shown.

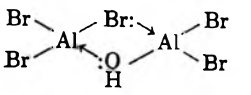
$$2Al^{+3} + 6Br^- \xrightarrow{\text{dehydration}} Al_2Br_6 \cdot 6H_2O$$

$$Al_2Br_6 \xrightarrow{\text{xs } H_2O} \xrightarrow[\text{fast}]{0.5 \text{ mole } H_2O \text{ or less}}$$

$$Al_2Br_6 \cdot H_2O \xrightarrow{\text{slow}} HBr + Al_2Br_5OH$$

Aluminum bromide ionizes readily in the presence of excess water and the hexahydrate can be recovered from solutions containing Al^{+3} and Br^- ions.[5] If a deficiency of water exists, acid–base interaction of aluminum bromide and water may occur to form $Al_2Br_6 \cdot H_2O$. This complex of aluminum bromide loses hydrogen bromide slowly to form Al_2Br_5OH, which is responsible for the OH band that is observed in 1,2,4-trichlorobenzene.

It is interesting to speculate on the possible structure of the catalytic agent. A hydroxyl group might replace any of the six bromine atoms in Al_2Br_6. Thus, a possible structure is one in which an OH group replaces a Br atom forming a bridge between two aluminum atoms.



This complex may be more acidic than one in which a nonbridge bromine atom is replaced by OH, since the oxygen is held by two aluminum atoms more strongly here, and, therefore, it would be a more active isomerization catalyst. The isomerization catalyst could function as a strong protonic acid as mentioned previously.

Experimental

Aluminum bromide was prepared by doubly distilling commercially available material and using the heart cut of the second distillate.

1,2,4-trichlorobenzene, research grade, was obtained from the Matheson Coleman and Bell Co. Infrared analysis indicated that it contained about 5 wt. % of 1,2,3- and 1,3,5-trichlorobenzene.

Solutions were prepared by dissolving 0.05 mole of aluminum bromide in 25 cc. of 1,2,4-trichlorobenzene, and small amounts of water were added slowly to these solutions. The temperature of the solutions during preparation was kept approximately constant at 23 ± 3°. At a nominal water–aluminum bromide mole ratio of 0.5 the water concentration in solution was less than about 0.8 wt. %.

Infrared spectra were obtained using a Perkin-Elmer Infracord and a Perkin-Elmer Model 21 instrument. Sodium chloride cells, 0.104-mm. thickness, were used. All infrared spectra of the soluble aluminum bromide complex were obtained in the absence of *n*-hexane.

Acknowledgment.—The authors wish to thank Esso Research and Engineering Company for permission to publish this research.

(5) C. Lowig, *Pogg. Ann.*, **14**, 485 (1828); J. B. Berthemot, *Ann. Chim. Phys.*, (3) **44**, 394 (1855).

Alkylation of the Purine Nucleus by Means of Quaternary Ammonium Compounds. I. Tetraalkylammonium Hydroxides

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Received January 21, 1963

The alkylation of various purines was carried out by heating a mixture of the purine and the tetraalkylammonium hydroxide under reduced pressure. 9-Methyl adenine (IIIa), -kinetin (IIIb), -guanine (IIIc), 9-ethyladenine (IIId), 9-*n*-propyladenine (IIIe), and caffeine (VI) were obtained in excellent yield and in one step from the readily available purine.

Purines are associated intimately with all living systems which have been studied. For the most part the natural purines, as they occur in the nucleic acids, puromycin, the vitamin B_{12} analogs, and the coenzymes, are substituted in the 9-position of the nucleus by a carbohydrate moiety attached through its anomeric carbon.[3] Purine derivatives substituted in the 9-position may be regarded as structural analogs of these compounds and, therefore, are of interest as potential inhibitors of biological processes.

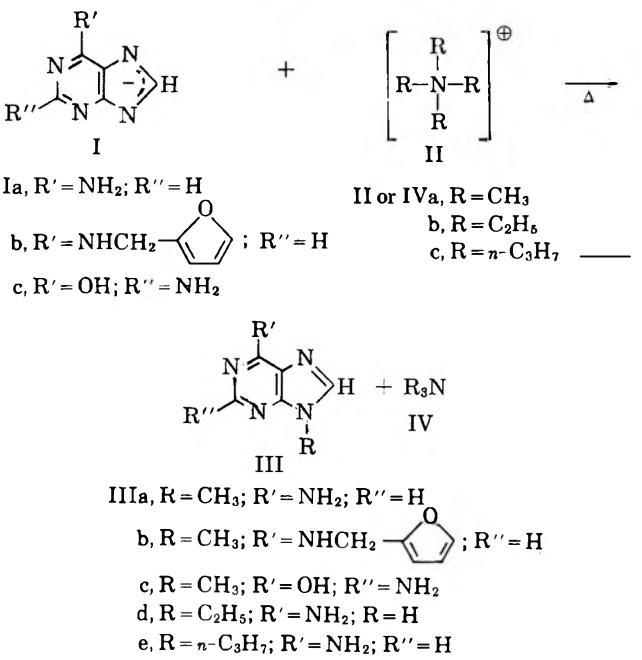
Syntheses of 9-substituted purines have been performed in general, either by the cyclization procedures which are modifications of the classical synthesis, *i.e.*, condensation of a substituted 4,5-diaminopyrimidine with a one carbon unit,[4] or by alkylation of the 9-position of a purine. This procedure involves the reaction of alkyl halides with alkali metal salts or chloromercuri salts of the purine and results usually in mixtures of the 7- and 9-substituted purines.[5]

The development of a facile method involving the direct alkylation of the purine nucleus at the 9-position was desirable since such a method would yield alkylpurines in one or two steps from readily available purines. In the search for suitable procedures a number of quaternary ammonium salts have been investigated as alkylating agents. The present paper concerns the use of tetraalkylammonium hydroxide in the alkylation of several purines.

N-Methylpurines in particular have been synthesized by a variety of methods, and the synthesis of 9-methylpurines has been reviewed by Robins.[6] The best synthetic method to date involves cyclization of substituted diaminopyrimidines, a procedure that has a number of disadvantages: several steps are required to obtain the desired pyrimidine and yields are not always high.

In the present work methylation was carried out by heating under reduced pressure the solid residue left after lyophilization of a solution of equimolar quantities of tetramethylammonium hydroxide and the purine to be methylated. When the temperature of the reaction mixture reached *ca.* 170° in the case of adenine (Ia), or *ca.* 260° in the case of guanine (Ic), the product sublimed from the mixture, in many cases in homologeneous form as determined by paper chromatography.

CHART I



This procedure was employed successfully to prepare 9-methyladenine (IIIa), 9-methylkinetin (IIIb), and 9-methylguanine (IIIc). The identity of the products was confirmed by analysis and by comparison with authentic samples. The infrared spectra[7] of 9-methyladenine (IIIa) and 9-methylkinetin (IIIb) were identical in all respects with those of authentic samples.[8] Paper chromatography[9] of 9-methylguanine (IIIc), prepared by alkylation, and an authentic sample[8] in two solvent systems gave identical results. In the case of the guanine a second product was obtained that exhibited an ultraviolet absorption spectrum similar to that of guanine (Ic) but migrated with a different R_f in one of the chromatographic solvents employed.

(1) U. S. Public Health Service Fellow 1956–1960. From a thesis submitted by L. D. Z. in partial fulfillment of the requirements for the Ph.D. degree, University of Illinois, 1961.

(2) To whom requests for reprints should be addressed at CIBA Pharmaceutical Co., Summit, N. J.

(3) E. C. Chargaff and J. N. Davidson, "The Nucleic Acids," Vol I, Academic Press, Inc., New York, N. Y., 1955, Chap. 3.

(4) (a) J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, 383 (1943); (b) J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956); (c) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **79**, 5238 (1957); (d) J. A. Montgomery and C. Temple, Jr., *ibid.*, **80**, 409 (1958); (e) H. H. Lin, *Dissertation Abstr.*, **20**, 500 (1959).

(5) (a) W. Traube and H. W. Dudley, *Ber. Chem. Ges.*, **46**, 3839 (1913); (b) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 318 (1944); (c) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954); (d) H. Bredereck, H. Ulmer and H. Waldmann, *Chem. Ber.*, **89**, 12 (1956); (e) H. J. Schaeffer and R. D. Weimar, Jr., *J. Am. Chem. Soc.*, **81**, 197 (1959); (f) J. A. Montgomery and C. Temple, Jr., *ibid.*, **83**, 630 (1961).

(6) R. K. Robins and H. H. Lin, *ibid.*, **79**, 490 (1957).

(7) Infrared spectra determinations were done by J. Broder or P. McMahon, University of Illinois, Urbana, Ill.

(8) Graciously donated by R. K. Robins.

(9) Paper chromatograms were run by the descending technique on Whatman no. 1 paper in 1-butanol–0.6 *M* ammonium hydroxide (6:1) (solvent A) or in 95% ethanol–1 *M* ammonium acetate pH 7.5 (7:3) (solvent B). The compounds were located by visual examination with the use of an ultraviolet lamp.

TABLE I

ALKYLATION OF THE PURINE NUCLEUS WITH VARIOUS QUATERNARY AMMONIUM COMPOUNDS

Reactants	Product	Reaction Temp., °C.	Reaction Time, hr.	Recrystallization solvent	% Yield crude sublimate
Ia + IIa	9-Methyladenine (IIIa)	170–200	6	95% ethanol	77
Ib + IIa	9-Methylkinetin (IIIb)	190–200	5	Acetone	85
Ic + IIa	9-Methylguanine (IIIc)	260	5.5	...	50
Ia + IIb	9-Ethyladenine (IIId)	150–160	2	Methyl ethyl ketone	74
Ia + IIc	9-*n*-Propyladenine (IIIe)	195	...	Methyl ethyl ketone	71
V + IIa	Caffeine (VI)	150	...	...	85
VII + IIa	Caffeine (VI)	210	...	...	87

TABLE II

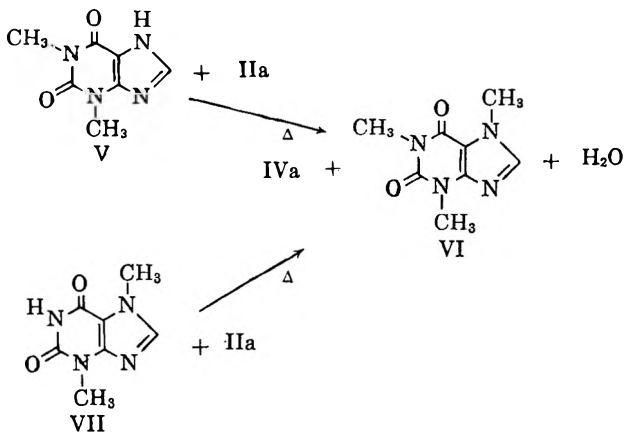
PHYSICAL CONSTANTS AND ANALYSES OF ALKYLPURINES

Alkylpurine	M.p., °C.[a]	Ultraviolet spectra or chromatographic identity[b]	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
9-Methyladenine (IIIa)	301–302[c]	Ultraviolet absorption maxima, 258 mμ	$C_6H_7N_5$	48.31	47.81	4.73	4.75	46.96	47.31
9-Methylkinetin (IIIb)	176.5–177.5	...	$C_{11}H_{11}N_5O$	57.64	57.47	4.63	4.94	30.57	30.49
9-Methylguanine (IIIc)	...	R_f (solvent A) 0.14[a] R_f (solvent B) 0.66 Identical to those of authentic sample[d] A second ultraviolet absorbing material was detected in crude sublimate R_f (solvent A) 0.26 R_f (solvent B) 0.55							
9-Ethyladenine (IIId)	192–194[e]	...	$C_7H_9N_5$	51.53	51.35	5.56	5.56	42.92	42.90
9-*n*-Propyladenine (IIIe)	168	R_f (solvent A) 0.87	$C_8H_{11}N_5$	54.23	54.00	6.26	6.10	39.52	39.44
Caffeine (VI)	...	R_f (solvent A) 0.55 R_f (solvent B) 0.84 Identical to those of sample							

[a] See ref. 12. [b] See ref. 9. [c] Melting point determined in a sealed tube. [d] See ref. 8. [e] Reported m.p. 194–195° (Ref. 4c).

This product was not identified but is believed to be a methylated guanine. The yields in the preparation of 9-methyladenine (IIIa) and 9-methylkinetin (IIIc) were about 80% based on the starting purine.

The methylation of other purines was then investigated. Theophylline (V) and theobromine (VII) were methylated using tetramethylammonium hydroxide (IIa) to form chromatographically pure caffeine (VI) in *ca.* 80% yield.



If quaternary ammonium hydroxides containing alkyl groups higher than methyl are employed, Hofmann degradation with alkene formation might be expected to compete with or even to abolish N-alkylation.[10] However, tetraethylammonium hydroxide (IIb) served to prepare 9-ethyladenine (IIId) in 74% yield. The product was characterized by melting point and elemental analysis; its infrared spectrum resembles that of 9-methyladenine. Similarly, 9-*n*-propyladenine (IIIe) was obtained in 71% yield by use of tetra-*n*-propylammonium hydroxide (IIc). The identity of the propyl residue as *n*-propyl, and not isopropyl, was determined by n.m.r. spectroscopy.

The reaction is believed to proceed as formulated in Chart I. The residue after lyophilization is assumed to be the tetraalkylammonium salt of the purine. Salts of this type have been isolated when the purine has been theophylline.[11] The intermediate salt decomposes on heating with alkylation of the purine nucleus and production of free trialkylamine. From the reaction of tetra-*n*-propylammonium hydroxide (IIc) with adenine (Ia), tri-*n*-propylamine (IVc) was isolated in 85% yield and characterized as its picrate and methiodide.

Further work is in progress on the use of other quaternary ammonium compounds as alkylating agents.

Experimental[12]

Starting Materials.—The tetraalkylammonium hydroxides solutions were prepared from the corresponding tetraalkylam-

(10) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927).

(11) G. S. Delmar and E. N. Macallum, U. S. Patent 2,678,311 (May 11, 1954).

monium halides (Eastman) by treatment of aqueous solutions of the salts with powdered silver oxide. Purines were obtained from commercial sources and used without further purification.

Alkylpurines.—The compounds were prepared as described for 9-methylkinetin (IIIb). Reaction time and temperature as well as recrystallization solvent are given in Table I. Physical constants and analysis of the products are given in Table II.

9-Methylkinetin.—A solution of 0.22 g. (2.38 mmoles) of tetramethylammonium hydroxide (IIa) and 0.50 g. (2.32 mmoles) of kinetin (Ib) in 5 ml. of water was lyophilized. The hydroscopic residue, in a sublimation apparatus, was heated slowly under oil pump vacuum (*ca.* 0.05 mm.) to a temperature of 190–200°. At this temperature a sublimate began to collect on the condenser. After 5 hr. 0.38 g. of sublimed product was collected. An additional 0.07 g. of product was collected on continued heating at 200°. The combined sublimates yielded 0.45 g. (85%) of crude product. A portion of the crude product was recrystallized twice from acetone to give white crystals, m.p. 176.5–177.5°, undepressed when admixed with an authentic sample of 9-methylkinetin.[8]

(12) Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The analyses were carried out at Micro-Tech Laboratories, Skokie, Ill. The ultraviolet absorption spectra were measured in aqueous solution on a Beckman DU spectrophotometer.

The Reaction of Nitric Oxide with Dialkyl Phosphonates

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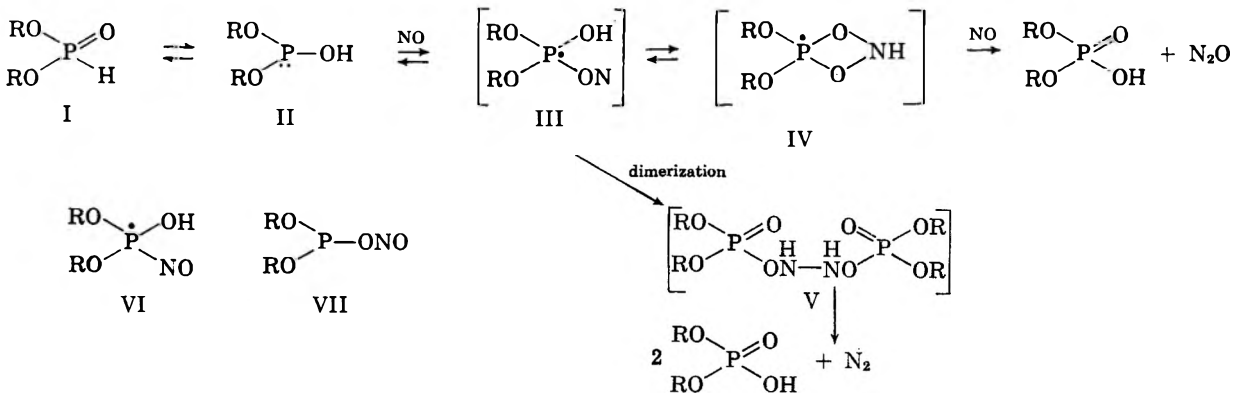
Received January 16, 1963

Nitric oxide reacts with dialkyl phosphonates to give the corresponding dialkyl phosphates in high yield. Both tracer experiments with oxygen-18 and the gaseous reaction products indicate that the reaction proceeds *via* two mechanisms.

A number of reactions between derivatives of trivalent phosphorus and various oxides of nitrogen and related compounds have been reported and recently been reviewed.[1]

It appears that nitric oxide is a particularly efficacious reagent for the oxidation of triphenylphosphine[2] and methylphosphines[3] to the phosphine oxides and of triethyl phosphite to triethyl phosphate.[4] In connection with our studies on the properties of the P–H bond,[5] we have examined the reaction of nitric oxide with dialkyl phosphonates and found that the corresponding dialkyl phosphates are formed readily in excellent yield. The reaction occurs at room temperature both with and without a solvent. The gaseous product obtained is mainly nitrogen with some nitrous oxide. The proportion of the latter component is increased on increasing dilution of the phosphonate in benzene solution. In order to elucidate the mechanism, reaction was run using nitric oxide with ~78 atom % O^{18} and diethyl phosphonate. Both the recovered unchanged nitric oxide, and the product nitrous oxide had a considerably reduced O^{18} content (of the order of 57%) indicating that at some stage the oxygen of nitric oxide is in a reversible equilibrium with a normal oxygen atom which in this case can only be the "phosphoryl" oxygen atom of the phosphonate. The following mechanism is proposed on the basis of the products and in order to account for these isotopic results. The isomerization I ⇄ II is well known[6] and, although no physical evidence for the existence of appreciable concentrations of II has been obtained, many reactions of dialkyl phosphonates are assumed to proceed *via* this intermediate.[5] The intermediate III was not isolated but has a radical type structure formed by attack of oxygen on phosphorus and is analogous to one of the structures proposed by Kuhn[4] for the reaction of nitric oxide with triethyl phosphite. His alternative suggestion of compound with a P–N bond (VI) is not likly in this case since the reversible steps II ⇄ III ⇄ IV are required in order to account for the equilibration of isotopic oxygen in the products. In a control experiment nitric oxide was found not to exchange oxygen with diethyl phosphate. The exact structure of IV is not known, but the alternative reaction involving abstraction of hydrogen and attack on *oxygen* by nitric



oxide to form compound VII is excluded by the observation that the intermediate in this case, prepared directly from the phosphorochloridite and silver nitrite is known[7] to form tetralkyl pyrophosphate in high

(1) J. I. G. Cadogan, *Quart. Rev.* (London), 208 (1962).

(2) M. H. Abraham, J. H. N. Garland, J. A. Hill, and L. F. Larkworthy, *Chem. Ind.* (London), 1615 (1962).

(3) M. Halmann and L. Kugel, *J. Chem. Soc.*, 3272 (1962).

(4) L. P. Kuhn, J. O. Doati, and C. Wellman, *J. Am. Chem. Soc.*, **82**, 4792 (1960).

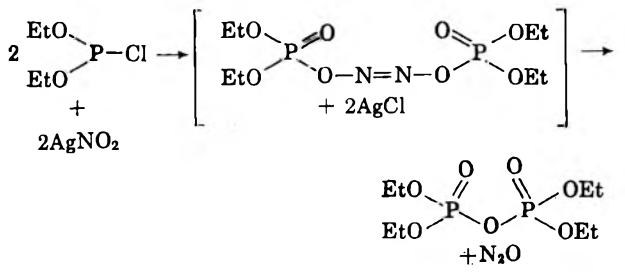
(5)(a) Z. Luz and B. Silver, *ibid.*, **83**, 4518 (1961); **84**, 1095 (1962); (b) B. Silver and Z. Luz, *ibid.*, **84**, 1091 (1962).

(6) G. O. Doak and L. D. Freedman, *Chem. Rev.*, **61**, 31 (1961).

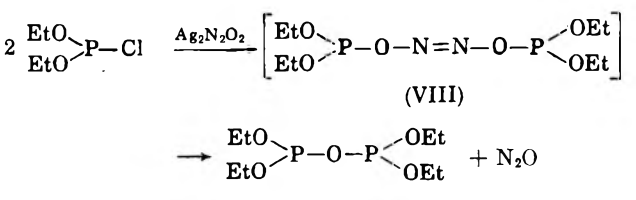
(7) D. Samuel and B. L. Silver, *Chem. Ind.* (London), 2063 (1962).

yield. The mechanism of reaction of IV to give products, nitrous oxide and dialkyl phosphate, is not yet understood, but may involve a "nitroxyl" intermediate. It should be noted, however, that recently Hudson[8] has shown that the analogous cyclic carbonyl intermediate was not formed in the reaction of carbonyl chloride with alkyl phosphinates.

Dimerization of the suggested intermediate III to structure V is a type of mechanism that has been proposed in the reaction of nitrosyl chloride and dialkyl phosphonates to form tetraalkyl pyrophosphates.[9] Support for dimers of type V in also provided by the reaction of silver nitrite and diethyl phosphorochloridite to give tetraethyl pyrophosphates and nitrous oxide,[7] the nitrogen–nitrogen bond probably being formed by dimerization of the initial reaction product. A dimer



analogous to V is almost certainly an intermediate[10] (VIII) in the reaction of silver hyponitrite and diethyl phosphorochloridite, breaking down immediately to give tetraethyl pyrophosphite and nitrous oxide.



However, the nitrogen-bridged intermediate (V) suggested for this reaction discussed in this paper differs from the others in that it contains a hydrazo rather than an azo bridge (*cf.* VIII). This may account for the formation of nitrogen rather than nitrous oxide as the second product.

The fact that dialkyl phosphonates react with nitric oxide to give phosphates and with nitrosyl chloride to give pyrophosphates[8,9] indicates that the latter reaction does not involve prior dissociation of nitrosyl chloride to nitric oxide and chlorine. The existence of two competing reactions III to IV and V also is supported by the observation that the proportion of nitrogen in the product is reduced on dilution of the phosphonate component, due to the decreasing chances of dimerization as the concentration of III decreases (*cf.* Table I).

(8) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 217 (1962).
(9) J. Michalski and Z. Zwierzak, *Roczniki Chem.*, **35**, 619 (1961).
(10) D. Samuel and B. L. Silver, *J. Chem. Soc.*, in press.

Experimental

Dialkyl phosphonates were prepared from phosphorus trichloride and the corresponding alcohol[11] and twice distilled: dimethyl phosphonate, b.p. 57–58° (9 mm.) [lit.[12] 56–58° (10 mm.)]; and diethyl phosphonate, b.p. 72° (9 mm.) [lit.[13] 72–73 (9 mm.)].

Diethyl phosphate (Hopkins and Williams) was distilled twice, b.p. 118–120° (0.01 mm.) [lit.[14] 116–118° (0.01 mm.)].

Nitric oxide-O^{18} was prepared by equilibration of normal nitric oxide with acidified H_2O^{18}.[15] Both gas and isotopic analyses were carried out on a Consolidated Engineering Corp. 21–405 mass spectrometer.

Action of Nitric Oxide on Dialkyl Phosphonates.—Nitric oxide (Matheson) was bubbled slowly through 10.04 g. of diethyl phosphonate; heat was evolved; and the solution became green. After 3 hr. no further increase in weight occurred; the final weight of the product was 11.08 g. corresponding to an uptake of ~0.99 mole of oxygen per mole of phosphonate. The product was degassed and distilled under high vacuum. A 9.8-g. sample of diethyl phosphate was collected, b.p. 118–119° (0.01 mm.), yield 90%. The product was identified by (a) titration with sodium hydroxide solution, titration equivalent, 159.7, calcd. for $(EtO)_2PO{\cdot}OH$, 154; (b) phosphorus analysis: P found, 19.9%, calcd. for $(EtO)_2PO{\cdot}OH$, 20.1%; (c) the infrared spectra gave peaks at 1230 cm.$^{-1}$ (P=O) and 1040 cm.$^{-1}$ (P—O—Et). No peaks at 945–985 cm.$^{-1}$ (P—O—P) or 2460 cm.$^{-1}$ (P—H) were observed. Similarly dimethyl phosphonate gave dimethyl phosphate in 85% yield, b.p. 105° (0.01 mm.); P found, 25.0%, calcd. for $(MeO)_2PO{\cdot}OH$, 24.6%. To determine the composition of the gaseous products of the reaction, samples of diethyl phosphonate, some in solvent benzene, were sealed in glass ampoules containing nitric oxide. After 7 days at room temperature, the gases were analysed in the mass spectrometer. The results are shown in Table I.

TABLE I

Reaction mixture			Gaseous products, %		
Nitric oxide	Diethyl phosphonate	Solvent	N_2	NO	N_2O
0.22 mmole	...[a]	...	3.2	93.6	3.1
0.22 mmole	0.35 mmole	...	6.4	82.1	11.5
0.22 mmole	0.35 mmole	...	6.5	81.8	11.7
0.22 mmole	0.35 mmole	...	6.5	81.9	11.6
0.55 mmole	0.35 mmole	Benzene	30.2	55.1	14.7
0.55 mmole	0.7 mmole	10 ml.	51.9	28.6	19.5
0.55 mmole	...[a]	Benzene 10 ml.	3.4	93.4	3.1

[a] Blank runs indicate purity of nitric oxide used in these reactions.

Oxygen-18 Tracer Experiments.—Di-*n*-propyl phosphonate (100 mg.) and NO^{18} (~5 ml. at NTP, 77.6 atom % O^{18}) were sealed in glass ampoules and left at room temperature for 7 days. The gases were analyzed mass spectrometrically. Diethyl phosphate was treated similarly. The results are given in Table II.

TABLE II

		Recovered gases, atom % O^{18}	
NO^{18}	Phosphorus ester	NO	N_2O
0.22 mmole	Diethyl phosphonate, 0.7 mmole	55.3	58.5
0.22 mmole	...	77.6	..
0.22 mmole	Diethyl phosphate, 0.7 mmole	74.7	..

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The Reaction of Lithium Diphenylphosphide and Simple Aryl Halides

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Lithium diphenylphosphide has been found to react with *p*-bromo- and *p*-iodotoluene, *m*-bromotoluene, *p*-bromobiphenyl, and *p*-dibromobenzene producing diphenyl(*p*-tolyl)phosphine, diphenyl(*m*-tolyl)phosphine, diphenyl(*p*-biphenyl)phosphine, and *p*-bis(diphenylphosphino)benzene, respectively, in 70–80% yields. Gas–liquid partition chromatography at 240–300° was used to establish the presence of only one phosphine in each of these reactions. The products were isolated as oxides. Addition of phosphide to aryl halide has been found to lead to little or no tertiary aryl phosphine in the reactions of the tolyl halides, but addition of lithium diphenylphosphide to a mixture of aryl halide and lithium chloride was found to lead to tertiary phosphine in fair to good yields. It was concluded that the reaction does not occur by an elimination–addition mechanism nor a simple halogen–metal interchange. A transition state involving two molecules of lithium diphenylphosphide is suggested in which one molecule of lithium diphenylphosphide coordinates with the halide atom while the other displaces it from carbon.

Although the reaction of alkali metal organophosphides with aryl halides which are unactivated toward nucleophilic displacement has been reported, none of these reports involve monoalkali metal phosphides.[3,4]

$$PhPLi_2 + 2PhBr \longrightarrow Ph_3P + 2LiBr \quad (1)$$

$$[PhPNa]_2 + 2PhBr \longrightarrow [Ph_2P]_2 + 2NaBr \quad (2)$$

No attempt seems to have been made toward elucidation of the mechanism of these reactions. In the course of work on organophosphorus systems an investigation of this problem was undertaken.

Results

It has been found that lithium diphenylphosphide reacts with simple aryl bromides and iodides in tetrahydrofuran at room temperature with the evolution of heat. Diphenylarylphosphines isolable as such or as their oxides are produced in high yields as shown by equation 3. Results are tabulated in Table I.

$$Ph_2PLi + ArX \longrightarrow Ph_2PAr + LiX \quad (3)$$

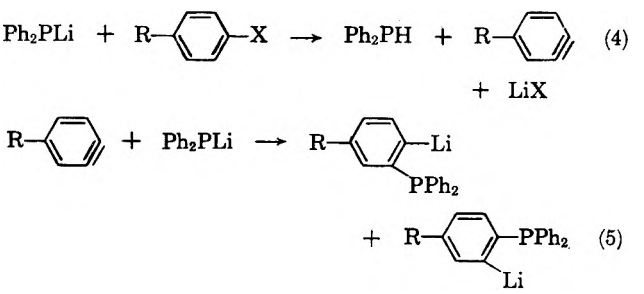
X = bromide or iodide
Ar = *p*-tolyl, *m*-tolyl, *p*-biphenyl, *p*-biphenylene

Gas chromatographic analysis of the reaction mixtures after steam distillation has shown that no diphenyl(*p*-tolyl)phosphine is produced from *m*-bromotoluene and that no *meta* isomer is produced from *p*-bromotoluene. Diphenyl(*p*-tolyl)phosphine has a longer retention time than the *meta* isomer on a silicone DC-200 column. The same is true of the corresponding oxides. This represents, to the best of our knowledge, the first reported separation of positionally isomeric tertiary arylphosphines and oxides by gas–liquid partition chromatography.[5] The same method was employed to demonstrate that only diphenyl(*p*-biphenylyl)phosphine is obtained from the reaction of lithium diphenylphosphide and 4-bromobiphenyl. Higher temperatures and faster flow rates were found necessary to establish that only the known *p*-bis(diphenylphosphino)benzene dioxide resulted from *p*-dibromobenzene. This represents the first use of gas–liquid partition chromatography on diphosphines and their mono- and dioxides.

Discussion

Several paths may be envisaged for the replacement of halide by lithium diphenylphosphide, *e.g.*, through a benzyne mechanism, a halogen–metal interchange, and a displacement on carbon.

There is evidence indicating that lithium diphenylphosphide is too weak a base to abstract an *ortho* hydrogen from simple aryl halides.[6,7] Nevertheless, the possibility of elimination producing an aryne intermediate followed by addition of lithium diphenylphosphide presents itself as a possibility.



If *p*-bromotoluene and *m*-bromotoluene were to react by the path shown in equations 4 and 5, isomeric diphenyltolylphosphines would be produced in each case. It would seem, therefore, that elimination–addition does not occur to any extent in the reaction of aryl bromides or iodides and lithium diphenylphosphide.

In view of the work of Brook and Wolfe[8] who showed that halogen–metal interchange is the major path by which simple aryl halides and triphenylsilylpotassium react to form tetraarylsilanes, halogen–metal interchange might be suspected in the present reaction. Halogen–metal interchange would lead to aryllithium and diphenylphosphinous halide. These products could then either react with each other producing tertiary arylphosphine (equation 6) or, if separation of these species beyond reaction distance occurred, they might react with other species in the reaction milieu (equation 7). Since diphenylphosphinous halides are known to react with lithium diphenylphosphide to produce tetraphenylbiphosphine,[4,9] addition of aryl halide to lithium diphenylphosphide might be expected to produce large amounts of tetraphenylbiphosphine

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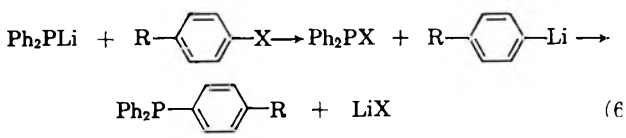
TABLE I

YIELDS OF REACTION OF LITHIUM DIPHENYLPHOSPHIDE WITH ARYL HALIDES[a]

	p-Bromotoluene			*p*-Iodotoluene			*m*-Bromotoluene			*p*-Bromobiphenyl		*p*-Dibromobenzene
Manner of addition[b]	N	I	I–L[f]	N	I	I–L[f]	N	I	I–L[f]	N	I	N
% Yield of Ph_2POOH[c]	0	60	36	9	47	0	0	65	3	3	4	5
% Yield of product[d]	65	0	38	68	9	57	68	3	65	70	75	75
% Recovery of Ph_3P[e]	12	11	8	6	10	17	8	6	17	7	5	6
% Recovery of Ph_3PO[e]	2	2	9	4	2	7	1	5	12	9	8	8

[a] All per cents are based on starting triphenylphosphine used in the preparation of the phosphide.[6,7] [b] N refers to normal addition which is dropwise addition of aryl halide to a refluxing solution of phosphide, I signifies inverse addition or addition of phosphide to aryl halide, and I–L indicates inverse addition of phosphide to a solution of the halide containing lithium chloride. [c] Calculated from weight of material isolated and characterized by infrared and mixture melting points. [d] Refers to combined phosphine and corresponding oxide. Over 75% of the reported yields represent oxide isolated in pure form and characterized by infrared spectral comparison, gas chromatographic retention time comparison, and mixture melting point with material prepared from the corresponding organometallic and diphenylphosphinous chloride followed by oxidation. The remaining portion of the reported yield was obtained from quantitative gas chromatographic analysis of remaining fractions after isolation of the major portion of product. This was cross checked by gas chromatographic analysis before isolation. [e] Calculated from gas chromatographs of the remaining fractions after isolation of the major portion of product and cross checked by gas chromatographic analysis of the reaction mass before isolation of product. These materials were present from the preparation of the lithium diphenylphosphide as described in the Experimental section.[6,7] [f] The apparent high material balance in these cases is probably due to the presence of lithium halides in the acetone solution (possibly complexed with the phosphines and oxides) which are not determined gas chromatographically but add to the total weight.



$$Ph_2P\text{–}C_6H_4\text{–}R + LiX \qquad (6)$$

$$Ph_2PX + Ph_2PLi \longrightarrow (Ph_2P)_2 + LiX \qquad (7)$$

$$(Ph_2P)_2 + 3H_2O_2 \longrightarrow 2Ph_2POOH + 2H_2O \qquad (8)$$

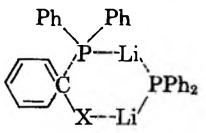
and correspondingly low yields of tertiary arylphosphine.

The tetraphenylbiphosphine would show up as diphenylphosphinic acid after oxidation,[4] as shown in equation 8. As can be seen from Table I, very little phosphinic acid was produced on normal addition. This result, accompanied by the high yields of tertiary aryl phosphines, would seem to negate the possibility of halogen–metal interchange followed by separation of the primary products. Furthermore, addition of carbon dioxide has not led to isolation of toluic acids.[10]

If halogen–metal interchange is occurring to any extent, it would seem that inverse addition should lead to higher yields of product and correspondingly lower yields or phosphinic acid than normal addition. As shown in Table I inverse addition of the reagents has been found, in the reactions of *para*- and *meta*-tolyl bromides and iodides, to lead to very little or no product. Most of the phosphorus appears as phosphinic acid. This acid does not arise from the oxidative hydrolysis of unchanged lithium diphenylphosphide upon steam distillation. The red color of the latter species is discharged upon addition of the phosphide to the tolyl halide. Accumulated lithium diphenylphosphide would be expected to react with the aryl halide during the reflux period. This was shown by mixing the reagents at a temperature low enough for little or no reaction to occur (0–10°) and allowing the mixture to come to reflux. Under these conditions the same results were obtained as when normal addition was employed. It appears that other path(s) of reaction are open to the reagents. Low concentrations of lithium diphenylphosphide favor these, as yet undisclosed, paths over the replacement reaction.

(10) There remains the possibility of very rapid reaction of the aryllithium and halophosphine formed in a halogen–metal interchange.

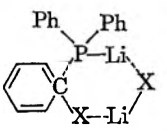
The possibility that a transition state, I, involving two molecules of lithium diphenylphosphide and one of aryl halide, is essential to the replacement of halide is consistent with the difference in results between normal and inverse addition. The role of the second molecule of phosphide would involve the complexing action of the lithium ion, which has a high charge density, with the aryl halide. Another way of visualizing this concept is that the reaction mechanism is of the "push-pull" type.



I

Isslieb and Tzschach[11] have concluded from molecular weight determinations that lithium diphenylphosphide is present as a dimeric associated complex in dioxane solution.

The presence of lithium chloride in the solution of lithium diphenylphosphide must be considered. This salt arises in the preparation of lithium diphenylphosphide from triphenylphosphine, lithium, and *t*-butyl chloride.[5,6] Lithium chloride may take the place of one of the two molecules of phosphide. Furthermore, we would expect it to be a better complexing agent. Addition of the diphenylphosphide reagent



II

to a solution of tolyl halide containing lithium chloride was carried out. As Table I indicates, this gave results closer to those obtained upon normal addition.

Experimental

1. **Preparation of Lithium Diphenylphosphide.**[6,7] A solution of 2.1 g. (0.3 g.-atom) of lithium ribbon and 26.2 g. (0.1 mole) of triphenylphosphine in 150 ml. of tetrahydrofuran was allowed to react under nitrogen with agitation for 3 hr. After addition of

(11) K. Issleib and A. Tzschach, *Chem. Ber.*, **92**, 1118 (1959).

9.3 g. (0.1 mole) of *t*-butyl chloride and heating to reflux for 10 min., the reaction mass was allowed to cool to ambient temperature and transferred under nitrogen to a dropping funnel on a second vessel under nitrogen.

2. General Procedure Used in the Reaction of Lithium Diphenylphosphide with Aryl Halides. Method A. Normal Addition.—The red reaction solution from 1 was allowed to run rapidly into the vessel leaving unchanged metal in the funnel. After the dropping funnel was replaced, the solution was heated to reflux and a solution of the aryl halide in tetrahydrofuran was added dropwise with rapid stirring under nitrogen.

Method B. Inverse Addition.—The red reaction solution was allowed to drop slowly into a rapidly stirred, refluxing solution of the aryl halide in tetrahydrofuran under nitrogen.

After addition was complete the reaction mixture was refluxed for 2 hr. and then allowed to return to ambient temperature. The flask was opened to air, most of the tetrahydrofuran distilled, and the residual mass steam distilled. After cooling the residue, the supernatant aqueous layer was separated from the bottom oily layer by extraction with chloroform. Acidification of the basic aqueous layer precipitated most of the phosphinic acid in it. This accounted for most of the phosphinic acid produced with little additional acid being isolated after treatment with 3% hydrogen peroxide at a later stage in the work-up.

The chloroform layer was then subjected to gas chromatographic analysis. The instrument was a Research Specialties Model 60-1A gas chromatograph with a flame ionization detector operating at 240–290°, which contained a 3-ft. column of 5% silicone oil DC-200 on 80–100-mesh Chromasorb (W-AW). In all cases a small amount of triphenylphosphine and its oxide were present. These materials presumably arose from uncleaved triphenylphosphine in the initial step. The per cent of uncleaved triphenylphosphine (calculated from chromatographic curve areas and conversion ratios arrived at from mixtures of known compositions) was usually between 10 and 15%.

The chromatographs of this chloroform solution showed peaks due to triphenylphosphine, triphenylphosphine oxide, small peaks of short retention times (due to unknown components and diphenylphosphine), and only two other peaks. These two were shown to be due to the phosphine and phosphine oxide expected from direct substitution of halide by the diphenylphosphide group.

Evaporation of the chloroform solution and dissolution of the remaining semisolid in acetone followed by addition of 3% hydrogen peroxide solution gave a clear solution which was allowed to stand overnight. The addition of peroxide was accompanied by heat evolution in most cases. Concentration of this solution, followed by addition of water and reconcentration, removed the acetone and produced a precipitate of semisolid. The supernatant aqueous layer was acidified after decantation and any precipitating phosphinic acid was isolated. Acetone trituration of water-insoluble material separated any remaining phosphinic acid as insoluble solid. The acetone filtrate solution was subjected to gas chromatographic analysis which, in most cases, disclosed peaks representing solvent, a small amount of triphenylphosphine, an even smaller amount of triphenylphosphine oxide, and a very large peak due to the diphenylarylphosphine oxide produced. Curve areas, conversion factors, and the weight of solid obtained on evaporation of acetone were used to calculate crude yields. Isolation of product in pure form was accomplished by crystallization.

3. Preparation of Diphenyl(*m*-tolyl)- and Diphenyl(*p*-tolyl)-phosphines.—The infrared spectra of the tolylphosphine oxides was that expected for *meta* and *para* isomers, respectively. The melting points of the isolated materials were identical with those reported in the literature.[12]

4. Preparation of Diphenyl-*p*-biphenylphosphine Oxide.—Diphenyl-*p*-biphenylphosphine oxide (m.p. 143–144°), previously unreported, showed no depression of mixture melting points with material prepared from the corresponding organometallic and diphenylphosphinous chloride, followed by oxidation. The two materials also had identical retention times under the conditions mentioned in connection with gas chromatographic separation of the isomeric tolyl oxides; their infrared spectra were identical.

Anal. Calcd. for $C_{24}H_{19}PO$: C, 81.4; H, 5.37; P, 8.75. Found: C, 81.71; H, 5.45; P, 8.28.

5. Preparation of *p*-Bis(diphenylphosphino)benzene Dioxide.—*p*-Dibromobenzene led, on normal addition, to *p*-bis(diphenylphosphino)benzene dioxide as shown by analysis, mixture melting points and infrared spectral comparison with the known material.[13,14] Gas–liquid partion chromatography at 320° employing very rapid carrier gas flow indicated that the crude reaction mixture contained only one diphosphine, the corresponding monoxide, and dioxide.

Acknowledgment.—This work has been supported in part by a grant from the National Science Foundation for the participation of undergraduates in research. The investigation was initiated by a grant from Research Corporation. We wish to acknowledge the technical assistance of Mr. William Pfeifer in the initiation of the problem.

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Aluminum Chloride-Induced Halogen Exchange of Alkyl Halides

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Halide exchange between *n*-propyl bromide or *n*-propyl iodide and aluminum chloride yields, initially, an exchange product containing a high per cent of *n*-propyl chloride. Interchange of halogen between ethyl and *n*-propyl halides, catalyzed by aluminum chloride, also gives initial exchange products rich in the *n*-propyl halide. An equilibrium constant for the exchange of propyl bromide with aluminum chloride is estimated and mechanistic implications of the results are considered.

Although much work has been done on aromatic substitution by means of the Friedel–Crafts, aluminum trichloride-catalyzed reaction, relatively little attention has been given to halogen exchange between alkyl halides and aluminum trichloride.

Isotopic studies reveal that alkyl and acyl halides will exchange halogen atoms with the corresponding aluminum trihalides,[1,2] and interchange of methyl halides with aluminum halides has been studied.[3] Aluminum trihalide also may catalyze exchange of halogen between one alkyl halide and another[4]; thus a mixture of carbon tetrachloride, ethyl iodide, and aluminum chloride affords carbon tetraiodide.[5] Recent

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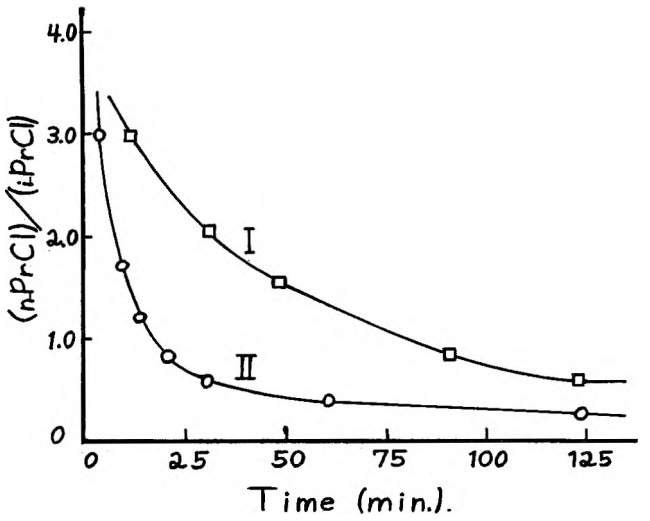

Fig. 1.—*n*-Propyl chloride to isopropyl chloride mole ratios in the aluminum chloride exchange reactions: I, *n*-propyl iodide plus aluminum chloride exchange reaction; II, *n*-propyl bromide plus aluminum chloride exchange reaction.

work demonstrates halide exchange of halobenzenes effected by aluminum halides.[6]

One possible mechanism for the exchange of AlX_3 with RX includes ionization of the alkyl halide.

$$RX, AlX_3 \rightleftharpoons R^+AlX_4^- \rightleftharpoons R^+ + AlX_4^-$$ [1,2,7]

If the reaction involves a carbonium ion (R^+), as in this mechanism, then one would expect products of an exchange reaction between *n*-propyl bromide or *n*-propyl iodide and aluminum chloride to consist predominantly of isopropyl chloride isomer formed by rearrangement of the primary carbonium ion.

This paper presents results of *n*-propyl bromide and *n*-propyl iodide interchange with aluminum chloride. The initial product of this exchange reaction contains a higher per cent of *n*-propyl chloride than of isopropyl chloride. The fact that exchange occurs readily without concomitant rearrangement is thought to indicate that halide interchange probably occurs through a mechanism not involving a carbonium ion. We also examined aluminum chloride-induced halogen exchange between propyl and ethyl halides and found that these reactions yield *n*-propyl halide as the predominant first product of interchange.

Experimental

Materials.—Aluminum chloride (Fisher Co., anhydrous sublimed) was used without further purification; it was transferred to small, screw-cap vials in a dry box and the vials were stored in a desiccator until used. Ethyl chloride was obtained from the Ohio Chemical Co. *n*-Propyl chloride, bromide, and iodide were from Eastman Organic Chemicals. Ethyl bromide and iodide were purchased from the Fisher Co. The ethyl iodide and *n*-propyl chloride used were shown by vapor phase chromatography to contain no more than 1.5 mole % of impurities. All other organic reagents used were shown by v.p.c. to be 99.5 mole % pure or better. All organic reagents were dried over anhydrous magnesium sulfate prior to use. The *n*-propyl bromides and iodides used were found, by injecting a large quantity (*ca.* 40 μl.) into the v.p.c. apparatus, to be free of detectable amounts of *n*- and isopropyl chlorides.

Exchange Reactions.—All experiments were carried out in an ice bath at 0° and the reacting mixtures were magnetically stirred. Reactions were performed in a 125-ml. erlenmeyer flask with a two-hole rubber stopper fitted with a calcium chloride drying tube and a piece of 5-mm. glass tubing leading to a test tube containing 3 ml. of water into which samples of approximately 2 ml. each could be withdrawn by suction. Samples were quenched by shaking with water; the organic layer then was withdrawn, dried over magnesium sulfate, and analyzed by v.p.c. To prevent losses due to volatility, samples were kept cold in ice at all times and the syringe used for v.p.c. injections was kept in a refrigerator at about 4°. Time of sample withdrawal was recorded with a stopwatch, and zero time was taken as the moment at which aluminum chloride was added to the organic compounds.

Quantities of reagents used are listed in Tables I and II; 560 mmoles of each alkyl halide was used for the reactions so that the mixed alkyl halide starting material was equimolar. Approximately 1.1 g. (8.27 mmoles) of aluminum chloride was used for all reactions, so that aluminum trichloride comprised about 0.8 mole % of mixed alkyl halide systems and 1.6 mole % of the aluminum chloride exchange reaction mixtures. No solvent was used.

Analysis.—For analysis of product mixtures, an Aerograph A-90-P gas chromatograph was used with a Sargent Model SR recorder. A 50-ft. column of 0.25-in. copper tubing packed with 20% L.A.C.-446 (Wilkens Instrument and Research Inc., California) on 30–60-mesh firebrick was used. The column was maintained at 85° in an air bath, and a flow rate of 100 cc./min. was used with helium as the carrier gas. This column completely resolved all reaction products, which were identified by comparison of their relative retention ratios with those of known standard samples. Gas chromatographic analyses of weighed standard mixtures of the alkyl halides encountered in this study show that the per cents calculated from v.p.c. peak areas correspond to mole per cents of the mixtures within 2% error in all cases. Although the mole per cents of propyl chlorides present in samples from exchange reactions of *n*-propyl bromide or *n*-propyl iodide with aluminum chloride were difficult to determine accurately due to the small quantities present, relative amounts of *n*-propyl chloride and isopropyl chloride could be measured easily by the technique of injecting large samples (*ca.* 40 μl.) into the v.p.c. apparatus, recording propyl chloride peaks with the attenuator on ×1, and then attenuating to ×64 in order to record the propyl bromide or propyl iodide peaks.

Results

Aluminum chloride dissolved readily in the alkyl halide mixtures in two to three minutes to give homogeneous systems; it required seven minutes to dissolve in pure *n*-propyl bromide. The catalyst did not dissolve completely in pure *n*-propyl iodide and the *n*-propyl iodide–aluminum chloride system remained heterogeneous throughout the reaction.

Preliminary experiments on the mixed alkyl halide systems showed that the ice bath held reaction temperatures at 0 ± 1° at all times, and the reactions evolved less than 10 ml. of gas (STP)—dehydrohalogenation reactions were insignificant under the conditions used. We observed no appreciable polymerization in these reactions.

Table I lists chromatographic analyses of samples from the *n*-propyl bromide or *n*-propyl iodide plus aluminum chloride exchange reactions. Total mole per cent of propyl chlorides is given in the fourth column of Table I, and the fifth column contains the mole ratio of *n*-propyl chloride to isopropyl chloride. The aluminum chloride was only slightly soluble in *n*-propyl iodide whereas it dissolved completely in *n*-propyl bromide; the much slower rate for exchange of *n*-propyl iodide with aluminum chloride may be caused primarily by low solubility of aluminum chloride in the iodide.

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TABLE I

ALUMINUM CHLORIDE EXCHANGE REACTIONS

V.p.c. analysis of *n*-PrBr and $AlCl_3$ reaction
(1.1150 g. of $AlCl_3$; 51.0 ml. of *n*-PrBr)

Time, min.	Mole %: *n*-PrBr	*i*-PrBr	(*n*-PrCl + *i*-PrCl)	(*n*-PrCl)/(*i*-PrCl)[a]
0.0	100.0	0.0	0.0	...
4.5	92.1	6.9	1.0	3.00
8.5	84.1	14.8	1.1	1.71
12.5	78.5	20.4	1.1	1.19
20.5	70.7	28.2	1.1	0.85
30.0	65.3	33.6	1.1	.62
60.0	55.5	43.4	1.1	.39
123.5	46.1	52.8	1.1	.27
175.0	40.8	58.3	1.0	.23

V.p.c. analysis of *n*-PrI and $AlCl_3$ reaction
(1.3337 g. of $AlCl_3$; 54.1 ml. of *n*-PrI)

Time, min.	Mole %: *n*-PrI	*i*-PrI	(*n*-PrCl + *i*-PrCl)	(*n*-PrCl)/(*i*-PrCl)[a]
0.0	100.0	0.0	0.00	...
11.0	99.7	0.3	.02	3.0
30.5	99.3	0.7	.03	2.1
48.5	98.7	1.3	.04	1.6
91.0	97.3	2.6	.05	0.9
123.5	95.9	4.0	.08	.6
252.0	88.6	11.3	.15	.4
410.0	82.0	17.8	.18	.2

[a] Since a greater quantity of propyl chlorides was formed in the *n*-PrBr + $AlCl_3$ exchange reaction, the (*n*-PrCl)/(*i*-PrCl) ratio could be determined more accurately than that for the *n*-PrI + $AlCl_3$ reaction.

Figure 1 shows a plot of the *n*-propyl chloride to isopropyl chloride mole ratios for the two aluminum chloride interchange reactions of Table I.

Results of v.p.c. analyses of ethyl and propyl halide exchange catalyzed by aluminum chloride appear in Table II. A number of points are listed for the first reaction (*n*-PrCl + EtI), and a graph (Fig. 2) showing the mole per cents of the exchange products in this reaction is given. Data also are presented for the reverse reaction (*n*-PrI + EtCl).

TABLE II

ALKYL HALIDE EXCHANGE REACTIONS

V.p.c. analysis of *n*-PrCl and EtI reaction
(1.1256 g. of $AlCl_3$; 45.3 ml. of EtI; 49.4 ml. of *n*-PrCl)

Time, min.	Mole %: *n*-PrCl	EtI	*i*-PrCl	*n*-PrI	*i*-PrI	EtCl
0.0	49.2	50.8	0.0	0.0	0.0	0.0
12.0	39.5	41.7	0.3	9.2	.0	9.3
30.0	32.0	34.8	1.3	15.7	.0	16.2
60.5	26.5	32.0	3.2	19.3	.2	18.8
91.0	24.0	30.3	5.0	19.6	.3	20.8
125.5	22.6	31.3	6.6	19.5	.6	19.4

V.p.c. analysis of *n*-PrI and EtCl reaction
(1.0152 g. $AlCl_3$; 40.0 ml. EtCl; 54.1 ml. *n*-PrI)

Time, min.	Mole %: *n*-Pr I	EtCl	*i*-PrI	*n*-PrCl	*i*-PrCl	EtI
0.0	50.0	50.0	0.0	0.0	0.0	0.0
26.0	31.0	30.1	.0	15.9	2.9	20.2
64.5	25.6	25.6	.0	16.7	6.8	25.3
120.0	24.1	23.6	.6	14.2	10.3	27.2

The remaining four aluminum chloride-induced propyl–ethyl exchange reactions were also run at 0° and with the same catalyst concentration as those of Table II. They are represented as shown.

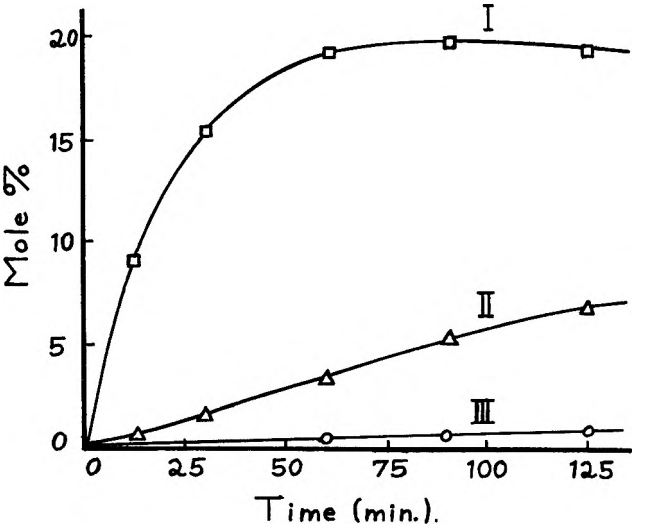

Fig. 2.—Product mole per cent in the *n*-propyl chloride plus ethyl iodide exchange reaction: I, *n*-propyl iodide; II, isopropyl chloride; III, isopropyl iodide.

$$n\text{-PrCl} + \text{EtBr} \rightleftharpoons n\text{-PrBr} + i\text{-PrBr} + \text{EtCl} + i\text{-PrCl} \quad (1)$$

$$n\text{-PrBr} + \text{EtCl} \rightleftharpoons n\text{-PrCl} + i\text{-PrCl} + \text{EtBr} + i\text{-PrBr} \quad (2)$$

$$n\text{-PrBr} + \text{EtI} \rightleftharpoons n\text{-PrI} + i\text{-PrI} + \text{EtBr} + i\text{-PrBr} + \frac{\text{EtCl} + n\text{-PrCl} + i\text{-PrCl}}{(\text{Total} = 0.6\%)} \quad (3)$$

$$n\text{-PrI} + \text{EtBr} \rightleftharpoons n\text{-BrBr} + i\text{-PrBr} + \text{EtI} + i\text{-PrI} + \frac{\text{EtCl} + n\text{-PrCl} + i\text{-PrCl}}{(\text{Total} = 0.4\%)} \quad (4)$$

These reactions proceed in essentially the same manner as the *n*-propyl chloride system of Fig. 2; exchange, which is more rapid than rearrangement, gives *n*-propyl halide as the predominant first product. (For example, reaction 1 yields an exchange product containing more *n*-propyl bromide than isopropyl bromide.) As indicated, reactions 3 and 4 exhibit exchange with the aluminum chloride present to give a total alkyl chloride concentration of about 0.5 mole %.

It also has been found in this study that, under the influence of aluminum trichloride, methyl iodide will exchange readily with ethyl chloride and *n*-propyl chloride and that butyl halides undergo halogen interchange with propyl, ethyl, and methyl halides.

Discussion

The results of these experiments show clearly that halogen interchange of *n*-propyl halides, with both aluminum chloride and ethyl halides, proceeds more rapidly than rearrangement of exchange products. Thus, it is possible to prepare unrearranged RY from RX by means of aluminum chloride-catalyzed exchange.

Constancy of (*n*-PrCl + *i*-PrCl) total concentration in the *n*-propyl bromide plus aluminum chloride exchange reaction (*cf.* Table I) suggests that exchange equilibrium was reached during the first four and one-half minutes of reaction. On this basis, an equilibrium constant can be estimated for the interchange of propyl bromides with aluminum chloride. Ignoring the presence of $AlCl_2Br$ and $AlClBr_2$, we may write the reaction as shown.

$$\underset{(554)}{3PrBr} + \underset{(6.2)}{AlCl_3} \rightleftharpoons \underset{(6.2)}{3PrCl} + \underset{(2.1)}{AlBr_3}$$

$$K_{eq} \approx \frac{(6.2)^3(2.1)}{(554)^3(6.2)} = 4.7 \times 10^{-7}$$

The symbols PrBr and PrCl represent sums of the propyl halides, (*n*-PrBr + *i*-PrBr) and (*n*-PrCl + *i*-PrCl), respectively. The number of mmoles of each species present at equilibrium, calculated from the data of Table I, is shown in parentheses under the reaction. In view of small equilibrium constant for the previous reaction, it is not surprising that the following analogous reactions were found to be essentially irreversible.[5]

$$MeCl + AlBr_3 \longrightarrow MeBr + AlCl_3$$

$$MeCl + AlI_3 \longrightarrow MeI + AlCl_3$$

Both AlY_3 + *n*-PrX and EtY + *n*-PrX exchange reactions proceed rapidly, and both interchanges yield initial products rich in the *n*-PrY isomer. These similarities suggest that the two exchange processes occur *via* the same mechanism and exchange of halogen between two alkyl halides may result from successive exchanges of alkyl halide with aluminum halide.

Unrearranged interchange products point to a noncarbonium ion mechanism for the exchange reaction, since carbonium ion intermediates would be expected to yield predominantly rearranged products.

Without implying ionization, a pathway involving bimolecular nucleophilic substitution could explain the observed results. A displacement mechanism for alkyl halide–aluminum halide interchange is consistent with the finding that the exchange of ethyl bromide (labeled with radioactive bromine) and aluminum bromide is a third-order reaction. The reaction rate is proportional to the concentration of ethyl bromide and to the square of the concentration of aluminum bromide.[2] Conductivity and transport measurements of solutions containing aluminum bromide in ethyl bromide are compatible with the absence of carbonium ions in the exchange mechanism. Formation of $AlBr_4^-$ and $RBrAlBr_2^+$ ions best explains the findings of these experiments.[8]

In many cases, Friedel–Crafts alkylations can yield unrearranged alkyl benzenes.[9] It is possible that these alkylations and the observed interchange reactions proceed by analogous displacement mechanisms of the type proposed by Brown based on kinetic data.[10,11]

Acknowledgment.—This work was supported in part by the National Science Foundation. We also wish to thank Dr. Gerard V. Smith of this laboratory for valuable advice during the course of the work and for the use of v.p.c. equipment.

(8) F. Fairbrother and N. Scott, *J. Chem. Soc.*, 452 (1955).
(9) See, for example, S. H. Sharman, *J. Am. Chem. Soc.*, **84**, 2945 (1962).
(10) H. C. Brown, *Ind. Eng. Chem.*, **45**, 1462 (1953).
(11) H. C. Brown and M. Grayson, *J. Am. Chem. Soc.*, **75**, 6285 (1953).

Synthesis of Eight New Halodeoxyinositols. Configurations of Chloro, Bromo, and Iodo Derivatives of Cyclohexanepentol[1,2]

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A 6-chloro, a 6-bromo, and a 6-iodo derivative of *cis*-quercitol, each of the *meso* configuration (12345/6), were prepared by reaction of 1,2-anhydro-*cis*-inositol (diketal) with the appropriate aqueous hydrohalic acid. Reaction of 1,2-anhydro-*allo*-inositol (diketal) with aqueous hydrochloric acid gave a mixture of two chloro quercitols, m.p. 215 and 236°, and with hydriodic acid, two iodoquercitols, m.p. 181 and 254°, the lower melting product predominating in each case. The predominant isomers were shown to have the configuration (125/346) corresponding to *gala*-quercitol, since the nonpredominant isomers on hydrogenolysis gave *talo*-quercitol and thus had the configuration (123/456). A bromoquercitol pentaacetate (m.p. 153°) prepared from *epi*-inositol in 1955 has for the first time been converted to the corresponding free bromoquercitol and by hydrogenolysis of the latter to *allo*-quercitol is now shown to have the configuration DL(1234/56), instead of the previously proposed (1235/46). New derivatives of *epi*-inositol and of pinitol are described.

The haloquercitols or halodeoxyinositols (6-halo-1,2,3,4,5-cyclohexanepentols, I) are of interest because of their possible inositol or anti-inositol activity in biological systems, as intermediates for synthesis of other cyclitols, and as model substances for the application to carbohydrates of such physical methods as nuclear magnetic resonance.[4]

Twenty diastereomers (eight *meso*, twelve active or racemic) are predicted for any such monosubstituted inositol, so that the stereochemistry of the haloquercitols is unusually complex and interesting. Previous work in our own and other laboratories has led to the synthesis of not less than ten of the twenty predicted bromoquercitols; not less than three of the chloroquercitols; but of only one of the iodoquercitols.[5]

We now wish to report the preparation and configurational characterization of three new chloroquercitols, two new bromoquercitols, and three new iodoquercitols. Crystalline pentaacetates have been obtained for all but two of these. The recently prepared haloquercitol diastereomers are summarized in Table I, which includes all known iodoquercitols. The previously known

(1) Paper XV on Cyclitol Stereochemistry by G. E. McCasland and coworkers: for preceding publication, see *J. Org. Chem.*, **28**, 894 (1963).
(2) Presented in part by V. B. to the 13th Annual Convention of the Student Affiliates of the American Chemical Society, Reno, Nev., May 4, 1962.
(3) Aided by the National Science Foundation Undergraduate Participation Program at the Department of Chemistry, University of San Francisco, 1962.
(4) See G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Am. Chem. Soc.*, (a) **83**, 4243 (1961); (b) **83**, 2335 (1961).
(5) The number of known chloro and bromo isomers is somewhat uncertain because of similarities in melting points, and the fact that some haloquercitol pentaacetates have not yet been correlated with their parent haloquercitol.

TABLE I

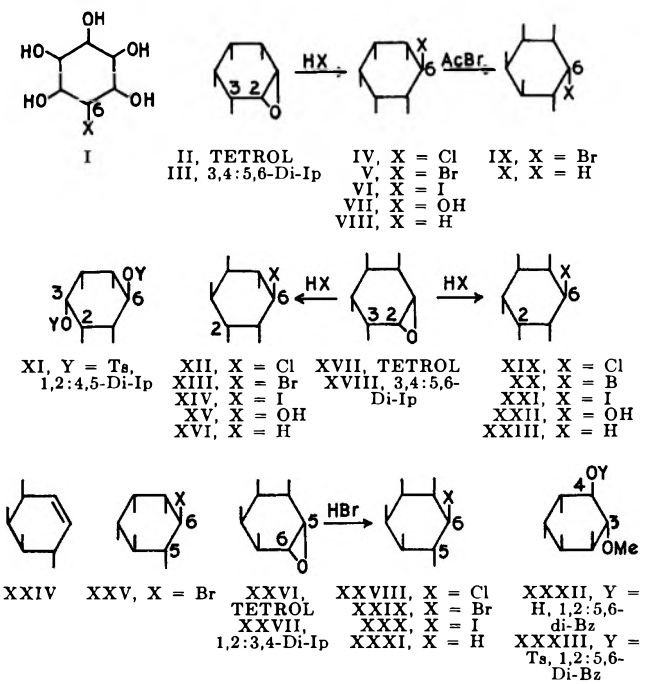
RECENTLY PREPARED DIASTEREOMERS OF 6-CHLORO-, 6-BROMO-, AND 6-IODOQUERCITOLS (HALODEOXYINOSITOLS)

Halogen	Configuration (X at 6)	Quercitol	Related inositol[a]	M.p.,[b] °C. (spec. rot.) Halopentol	Pentaacetate	Reference
Chlorine	*meso* (12345/6)	*cis*	*epi*-(6)	216	185	This article
Chlorine	D (125/346)	*gala*	L-(3)	215 (−53°)	Sirup	This article
Chlorine	D (123/456)	*talo*	*neo*-(1)	236 (−22°)	177 (+67°)	This article
Chlorine	DL (134/256)	*proto*	DL-(2)	206	144	12b
Chlorine	DL (124/356)?	*vibo*	DL-(1)	...	108	12b
Chlorine	DL (12346/5)	*allo*	*epi*-(1)	192	158	4a
Bromine	*meso* (12345/6)	*cis*	*epi*-(6)	202	191	This article
Bromine	D (125/346)	*gala*	L-(3)	203 (−44°) (DL 192)	... (DL 159)	4b, 12a
Bromine	D (123/456)	*talo*	*neo*-(1)	229 (−137°) (DL 214)	...	4b, 12a
Bromine	DL (1234/56)	*allo*	*allo*-(5) or *allo*-(6)	160	153	This article, 8, 12a
Bromine	DL (12346/5)	*allo*	*epi*-(1)	214	159	4a
Iodine	*meso* (12345/6)	*cis*	*epi*-(6)	202	183	This article
Iodine	D (125/346)	*gala*	L-(3)	181 (−31°)	Sirup	This article
Iodine	D (123/456)	*talo*	*neo*-(1)	254 (−45°)	190 (+65°)	This article
Iodine	DL (12346/5)	*allo*	*epi*-(1)	214 dec.	161	4a

[a] Number specifies inositol hydroxyl whose replacement without inversion would give the haloquercitol. [b] The halopentols typically melt with decomposition; the pentaacetates do not.

CHART I

(Ip = isopropylidene, Bz = benzylidene, Ts = *p*-toluenesulfonyl)



chloro and bromo diastereomers were tabulated in our recent publication.[4a]

The haloquercitols typically are colorless, crystalline, water-soluble compounds, which can be recrystallized from aqueous ethyl or isopropyl alcohol. On hydrogenolysis a haloquercitol is converted[6] to the corresponding quercitol (I, X = H).

Methods which have been used for the preparation of haloquercitols include: (1) reaction of a cyclohexenetetrol (conduritol) with hypobromous acid[7]; reaction of an inositol with (2) hot acetyl halide[6,8-10] or (3) thionyl chloride[11]; (4) reaction of an inositol hexaacetate with hot hydrogen halide[9] in acetic acid; reaction at room temperature of an anhydro-inositol or its diketal with hydrogen halide in (5) acetic acid,[4b] or (6) water.[4,12] Method 6 now appears to be by far the most convenient. Iodoquercitols have been prepared only by method 6.

Derivatives of *cis*-Quercitol

The reaction of an HX type reagent with 1,2-anhydro-*cis*-inositol (II) would be expected to yield only a single product, *e.g.*, I , which would be a *meso* diastereomer with the (12345/6) or *epi*-inositol configuration, VII.[13] Experimentally, the reaction of concentrated aqueous hydrochloric acid with the diketal,[14-16a] III, readily gave the expected chloroquercitol, IV, m.p. 216° dec. (pentaacetate 185°). Hydrobromic acid similarly gave the bromoquercitol, V, m.p. 202° dec. (pentaacetate 191°). Attempted preparation of the iodoquercitol with aqueous hydriodic acid gave at first only a discolored sirup (probably due to autoxidation of some of the hydrogen iodide). The procedure was then repeated under oxygen-free nitrogen and excess hy-

(6) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **75**, 4020 (1953). The acetyl bromide was diluted with acetic anhydride to favor the monobromo product.

(7) K. Kubler, *Arch. Pharm.*, **246**, 620 (1908).

(8) G. E. McCasland and John Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955).

(9) H. Muller, *J. Chem. Soc.*, (a) **91**, 1790 (1907); (b) **101**, 2383 (1912).

(10) E. Griffin and J. Nelson, *J. Am. Chem. Soc.*, **37**, 1552 (1915).

(11) R. Majima and H. Simanuki, *Proc. Imp. Acad. Japan (Tokyo)*, **2**, 544 (1926).

(12) (a) M. Nakajima and N. Kurihara, *Chem. Ber.*, **94**, 515 (1961); (b) M. Nakajima, personal communication, April, 1961.

(13) For explanation of configurational symbols such as "(12345/6)," see preceding articles in this series.

(14) The product III prepared by Angyal and Gilham's procedure contains considerable starting material, which must be removed by sublimation, even when the reaction time is increased from five to eight hours. The crude product also contains a by-product, m.p. 105–106°, which presumably is the monomethyl ether diketal [reported m.p. 104–105°; see *Advan. Carbohydrate Chem.*, **14**, 201 (1959)]. Yields of the pure product, which melted at 142–143° as reported, are often below the reported 54%. The over-all yield can be improved by recycling of the recovered starting material. The monomethyl ether diketal sublimes with the product.

(15) Each batch of the epoxide diketal (III or XVIII) should be tested for sulfur, to detect unchanged starting material sometimes present. An increase in reaction time may be helpful.

(16) (a) S. J. Angyal and P. Gilham, *J. Chem. Soc.*, 3691 (1957); (b) S. J. Angyal and D. McHugh, *ibid.*, 3686 (1957); (c) S. J. Angyal and N. Matheson, *J. Am. Chem. Soc.*, **77**, 4343 (1955); (d) S. J. Angyal and M. Tate, *J. Chem. Soc.*, 4116 (1961); (e) S. J. Angyal and C. Macdonald, *ibid.*, 686 (1952).

driodic acid was removed by use of an ion exchange resin prior to evaporation. A good yield of the colorless crystalline iodoquercitol, VI, was then obtained, m.p. 202° dec. (pentaacetate, m.p. 183°).

cis-Quercitol itself, VIII, also was prepared, by hydrogenolysis of 1,2-anhydro-*cis*-inositol[16a] (II, not the diketal) in aqueous solution with Raney nickel. This new method of preparation is more convenient than the hydrogenations of quinonetetrol or *cis*-inosose previously employed.[16b]

An inositol ditosylate of same (*epi*-inositol) configurational series as the preceding haloquercitols was prepared by reaction of 1,2:4,5-di-O-isopropylidene-*epi*-inositol[16c] (VII, diketal) with *p*-toluenesulfonyl chloride. The ditosyl diketal product (XI) was allowed to react with methanolic sodium methoxide in the hope of obtaining a 1,4-anhydroinositol, but after forty hours boiling only starting material was obtained.

Derivatives of *gala*- and *talo*-Quercitol

In a previous publication[4b] we described the reaction of the 1,2-anhydro-*allo*-inositol diketal[16c] (XVIII) with hydrogen bromide in acetic acid at room temperature to give a mixture of the two diastereomeric bromoquercitols, XIII and XX, whose configurations were established by nuclear magnetic resonance spectra. By hydrogenolysis, *gala*- and *talo*-quercitol themselves (XVI and XXIII) also were prepared.[4b]

In a similar manner, but using *aqueous* hydrohalic acids at room temperature, we have now converted the anhydro diketal, XVIII, to the two chloroquercitols, XII, m.p. 214° dec. (pentaacetate, a sirup), and XIX, m.p. 236° dec. (pentaacetate, m.p. 177°). Likewise, using hydriodic acid, there were obtained the two iodoquercitols, XIV, m.p. 180° dec. (pentaacetate, a sirup), and XXI, m.p. 254° dec. (pentaacetate, m.p. 190°).

The configuration XIX for the chloroquercitol, m.p. 236°, was established by hydrogenolysis to give the previously known[4b] *talo*-quercitol, XXIII. The other chloroquercitol, m.p. 214°, then necessarily has the remaining configuration XII and is a derivative of *gala*-quercitol.[4b] Hydrogenolysis of the two diastereomeric iodoquercitols similarly showed that the one of m.p. 254° has the configuration XXI (*talo*-quercitol derivative), so that the remaining configuration XIV can be assigned to the isomer, m.p. 180° (*gala*-quercitol derivative.

It is of interest that in the reaction of 1,2-anhydro-*allo*-inositol diketal, XVIII, with aqueous hydrochloric or hydroiodic acid the product of (125/346) configuration, *e.g.* XII, predominates over that of (123/456) configuration, *e.g.*, XIX, by a ratio of about three or four to one. A similar predominance of the (125/346) product previously was observed[4b] in the reaction with hydrogen bromide in glacial acetic acid. This predominance of (125/346) product corresponds to attack by bromide ion at position 2 of the protonated epoxide ring of XVII or XVIII in preference to position 1. From examination of Dreiding stereomodels it appears that the 2-position would be less hindered than 1 with respect to S_N2 attack. It should be noted that the cyclohexane ring in XVIII would be somewhat distorted by the two isopropylidene ketal rings and it is uncertain (especially when acetic acid is used as solvent) whether or not the ketal rings are cleaved before the epoxide ring is cleaved. The major product in each reaction has the configuration of *L*-inositol, XV; the minor product that of *neo*-inositol, XXII.

Derivatives of *allo*-Quercitol

In 1955, J. Reeves[8] working with one of us at Toronto treated *epi*-inositol (VII) with hot acetyl bromide and obtained the pentaacetate, m.p. 153°, of a bromoquercitol. All attempts at that time to obtain the pure bromoquercitol itself by hydrolysis of the pentaacetate were unsuccessful. However, on reaction with zinc in acetic acid the bromo pentaacetate did give the tetraacetate of conduritol-*C*, XXIV.[8] On the basis of limited evidence, the bromo pentaacetate, m.p. 153°, was tentatively assigned[8] the configuration (1235/46), XXV. We now find that the free bromoquercitol (unlike other isomers) is hygroscopic and can readily be prepared in a crystalline state by hydrolysis of the pentaacetate if the crystals are protected from atmospheric moisture. The crystals melt at 160° dec. We also find that this diastereomer actually has the configuration (1234/56), IX, since on hydrogenolysis it gives the known *allo*-quercitol, X. (The bromo pentaacetate, IX, also was prepared by Nakajima,[12] using a different method.) The epimer (12346/5) XXIX also yields *allo*-quercitol on hydrogenolysis,[4a] but is known to be nonidentical with Reeves' product.

In 1961 the nuclear magnetic resonance spectrum of a bromoquercitol of m.p. 229°, XX, related to *talo*-quercitol was interpreted successfully.[4b] More recently we have examined the n.m.r. spectra of 6-chloro, 6-bromo, and 6-iodo derivatives of *allo*-quercitol (XXVIII–XXX) in an attempt to confirm their previously assigned[4a] configurations. This attempt has so far been unsuccessful due to the complex spin–spin coupling resulting in these isomers from the six neighboring ring protons in each molecule. Spectra are described in Experimental.

Benzylidenepinitol. — Although numerous isopropylidene derivatives of cyclitols are known, and cyclohexylidene derivatives[16d] have recently been employed, very few benzylidene[17] derivatives have been reported. In connection with experiments on diisopropylidene derivatives of (−)-inositol, the synthesis and characterization of the dibenzylidene derivative XXXII of (+)-inositol 3-methyl ether (*pinitol*) was carried out.[18,19] The corresponding monotosylate XXXIII also was prepared (see Experimental).

Mercaptoquercitol.—By reaction of 1,2-anhydro-*cis*-inositol diketal (III) with benzylmercaptan, reduction, and hydrolysis we have prepared recently a mercaptoquercitol (VIII, X = SH). Details will be given in a subsequent publication.

Experimental

All melting points were corrected and were measured with a Nalge-Axelrod micro hot stage, if not otherwise noted. Micro-

(17) See E. Shneour and C. E. Ballou, *J. Am. Chem. Soc.*, **80**, 3960 (1958).

(18) Preparation conducted by Robert Horvat, formerly of this laboratory.

(19) Dibenzylidenepinitol should be able to exist in four different configurations due to the two additional asymmetric carbon atoms in the benzylidene groups. The product isolated by us appears to consist of a single pure stereoisomer, whose configuration at the benzylidene asymmetric carbon atoms has not been determined.

analyses were by the Micro-Tech Laboratories, Skokie, Ill. Nuclear magnetic resonance spectra were recorded with a Varian Model HR-60 high resolution n.m.r. spectrometer. Infrared spectra using potassium bromide pellets were recorded with a Perkin-Elmer Model 137 Infracord spectrometer. Optical rotations were measured with a Kern Full-Circle polarimeter.

The infrared spectrum was recorded for each new compound prepared; the spectra for haloquercitols and their pentaacetates showed absorption at the usual frequencies. It appears that haloquercitols of the same configuration have fingerprint regions of nearly identical shape; the exact locations of the fingerprint region absorption maxima shift in a regular manner for each Cl:Br:I series. Further work will be necessary to find out if these relationships are general.

Acetylation products were isolated by evaporation of the excess acetic anhydride and distribution of the residue between chloroform and water. The separated, washed, and dried chloroform phase was evaporated to give the crude product.

A qualitative sodium fusion test for halogen was made on each new halogen compound.

All nonaqueous solutions to be evaporated were dried with an appropriate desiccant. All evaporations were performed under reduced pressure. Crystals were washed with an appropriate solvent, and dried *in vacuo* to constant weight. Darco G-60 brand[20] of decolorizing charcoal was used.

1,2-Anhydro-*cis*-inositol, II.—A 300-mg. portion of the diketal[14-16a] (m.p. 143°) was treated by the procedure of Angyal and Gilham,[16a] giving 110 mg. (55%) of colorless crystals, m.p. 161–163°. This material was recrystallized twice more from absolute ethanol, giving 50 mg. of product, m.p. 164–165°.

Since the desired product previously had been reported[16a] to melt at 59–60° (yield not reported), we confirmed the identity of our own preparation by microanalysis.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.01; H, 6.36.

The structure was further confirmed by an infrared spectrum which showed no hydroxyl absorption, excluding the monoketal structure, and a reaction with hydrobromic acid, which gave the expected 6-bromoquercitol, V, m.p. 202° dec.

In a second run, on 390 mg. of diketal, a product of the same m.p. 164–165° was again obtained.

New Method for Preparation of *meso*(12345) or All-*cis* Diastereomer of Quercitol (Deoxyinositol, Cyclohexanepentol), VIII.—A 220-mg. portion of 1,2-anhydro-*cis*-inositol was dissolved in 50 ml. of water, and 3.0 g. (moist weight) of commercial Raney nickel catalyst was added (probably the amount of catalyst can be reduced). The mixture was hydrogenated at 3 atm. at room temperature for 12 hr. The filtered mixture was evaporated and oily residue taken up in 80% ethanol (treated with charcoal). The crystals, which had separated from the filtrate after 12 hr., were collected, giving 100 mg. of colorless product, m.p. 238–240° (reported[16b] 235–240°). Including a 20-mg. second crop (m.p. 236–240°), the yield was 55%.

epi-Inositol Configurational Series

***meso(12345/6) Diastereomer of 6-Chloroquercitol, M.p. 216°. 6-Chloro-6-deoxy-*epi*-inositol, IV.**—A mixture of 200 mg. of the anhydro-inositol diketal[16a] (m.p. 143°) with 5.0 ml. of 12 *M* aqueous hydrochloric acid was stirred for 1 hr. at room temperature, and the resulting solution evaporated. To the residue was added 5.0 ml. of 2-propanol and the evaporation repeated; the addition and evaporation were then again repeated. The residue was taken up in 7.0 ml. of water, the solution treated with charcoal, and the filtrate evaporated. The crystalline residue was recrystallized from 75% aqueous ethanol, giving 150 mg. (91%) of colorless crystals, m.p. 214–215° dec. This product was again recrystallized, for analysis, giving 130 mg. of pure product, m.p. 215–216° dec. (preheat stage for each m.p. to 190°).

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.33; H, 5.65; Cl, 17.61.

***meso(12345/6) Diasteromer of 6-Chloroquercitol Pentaacetate, M.p. 185°, IV.**—A mixture of 50 mg. of the chloropentol (m.p. 216°) with 50 mg. of fused sodium acetate and 3.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. (anhydrous conditions). The product was isolated in the usual manner and recrystallized twice from 2-propanol, giving 50 mg. (49%) of the pure product, m.p. 184.5–185°.

Anal. Calcd. for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 46.89; H, 5.10; Cl, 8.43.

To test for possible displacement of chlorine by the sodium acetate catalyst used, a sample of the acetylation mixture was evaporated and the residue distributed between chloroform and water. The separated aqueous phase gave a negative silver nitrate test for halogen.

***meso(12345/6) Diastereomer of 6-Bromoquercitol, M.p. 202°. 6-Bromo-6-deoxy-*epi*-inositol, V.**—The anhydro diketal (m.p. 143°, 200 mg.) was treated with 8.8 *M* hydrobromic acid in exactly the manner described above for the chlorine analog. There was obtained 170 mg. (84%) of the once recrystallized product, m.p. 200–201° dec., and 140 mg. of the twice recrystallized product, m.p. 201–202° dec. (preheat to 190°).

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.77; H, 4.68; Br, 33.16.

***meso(12345/6) Diastereomer of 6-Bromoquercitol Pentaacetate, M.p. 191°, V.**—A 50-mg. sample of the bromopentol (m.p. 202°) was acetylated in the same manner described before for the chlorine analog, giving 60 mg. (64%) of the twice recrystallized product, m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.40; H, 4.67; Br, 17.63. Found: C, 42.29; H, 4.54; Br, 17.63.

A silver nitrate test on the acetylation mixture for free bromide ion (see chlorine analog) gave only a trace of silver bromide precipitate.

***meso(12345/6) Diastereomer of 6-Iodoquercitol, M.p. 202°. 6-Iodo-6-deoxy-*epi*-inositol, VI.**—Oxygen-free nitrogen gas was passed slowly through a solution of 150 mg. of the anhydro diketal (m.p. 143°) in 0.5 ml. of colorless 5.5 *M* hydriodic acid at room temperature. After 1 hr. the colorless solution was diluted with 5.0 ml. of water, and deionized by treatment with 2.5 ml. (moist volume) of Amberlite IR-45 exchange resin.[21] The solution (pH 5 or higher) was evaporated and the colorless crystalline residue recrystallized from 75% ethanol (treated with charcoal). The cooled filtrate gave 120 mg. (67%) of colorless product, m.p. 197–198° dec. (preheat to 190°). This material was again recrystallized, giving 90 mg. of product, m.p. 202° dec., which was analytically pure.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.93; H, 4.18; I, 43.63.

An earlier attempt to prepare the iodoquercitol without use of nitrogen, and without deionization before evaporation, gave only a dark oil.

***meso(12345/6) Diastereomer of 6-Iodoquercitol Pentaacetate, M.p. 183°, VI.**—A 50-mg. portion of the iodopentol (m.p. 202°) was acetylated in the same manner described for the chlorine analog, giving 70 mg. (81%) of once recrystallized (from absolute ethanol) product, m.p. 176–177.5°. After a second recrystallization there was obtained 55 mg. of colorless crystals, m.p. 182.5–183°, which were analytically pure.

Anal. Calcd. for $C_{16}H_{21}IO_{10}$: C, 38.41; H, 4.23; I, 25.37. Found: C, 38.32; H, 4.46; I, 25.15.

***meso*-1,2:4,5-Di-O-Isopropylidene-*epi*-inositol 3,6-Di-*p*-toluenesulfonate, XI.**—The diketal[16e] (0.5 g., m.p. 181°) and 1.5 g. of recrystallized *p*-toluenesulfonyl chloride were dissolved in 5.0 ml. of anhydrous pyridine. The solution was kept for 7 days at 25°. Crystals of pyridine hydrochloride were visible by the second day. The mixture was poured into 75 ml. of water at 0° with stirring. A colorless sirup separated and soon solidified. The crude product was collected, washed with 10 ml. of water, and without drying was dissolved in 35 ml. of chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried, and evaporated to dryness. The amorphous residue was taken up in 30 ml. of hot chloroform, and the solution evaporated to 15 ml. This solution on standing deposited crystals which were collected, washed, and dried, giving 0.7 g. of product, m.p. 223–226° dec. This material was recrystallized from chloroform, giving 0.5 g. (63%) of pure product, m.p. 228–229° dec.

Anal. Calcd. for $C_{26}H_{23}O_{10}S_2$: C, 54.91; H, 5.67; S, 11.28. Found: C, 54.63; H, 5.46; S, 11.09.

Attempted Conversion of the 3,6-Ditosylate to a 3,6-Anhydro Derivative.—A 285-mg. portion of the previous ditosylate diketal (m.p. 229°) was mixed with an absolute methanolic solution of

(20) A product of the Darco Division, Atlas Powder Co., Wilmington, Del.

(21) A product of the Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

sodium methoxide. The suspension was boiled for 40 hr. under reflux. The starting material did not appear to dissolve or react. From the precipitate and solution there was recovered a total of 263 mg. of material. This was shown to be identical with the starting material by means of mixture melting point and infrared spectra.

neo and DL-Inositol Configurational Series

D(123/456) Stereoisomer of 6-Chloroquercitol, M.p. 236°. 1-Chloro-1-deoxy-*neo*-inositol, XIX.—A mixture of 980 mg. of 1,2-anhydro-*allo*-inositol diketal[16c] (m.p. 108°) with 5.0 ml. of 12 *M* hydrochloric acid was stirred at room temperature for 2 hr., and the resulting solution evaporated to dryness. To the residue three 5.0-ml. portions of absolute 2-propanol were successively added and evaporated. The crystalline residue was recrystallized from 60% 2-propanol (treated with charcoal). After 12 hr. the crystals which had separated were collected, giving 130 mg. of colorless matted needles, m.p. 234–235° dec. A second crop of 40 mg., m.p. 232–234° dec., was obtained.

The second crop filtrate was reserved for preparation of the m.p. 215° isomer (see following text).

Recrystallization of the combined crops (170 mg., m.p. 232–235°) from 65% 2-propanol gave 140 mg. of nearly pure product, melting at 234–235° dec., $[\alpha]^{23}D$ −22° (*c* 0.5, water), MR −44° A sample recrystallized again, for analysis, melted at 235–236° dec.

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.28; H, 5.67; Cl, 18.05.

A sample of this isomer on hydrogenation was converted to *talo*-quercitol (see following text).

D(125/346) Stereoisomer of 6-Chloroquercitol, M.p. 215°. 3-Chloro-3-deoxy-*L*-inositol, XII.—Second crop filtrate from the m.p. 236° isomer (see preceding) was evaporated. Colorless crystalline residue was recrystallized from 65% 2-propanol (treated with charcoal). After 6 hr. the crystals which had separated were collected, giving 220 mg. of material, m.p. 214–215° dec. A second crop of 250 mg., m.p. 212–214° dec., was obtained. (Attempted isolation of a third crop gave 10 mg. of the other isomer, m.p. 230–234° dec.)

Recrystallization of the combined lower melting isomer crops (470 mg.) from 65% 2-propanol gave 350 mg. of colorless crystals, m.p. 214–215°, $[\alpha]^{23}D$ −53° (*c* 0.3, water), MR −105°. A sample recrystallized for analysis showed no change in melting point.

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.13; H, 5.55; Cl, 17.83.

Attempted acetylation of a 200-mg. sample of this chloroquercitol in the usual manner gave an oil, which we have not yet been able to crystallize.

D(123/456) Stereoisomer of 6-Chloroquercitol Pentaacetate, M.p. 177°, XIX.—A 50-mg. portion of the chloroquercitol (m.p. 236°) was acetylated in the same manner as that described for the (12345/6) diastereomer, giving 50 mg. of colorless once recrystallized (from absolute ethanol) product, m.p. 175–176°. Including a 30-mg. second crop, the yield was 78%. By recrystallization of the first crop there was obtained 40 mg. of colorless crystals, m.p. 176–177°, $[\alpha]^{25}D$ +67° (*c* 0.3, chloroform), MR +274°. A sample recrystallized again, for analysis, showed no change in melting point.

Anal. Calcd. for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 47.22; H, 5.02; Cl, 8.84.

D(123/456) Stereoisomer of 6-Iodoquercitol, M.p. 254°. 1-Iodo-1-deoxy-*neo*-inositol, XXI.—A mixture of 980 mg. of the 1,2-anhydro diketal (m.p. 108°) with 5.0 ml. of colorless 5.5 *M* hydriodic acid was stirred at room temperature for 2 hr. The resulting solution was evaporated. To the residue two 5.0-ml. portions of 2-methyl-1-propanol were successively added and evaporated. The residue was stirred for 10 min. with 25 ml. of acetone, and the mixture filtered. The residue was washed with 5 ml. more of acetone. (Evaporation of the combined, brown filtrates gave a discolored sirup, which has not been further characterized.)

The crude product was recrystallized from 65% 2-propanol, giving 100 mg. of colorless crystals, m.p. 246–248° dec. (closed capillary, preheat to 240°), $[\alpha]^{23}D$ −45° (*c* 0.2, water), MR −176°.

The mother liquor was reserved for preparation of the lower-melting isomer (see following text).

The crystals were recrystallized from 70% 2-propanol, giving 70 mg. of product, m.p. 248–249° dec. A sample recrystallized again, for analysis, melted at 253–254° dec.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.73; H, 3.43; I, 43.10.

On hydrogenation this isomer of 6-iodoquercitol gave *talo*-quercitol (see following text).

D(123/456) Stereoisomer of 6-Iodoquercitol Pentaacetate, M.p. 190°, XXI.—A 50-mg. portion of the iodoquercitol (m.p. 254°) was acetylated in the usual manner. The crude product, a sirup, was crystallized from 2-propanol (treated with charcoal). After 12 hr., the crystals were collected, giving 70 mg. (82%) of nearly pure product, m.p. 189–190°. A sample was recrystallized again for analysis, melting point unchanged, $[\alpha]^{25}D$ + 65° (*c* 0.2, chloroform), MR + 325°.

Anal. Calcd. for $C_{16}H_{21}IO_{10}$: C, 38.41; H, 4.23; I, 25.37. Found: C, 38.55; H, 4.26; I, 25.06.

D(125/346) Stereoisomer of 6-Iodoquercitol, M.p. 181°. 3-Iodo-3-deoxy-L-inositol, XIV.—The mother liquor from the previous m.p. 254° isomer was concentrated, giving 300 mg. of material, m.p. 179–184°. Two additional concentrations of the mother liquor yielded 160 mg. of material, m.p. 180–183°, and 5 mg., m.p. 180–181° (all melting points with decomposition).

Recrystallization of these combined crops (465 mg.) from 70% 2-propanol gave 350 mg. of colorless crystals, m.p. 180–181° dec. A sample recrystallized again, for analysis, showed no change in melting point, $[\alpha]^{27}D$ −31° (*c* 1, water), MR − 90°.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 25.44; H, 4.34; I, 43.91.

Attempted acetylation of the iodoquercitol, m.p. 181°, in the usual manner gave an oil, which we have not been able to crystallize.

Conversion of the Chloro- and Iodoquercitols, M.p. 236° and 254°, to (123/45) or *talo*-Quercitol, XXIII. (A) From Chloroquercitol.—To a 150-mg. sample of the chloroquercitol (m.p. 236°) in 50 ml. of water was added 3.0 g. (moist weight) of commercial Raney nickel catalyst and 2.0 g. (moist weight) of Amberlite IR-45 ion exchange resin.[21] The mixture was hydrogenated at 3 atm. and room temperature for 12 hr. The solids were removed by filtration and the filtrate evaporated to a sirup. Volatile impurities were removed by repeated additions and evaporations of 2-propanol, giving finally a crystalline residue. This residue was recrystallized from 90% ethanol, giving 100 mg. (80%) of colorless crystals, m.p. 245–248° dec. This product was recrystallized (treated with charcoal), giving 60 mg. of colorless product, m.p. 246–248° dec. The melting point was unchanged on further recrystallization. The infrared spectrum was identical with that of D-*talo*-quercitol.[4b] A portion was acetylated, giving a product, m.p. 181–183°, identical by mixture melting point and infrared spectrum with D-*talo*-quercitol pentaacetate.

(B) **From Iodoquercitol.**—A 160-mg. sample of the iodoquercitol (m.p. 254°) was hydrogenated in the same manner, giving 55 mg. of twice recrystallized product, m.p. 246–248° dec., identical by infrared spectrum with D-*talo*-quercitol.[4b] A portion was acetylated, giving a product identical by mixture melting point and infrared spectrum with D-*talo*-quercitol pentaacetate.

1,2:5,6-Di-O-benzylidene-D-inositol 3-Methyl Ether[18] (Dibenzylidenepinitol), XXXII.—A mixture of 25 g. of finely ground, fused zinc chloride with 18.7 ml. of freshly distilled benzaldehyde was stirred at room temperature for 40 min. A 5.0-g. portion of finely powdered dry pinitol (see Acknowledgment) was then added, and the mixture stirred for 50 hr. and allowed to stand an additional 24 hr. The mixture was poured into a mixture containing 200 ml. of petroleum ether (b.p. 60–90°), 25 g. of anhydrous potassium carbonate, and 400 ml. of water. The precipitate which separated was collected, giving 3.8 g. of product, m.p. 118–120°. A sample recrystallized from aqueous ethanol, for analysis, melted at 119–120°.

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.74; H, 6.26.

D(124/356) Stereoisomer of 1,2:5,6-Di-O-benzylidene-3-O-methyl-4-O-*p*-toluenesulfonylinositol[18] (Dibenzylidenepinitol Tosylate, XXXIII).—A solution of 1.0 g. of dibenzylidenepinitol (m.p. 120°) and 0.86 g. of *p*-toluenesulfonyl chloride in 10.0 ml. of dry pyridine was allowed to stand for 4 days at room temperature. Three-fourths of the pyridine was evaporated and the remaining sirup poured into 50 ml. of ice-cold water containing

1.0 g. of sodium bicarbonate. The oil which separated was collected with chloroform, and the separated chloroform extract washed successively with 0.1 *N* hydrochloric acid, sodium bicarbonate solution, and water, and dried. Evaporation gave an oil, which was taken up in 15 ml. of absolute ethanol. Two milliliters of petroleum ether (b.p. 30–80°) was added. After 4 days at 0–5°, the crystals which had separated were collected, giving 224 mg. (16%) of colorless product, m.p. 125–127°. A sample recrystallized again, for analysis, melted at 133–134°.

Anal. Calcd. for $C_{25}H_{28}O_8S$: C, 64.10; H, 5.34. Found: C, 64.22; H, 5.36.

On hydrolysis with 50% acetic acid, this product gave 4-O-*p*-toluenesulfonylpinitol, m.p. 191° dec. (reported m.p.[16c] 193° dec.).

allo-Inositol Configurational Series

DL(1234/56) **Diastereomer of 6-Bromoquercitol, M.p. 160°. 6-Bromo-6-deoxy-*allo*-inositol, IX.**—A mixture of 3.2 g. of the pentaacetate[8] (m.p. 153°), derived from *epi*-inositol by reaction with acetyl bromide, with 64 ml. of *M* hydrochloric acid in 50% ethanol was boiled under reflux for 5 hr. On evaporation a light brown sirup was obtained. Volatile impurities were removed by repeated addition and evaporation of absolute ethanol. The resulting sirup was taken up in 15 ml. of 2-methyl-2-propanol (treated with charcoal). After the solution had stood 24 hr. at room temperature, the *hygroscopic* crystals which had separated were collected on a sintered glass funnel *from which moist air was excluded*, and dried over phosphorus pentoxide *in vacuo*. The colorless crystals obtained weighed 0.95 g., m.p. 159–160° dec. Including a second crop, m.p. 158–160°, and a third crop, m.p. 158–160° dec., the yield was 1.40 g. (82%). A sample recrystallized again, for analysis, showed no change in melting point.

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.80; H, 4.73; Br, 32.27.

On hydrogenolysis, this product gave DL-*allo*-quercitol[4a] (see following text).

Conversion of the Bromoquercitol, M.p. 160°, to DL-*allo*-Quercitol, XXXI.—A 950-mg. sample of the bromoquercitol (m.p. 160°) was hydrogenated with Raney nickel and Amberlite IR-45 resin[12] in the same manner described for the m.p. 236° chloroquercitol isomer. The crude hydrogenation product was taken up in 15 ml. of absolute ethanol, and the solution kept at room temperature for 24 hr. The crystals which had separated were collected, giving 300 mg. of colorless product, m.p. 260–261° dec. The product was shown by mixture melting point and infrared spectrum to be identical with DL-*allo*-quercitol.[4a]

A sample of the quercitol was acetylated, giving DL-*allo*-quercitol pentaacetate, m.p. 92–94°, identical by mixture melting point and infrared spectrum with an authentic sample.[4a]

Nuclear Magnetic Resonance Spectra of the DL-(12346/5) Diastereomers of 6-Chloro-, 6-Bromo-, and 6-Iodoquercitol (XXVIII–XXX).—The spectra were taken in deuterium oxide, using tetramethylsilane external reference. A strong HDO peak appeared in each spectrum at about δ 5.2 p.p.m. The chloroquercitol[4a] (m.p. 192°) showed a 1-proton multiplet (about 8 peaks) centered at δ 4.1; another 1-proton multiplet (about 5 peaks) centered at 4.3; and a 4-proton multiplet (about 7 peaks) centered at δ 4.6. The 4-proton multiplet was almost split at its center into two 2-proton multiplets (δ 4.5, 4.7).

The spectra of the bromoquercitol[4a] (m.p. 203°) and iodoquercitol[4a] (m.p. 214°) were similar to that of the chloro analog, but showed no tendency for separation of the 4-proton multiplet at δ 4.6 into two smaller multiplets.

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Synthesis of Δ⁵-Pregnene-3α,16α,20α-triol[1]

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The partial syntheses of Δ⁵-pregnene-3α,16α,20α-triol and its 20β-epimer are described.

Recently[3] we reported the isolation and characterization of Δ⁵-pregnene-3α,16α,20α-triol (Ha) from the urine of a patient with adrenocortical carcinoma, which was the first description of the natural occurrence of a 3α-hydroxy-Δ⁵ steroid. The partial synthesis of this unsaturated triol by an unambiguous route is described in the present report. In addition, all four Δ⁵-pregnene-3,16α,20-triols isomeric at positions 3 and 20 have been prepared by another route.

The starting material in both instances was 3β-acetoxy-Δ⁵,¹⁶-pregnadien-20-one (A). The 16α-hydroxyl group was introduced by the method of Julian and coworkers.[4] Selective oxidation of the Δ¹⁶ bond of A with alkaline hydrogen peroxide followed by reacetylation gave 3β-acetoxy-16α,17-oxido-Δ⁵-pregnen-20-one (B).[4] Reduction of the oxide B with chromous acetate[5] yielded 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (C). Impure C was generally carried directly to the next stage. Lithium aluminum hydride reduction of C gave a mixture of Δ⁵-pregnene-3β,16α,20α- and 20β-triols (D and Ea) which were separated readily by partition chromatography on silica gel. These epimers had been prepared and the configuration at C-20 assigned by Hirschmann and co-workers.[6] The triol Ea has been isolated from natural sources.[3,7,8]

The inversion of the 3β-hydroxy group of the 20α-triol E, while preserving the configurations at 16 and 20, was accomplished by a procedure based on studies of

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CA 03207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Pennsalt Chemicals Corporation, Philadelphia, Pa.

(3) D. K. Fukushima, M. Smulowitz, and K. I. H. Williams, *J. Biol. Chem.*, **236**, 3147 (1961).

(4) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *J. Am. Chem. Soc.*, **72**, 5145 (1950).

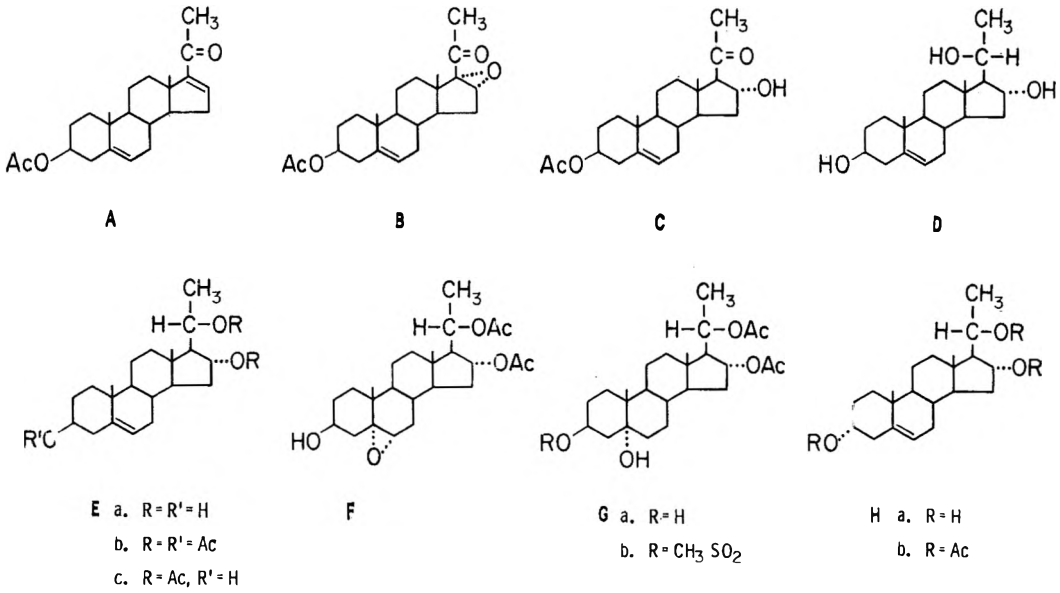
(5) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954). Chromous acetate was prepared by the method described in H. F. Walton, "Inorganic Preparations," Prentice-Hall, Inc., New York, N. Y., 1948, p. 161.

(6) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Am. Chem. Soc.*, **74**, 539 (1952).

(7) K. Fotherby, *Biochem. J.*, **71**, 209 (1959).

(8) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950).

CHART 1



Plattner and co-workers[9] on the rearrangement of cholesterol to epicholesterol (Δ^5-cholesten-3α-ol) *via* 3β-methanesulfonoxycholestan-5α-ol with diethylaniline and acetyl chloride. Δ^5-Pregnene-3β,16α,20α-triol (Ea) was converted to triacetate Eb which was then selectively saponified to diacetate Ec with one equivalent of sodium hydroxide in cold aqueous alcohol.[8] Epoxidation with monoperphthalic acid gave the 5α,6α-oxide F which was separated from the reaction mixture by crystallization from acetone; additional material was obtained by partition chromatography of the mother liquors.

Catalytic hydrogenation of 5,6α-oxido-5α-pregnane-3β,16α,20α-triol 16,20-diacetate (F) with Adams' catalyst in acetic acid resulted in a mixture from which 5α-pregnane-3β,5,16α,20α-tetrol 16,20-diacetate (Ga) was isolated. Treatment of Ga with methanesulfonyl chloride in pyridine gave the expected 3β-mesylate Gb in good yield. With acetyl chloride and diethylaniline in chloroform, followed by hydrolysis, Gb was converted to Δ^5-pregnene-3α,16α,20α-triol (Ha) identical with the natural product.

In the alternate synthesis of triol Ha the addition of benzyl alcohol to the Δ^{16}-20-ketone A and acetylation yielded 3β-acetoxy-16α-benzyloxy-Δ^5-pregnen-20-one (I) as described by Hirschmann.[6] Reduction with lithium aluminum hydride removed the acetyl group and yielded a mixture of 20-hydroxy epimers (J); fractional crystallization of a portion of the mixture yielded 16α-benzyloxy-Δ^5-pregnene-3β,20β-diol, characterized by conversion to Δ^5-pregnene-3β,16α,20β-triol (D).

In order to utilize the method by Ruzicka and Goldberg[10] described for the preparation of a 3α-hydroxy-Δ^5 steroid by Raney nickel hydrogenation of a 3-keto-Δ^5 compound, mixture J was oxidized with chromic acid in acetone.[11] A product with carbonyl absorptions at 1709 cm.$^{-1}$ and 1718 cm.$^{-1}$ and with a very weak hydroxyl absorption was obtained. These indicated that both the 3- and 20- hydroxyl groups had been oxidized to give 16α-benzyloxy-Δ^5-pregnene-3,20-dione (K). Without purification K was hydrogenated in 95% ethanol with W-2 Raney nickel catalyst. Although Hirschmann[12] earlier noted that Raney nickel hydrogenation cleaved a 16α-benzyl ether and simultaneously reduced a 20-ketone, the present reduction product retained the 20-ketone as judged by infrared spectrometry. The compound was formulated, therefore, as 3,16α-dihydroxy-Δ^5-pregnen-20-one (L). No attempts to separate the C-3 hydroxy epimers were made at this stage since the 3,16α,20-triols isomeric at C-3 and C-20 could be readily separated. Therefore, L was reduced with lithium aluminum hydride to give a mixture of the four triols. Digitonin precipitation separated the 3α-hydroxy triols Ha and M from the 3β-hydroxy triols D and Ea. Partition chromatography of the "α-fraction" gave Δ^5-pregnene-3α,16α,20α-triol (Ha), identical with the natural material as well as Ha prepared by the first route; this was followed by Δ^5-pregnene-3α,16α,20β-triol (M) in roughly a 1:3 ratio. A small amount of Δ^5-pregnene-3β,16α,20β-triol (D) also was isolated; this 3β-isomer has been reported previously[6] to appear in the soluble "α-fraction."

Partition chromatography of the "β-fraction" gave the previously described Δ^5-pregnene-3β,16α,20α-triol (Ea) and 3β,16α,20β-triol (D) in roughly a 1:3 ratio.

Experimental[13]

3β-Acetoxy-16α-hydroxy-Δ^5-pregnen-20-one (C).—Moist chromous acetate prepared from the reduction of 50 g. of potassium dichromate was added to a solution of 17 g. of 3β-acetoxy-16α,17-oxido-Δ^5-pregnen-20-one (B) in 450 ml. of acetic acid and 100 ml. of water.[5] The mixture was stirred at room temperature under nitrogen for 16 hr. and then filtered. The filtrate was poured into 1200 ml. of water and extracted with methylene chloride. The organic extract was washed with water, sodium bicarbonate solution, and water, dried, and the solvent evaporated. Re-

(9) Pl. A. Plattner, A. Fürst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948).

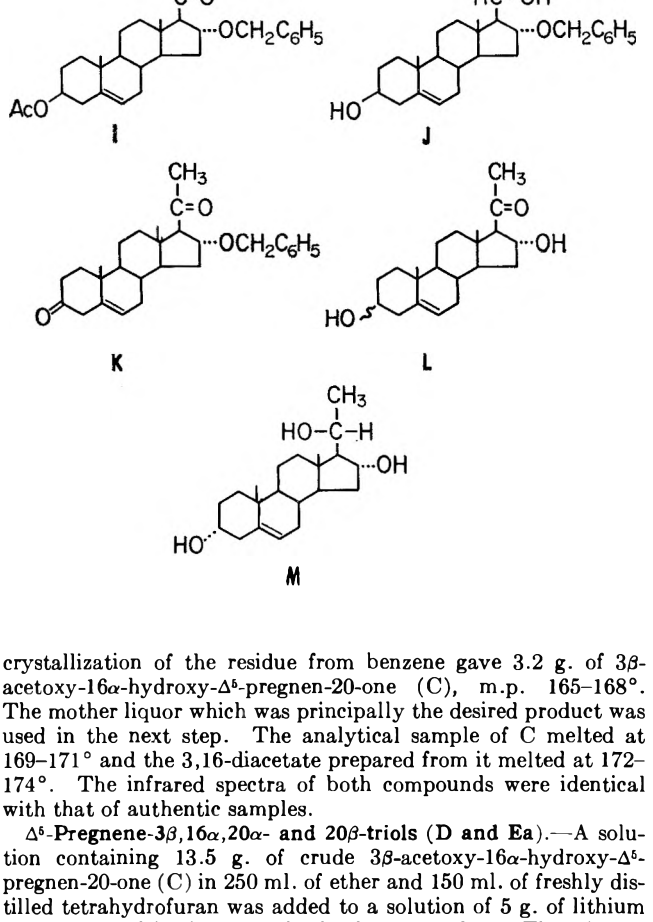
(10) L. Ruzicka and M. W. Goldberg, *ibid.*, **19**, 1407 (1936).

(11) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(12) H. Hirschmann, F. B. Hirschmann, and J. W. Corcoran, *ibid.*, **20**, 572 (1955).

(13) Melting points were taken on a micro hot stage and are corrected. Optical rotations were determined in chloroform unless otherwise stated. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer; calcium fluoride prism 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$, 1500–1280 cm.$^{-1}$; sodium chloride prism 1300–650 cm.$^{-1}$; sh = shoulder; * = not present in carbon tetrachloride solution.

CHART 2



crystallization of the residue from benzene gave 3.2 g. of 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (C), m.p. 165–168°. The mother liquor which was principally the desired product was used in the next step. The analytical sample of C melted at 169–171° and the 3,16-diacetate prepared from it melted at 172–174°. The infrared spectra of both compounds were identical with that of authentic samples.

Δ⁵-Pregnene-3β,16α,20α- and 20β-triols (D and Ea).—A solution containing 13.5 g. of crude 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (C) in 250 ml. of ether and 150 ml. of freshly distilled tetrahydrofuran was added to a solution of 5 g. of lithium aluminum hydride in 1000 ml. of anhydrous ether. The mixture was stirred for 4 hr. and excess reagent was destroyed with ethyl alcohol followed by 10% sulfuric acid. The product obtained was chromatographed on 1100 g. of silica gel containing 40% ethanol. Elution with 5% ethanol in methylene chloride yielded 3 g. of Δ⁵-pregnene-3β,16α,20α-triol (Ea) which on recrystallization from methanol melted at 247–248° (reported[6] m.p. 245–247°); $[\alpha]^{27}D$ −72.9° (ethanol). Acetylation with pyridine and acetic anhydride afforded the triacetate (Eb), m.p. 177–178° (reported[6] m.p. 178.5–180°).

Elution with 8% ethanol in methylene chloride gave 4 g. of Δ⁵-pregnene-3β,16α,20β-triol (D), m.p. 269,274–282° (reported[6] m.p. 294–298°). The triol was homogeneous as judged by chromatography on a thin layer of silica gel G with ethyl acetate. The triacetate prepared from it melted at 168–170°; $[\alpha]^{26}D$ −104° (reported[6] m.p. 167.5–168.5°; $[\alpha]D$ −93°).

Δ⁵-Pregnene-3β,16α,20α-triol 16,20-Diacetate (Ec).—T a solution of 1.57 g. (3.4 mmoles) of Δ⁵-pregnene-3β,16α,20α-triol triacetate (Eb) in 300 ml. of ethanol and 100 ml. of water was added 28.3 ml. (3.7 mmoles) of 0.12 *M* sodium hydroxide in methanol. The mixture was stored at 5° for 18 hr. and a drop of acetic acid added. The solvent was removed *in vacuo*. The residue was extracted with ethyl acetate, washed with water, dried, and the solvent evaporated. Chromatography on 100 g. of acid-washed alumina and elution with 10% ethyl acetate in benzene yielded 945 mg. of the 16,20-diacetate (Ec), m.p. 188–190° (reported[8] m.p. 185.5–187.5°). The completely saponified Δ⁵-pregnene-3β,16α,20α-triol (Ea), 157 mg., was eluted with 20% ethanol in ethyl acetate.

5,6α-Oxido-5α-pregnane-3β,16α,20α-triol 16,20-Diacetate (F).—A solution of 1.18 g. of Δ⁵-pregnene-3β,16α,20α-triol 16,20-diacetate (Ec), in 40 ml. of chloroform was mixed with 100 ml. of 0.16 *M* monoperphthalic acid in ether. The mixture was stored at 5° for 16 hr. and then diluted with ethyl acetate. The solution was washed with sodium bicarbonate solution and water, dried, and the solvent evaporated. The crystalline residue was washed with acetone yielding 517 mg. of 5,6α-oxido-5α-pregnane-3β,16α,20α-triol 16,20-diacetate (F), m.p. 211–218°. The analytical sample of F from acetone melted at 214–219°, $[\alpha]^{27}D$ −121°; ν_{max}^{KBr} 3480, 1737, 1707*, 1267, 1246, 1151, 1066, 1046, 1035, 1020 cm.⁻¹.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.64; H, 8.71.

An additional 400 mg. of the diacetate F was obtained upon chromatography of the acetone washes, 552 mg.

5α-Pregnane-3β,5,16α,20α-tetrol 16,20-Diacetate (Ga).—A solution of 820 mg. of the oxide diacetate F (see preceding section) in 35 ml. of acetic acid was hydrogenated for 21 hr. in the presence of 600 mg. of prereduced Adams' catalyst. The reduction mixture was extracted with methylene chloride, washed with dilute base and water, and the solvent removed. The residue was chromatographed on 100 g. of silica gel containing 40 ml. of ethanol. Elution with 2% ethanol in methylene chloride afforded 400 mg. of 5α-pregnane-3β,5,16α,20α-tetrol 16,20-diacetate (Ga). Recrystallization from benzene yielded 242 mg. of the tetrol diacetate (Ga), m.p. 196–199°; $[\alpha]^{27}D$ −56.9°; ν_{max}^{KBr} 3465 (sh), 3435, 1743, 1714*, 1272, 1255 (sh), 1245, 1166, 1036, 1028 (sh), 958 cm.⁻¹.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.78; H, 9.24. Found: C, 68.22; H, 9.37.

5α-Pregnane-3β,5,16α,20α-tetrol 3-Mesylate 16,20-Diacetate (Gb).—A mixture of 156 mg. of 5α-pregnanetetrol 16,20-diacetate (Ga), 0.5 mg. of methanesulfonyl chloride, and 5 ml. of pyridine was stored at room temperature for 2 hr. It was then poured into water and extracted with methylene chloride. The organic extract was washed successively with dilute acid and base and water and the solvent removed to give 210 mg. of product. Trituration with ether and filtration afforded 5α-pregnane-3β,5,16α,20α-tetrol 3-mesylate 16,20-diacetate (Gb), m.p. 157–158°; $[\alpha]^{25}D$ −49.7°; ν_{max}^{KBr} 3600, 3535, 1738 (sh), 1729, 1712*, 1264, 1252, 1175, 1040, 926, 868, 821 cm.⁻¹.

Anal. Calcd. for $C_{26}H_{42}O_8S$: C, 60.67; H, 8.23. Found: C, 60.27; H, 8.32.

Δ⁵-Pregnene-3α,16α,20α-triol (Ha).—A solution of crude mesylate Gb prepared from 40 mg. of tetrol diacetate Ga, 5 ml. of diethylaniline, 5 ml. of acetyl chloride, and 5 ml. of chloroform was refluxed for 5 hr. The solution was then concentrated *in vacuo* and diluted with ether. The ether solution was washed with dilute acid, dilute base, and water, dried, and the solvent evaporated to give an oily product. Chromatography on acid-washed alumina and elution with 3% ethyl acetate in benzene gave 20 mg. of oil. The infrared spectrum of the oil was identical with that of Δ⁵-pregnene-3α,16α,20α-triol triacetate (Hb) previously prepared from natural product. Saponification of the triacetate Hb with methanolic potassium hydroxide yielded 12 mg. of Δ⁵-pregnene-3α,16α,20α-triol (Ha), m.p. 230–232°; $[\alpha]^{27}D$ −84.9° (dioxane). The infrared spectrum in potassium bromide dispersion was identical with that of the natural product and the melting point of Ha was not depressed, 230–230.5°, on admixture with the natural triol, m.p. 230–231°.

16α-Benzyloxy-Δ⁵-pregnene-3β,20-diol (J).—A solution of 5 g. of 3β-acetoxy-16α-benzyloxy-Δ⁵-pregnen-20-one (I)[7] in 750 ml. of ether was added during 1 hr. to an ether solution containing a large excess of lithium aluminum hydride and the reaction mixture was heated at reflux for another hour. The excess reducing agent was destroyed and the reaction product was extracted thoroughly with ethyl acetate. The organic phase was washed successively with 10% sulfuric acid, water, 5% sodium bicarbonate, and finally with water to neutrality. The solution was dried and the solvent removed under reduced pressure. The crystalline residue weighed 5 g. after triturations with small volumes of carbon tetrachloride. Fractional crystallizations of a portion of the residue from acetone gave 16α-benzyloxy-Δ⁵-pregnene-3β,20β-diol (J), m.p. 162–166°; ν_{max}^{KBr} 3340, 1667, 1094, 1048, 970, 875, 740, 696 cm.⁻¹.

Anal. Calcd. for $C_{28}H_{40}O_3 \cdot {}^1/_2H_2O$: C, 77.56; H, 9.72. Found: C, 77.77; H, 9.57.

Acetylation of 16α-benzyloxy-Δ⁵-pregnene-3β,20β-diol with acetic anhydride in pyridine in the usual manner gave the diacetate, m.p. 112.5–114°; $\nu_{max}^{CS_2,\ CCl_4}$ 1734, 1667, 1243, 1071, 1028, 968, 732, 696 cm.⁻¹.

Anal. Calcd. for $C_{32}H_{44}O_6$: C, 75.55; H, 8.79. Found: C, 75.37; H, 8.53.

Hydrogenolysis of 16α-benzyloxy-Δ⁵-pregnene-3β,20β-diol with Raney nickel in ethanol gave Δ⁵-pregnenetriol-3β,16α,20β (D), the infrared spectrum of which was identical with an authentic sample.

Δ⁵-Pregnene-3,16α,20-triols.—To an ice-cold solution of 3.96 g. of 16α-benzyloxy-Δ⁵-pregnene-3β,20δ-diol (J) in 500 ml. of

acetone (freshly distilled from potassium permanganate) under a nitrogen atmosphere was added 5.7 ml. of chromic acid solution[11] (26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted to 100 ml. with water) over 1 min. with stirring. After an additional 3 min. of stirring, the mixture was poured into 10 l. of ice–water and filtered. The solid product was dried in a vacuum desiccator overnight, dissolved in methylene chloride, filtered, and evaporated to dryness in the cold to yield 3.18 g. of white solid. The infrared spectrum of this material in carbon disulfide solution showed carbonyl absorption at 1709 cm.$^{-1}$ (20-ketone) and 1718 cm.$^{-1}$ (sh) (3-ketone) as well as absorption bands consistent with the presence of a benzyl ether grouping and weak hydroxyl absorption. The carbonyl absorptions of another sample in a potassium bromide pellet were at 1711 and 1693 cm.$^{-1}$. The remainder of the product was carried to the next step without additional purification by solution in 500 ml. of redistilled 95% ethanol and shaking with hydrogen in the presence of several grams of W-2 Raney nickel at room temperature and atmospheric pressure. The reaction mixture was filtered and solvent removed. The product was triturated with a small volume of ether. The ether-insoluble material (1.54 g.) had a strong carbonyl absorption band at 1706 cm.$^{-1}$ in carbon disulfide solution and was presumably a mixture of 3α + β,16α-dihydroxy-Δ^5-pregnen-20-one (L). Since the desired isomeric Δ^5-pregnene-3,16α,20-triols could be separated readily, no attempts at fractionation of the 3α- and 3β-hydroxy epimers of L were made.

Crude L (1.5 g.) was dissolved in a minimum amount of freshly distilled tetrahydrofuran and added to an excess of lithium aluminum hydride in ether. The reaction mixture was allowed to stand at room temperature for 40 hr. and then worked up in the usual fashion. The solid product was triturated with a small volume of ether and the residual solid (1.37 g.) was treated with 6 g. of digitonin in 100 ml. of 90% ethanol. This was allowed to stand at room temperature overnight and extracted with ethyl acetate. The solvent was removed and 872 mg. of crude "α-fraction" was obtained. The insoluble digitonide was dissolved in 35 ml. of pyridine, diluted with 2 l. of ethyl acetate, and filtered. The filtrate was washed with 10% hydrochloric acid, water, sodium bicarbonate solution, and finally with water, dried over anhydrous sodium sulfate, and distilled to give 500 mg. of crude "β-fraction."

The "β-fraction" was chromatographed on 175 g. of silica gel containing 70 ml. of ethanol on the stationary phase. Elution with 6% ethanol in methylene chloride yielded 110 mg. of Δ^5-pregnene-3β,16α,20α-triol (Ea) which melted at 243.5–245.5° after recrystallization from methanol. Further elution with 6% and 8% ethanol in methylene chloride gave 270 mg. of Δ^5-pregnene-3β,16α,20β-triol (D), m.p. 268, 280–287°; the infrared spectrum in potassium bromide dispersion was identical with that of D obtained in the previous synthesis. The sample was free of impurity as judged by thin layer chromatography on silica gel G with ethyl acetate.

The "α-fraction" was chromatographed on 150 g. of silica gel and 60 ml. of ethanol. Elution with 4% ethanol in methylene chloride gave 83 mg. of **Δ^5-pregnene-3α,16α,20α-triol (Ha)** which melted at 229.5–230° after recrystallization from ethanol. The infrared spectrum in a potassium bromide dispersion was identical in all respects with that of the triol from natural sources. Acetylation with acetic anhydride and pyridine yielded the triacetate Hb, m.p. 136–137°, after recrystallization from methanol. The triacetate prepared from the urinary triol had m.p. 133–135°; m.m.p. was 137–139°. The infrared spectra of the two samples were identical in all respects in carbon disulfide solution.

Elution with 5% ethanol in methylene chloride gave 355 mg. of fractions containing Δ^5-pregnene-3α,16α,20β-triol (M), m.p. 224–225°, after recrystallization from methanol; $[\alpha]^{27}D$ −94.3° (ethanol); ν_{max}^{KBr} 3530 (sh), 3460, 3390, 1663, 1086, 1064, 1049, 1020, 881, 867, 804 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.23; H, 10.15.

The **triacetate** was prepared by the action of acetic anhydride in pyridine and melted at 137.5–140° after several recrystallizations from methanol; $[\alpha]^{26}D$ −81.6°; $\nu_{max}^{CS_2,\ CCl_4}$ 1738, 1667, 1239, 1158–1151 (sh), 1046, 1035, 1020 cm.$^{-1}$. Further elution with 5% ethanol in methylene chloride gave small amounts of Δ^5-pregnene-3β,16α,20β-triol (D) identical with that isolated from the β-fraction.

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Secondary Hydrogen Isotope Effects on Deoxymercuration[1]

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Secondary isotope effects on the rate of acid-induced deoxymercuration of 2-phenyl-2-methoxyethylmercuric iodide have been studied. Deuterium substitution at the 2-carbon gives k_H/k_D, 1.12. Deuterium substitution at the 1-carbon gives k_H/k_D, 0.91. The latter is one of a small number of inverse isotope effects that have been observed. From these and results previously presented it is concluded that the deoxymercuration transition state has a partial positive charge on the carbon from which oxygen is leaving and also has some olefin–mercuric iodide complex character.

In a previous paper[2] the acid-induced deoxymercuration rate for $CH_3OCD_2CD_2HgI$ (II) was compared with that for $CH_3OCH_2CH_2HgI$ (I). They were very similar (k_H/k_D = 1.06), and from this it was concluded that the transition state must resemble the protonated starting state, IX. More recent studies of relative reactivities[3] indicate that this view was oversimplified. It was shown that either the carbonium ion, VII, or the olefin mercuric iodide complex, VIII, or both, must contribute to the transition state electronic structure. The present paper describes further work on secondary hydrogen isotope effects, involving isotopic substitution in $C_6H_5CH(OCH_3)CH_2HgI$ (III) designed to shed more light on the electronic structure of the transition state and to explain the apparent discrepancy between the results obtained from the secondary isotope effect and those obtained from the effect of substitution.

Results

Well established synthetic methods were used to prepare III, $C_6H_5CD(OCH_3)CH_2HgI$ (IV), $C_6H_5CH(OCH_3)CD_2HgI$ (V), and $C_6H_5CD(OCH_3)CD_2HgI$ (VI). Acid-induced deoxymercuration rates were

(1) This work was supported by the Air Force Office of Scientific Research through contract no. AF 49(638)711. Reproduction in whole or in part is permitted for any purpose of the U. S. Government.

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measured for all of these in water containing 2% of methanol at 25.0°. First-order rate constants were evaluated spectrophotometrically in the usual way.[2] The acid was provided by acetic acid–sodium acetate buffers. Second-order rate constants, k, were obtained by dividing the first-order rate constants by the hydronium ion concentration. Ratios of rates were evaluated by comparing rates obtained from solutions that were made up from the same buffers and were run in the cell block at the same time, so that there would be no possibility of temperature or buffer discrepancies. Table I reports the mean of the various second-order rate constants, the probable error of each rate constant,[4] the ratio of k_{III} to each k, and the probable error of each ratio, as estimated from the average deviation from the mean of ratios of rate constants obtained simultaneously. Each reported mean value was obtained from four to six individual determinations.

TABLE I

KINETIC ISOTOPE EFFECTS IN THE DEOXYMERCURATION OF $C_6H_5CH(OCH_3)CH_2HgI$

Compound	k	Δk	k_{III}/k	$\Delta(k_{III}/k)$
III	12.16	0.08		
IV	11.03	.10	1.12	0.02
V	13.62	.13	0.91	.02
VI	11.50	.07	1.07	.02

In addition to random errors in measuring, rates k_{IV} may be a little high and k_{III}/k_{IV} a little low (each by a factor of 1.02) due to isotopic contamination. This is discussed in the Experimental.

It is not strictly required by theory that k_{III}/k_{VI} should be exactly given by the product of k_{III}/k_{IV} and k_{III}/k_V, but in other cases[5-7] where the data is sufficiently extensive such a product relationship has been found to hold approximately. Such a relationship is in accord with the rule of the geometric mean.[8] It is, therefore, reassuring that the present data does conform to such a pattern within the combined experimental uncertainties.

Spectroscopic Results.—Infrared spectra were made using a Perkin-Elmer Model 421 infrared spectrophotometer of thin liquid films of compounds III–VI. These serve to identify the stretching frequencies associated with the methylene and methine groups, but a complete experimental assignment of frequencies for molecules of this complexity is beyond our present capacity. The stretching frequencies are shown in Table II.

TABLE II

ALIPHATIC STRETCHING FREQUENCIES IN CM.$^{-1}$ FOR $C_6H_5CH(OCH_3)CH_2HgI$ AND ITS ISOTOPIC VARIANTS

Compound	Methine	Methylene (sym.)	Methylene (assym.)
III	2885	2910	2850
IV	2107	2910	2850
V	2885	2231	2138
VI	2107	2231	2138

Discussion

The results of isotopic substitution at the hydrogen α to the methoxy group is in good accord with data for other reactions whose rate-determining steps produce carbonium ions or related species.[5,6,9,10] Values of k_H/k_D are generally in the range 1.10 to 1.20 per isotopic substitution, and the present value falls well within that range. Such isotope effects have been attributed primarily to a lowering of one of the bending frequencies in the transition state,[5] and there is no reason to question that interpretation in the present case.

Inverse secondary hydrogen isotope effects are not without precedent,[11,12] although they seem to be fairly rare. The effect observed on deuterium substitution in the methylene group may be the result of an alteration of vibrational frequencies toward those appropriate to the olefin–mercuric ioide π-complex in the transition state. It previously has been pointed out that such a change would probably lead to an inverse isotope effect.[2]

It should be pointed out that both the previous prediction and the present results (for substitution in the methylene group) imply that it is possible to progress toward sp^2 hybridization from sp^3 hybridization with $k_H/k_D < 1.0$ at the carbon atom undergoing the change. Since this takes place without the intervention of a new incoming group, it is contrary to a previous suggestion that such changes should always $k_H/k_D > 1.0$.[5,13,14] It must be admitted, however, that deoxymercuration involves rather special structures and may be a special case. The reported stretch-in frequencies show no anomalies, which suggests that the origin of the effect is not in the starting state.

It now seems likely that the very small isotope effect previously observed[2] was due to an approximate cancellation of two effects of opposite sign, rather than to a transition state closely resembling the starting state, as was previously assumed. This, of course, resolves the apparent conflict between the conclusions previously based on the isotope effect and those based on relative reactivity[3] in favor of the latter. There is a substantial charge deficit in the transition state at the carbon from which the methoxy group is leaving. In terms of resonance structures there are important contributions to the transition state from VII as well as from the protonated starting state, IX. The explanation given before for the effect of deuterium substitution in the methylene group would also require significant contributions from VIII, but there is no evidence for the participation of X. The significant participation of X would probably yield $k_H/k_D > 1.0$ for deuterium substitution in the methylene group.

It is interesting that the quantitative parallel between the present results and the earlier ones[2] is not too good.

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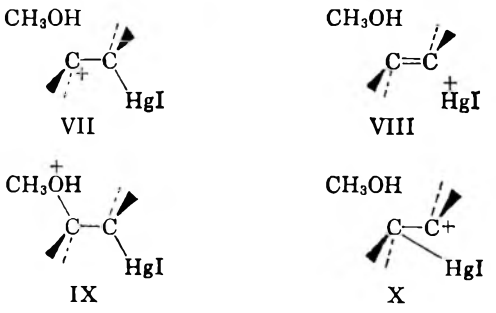

If it is assumed that double isotopic substitution at the hydrogens α to the methoxy group in I would contribute a factor $(k_{III}/k_{IV})^2$ to k_I/k_{II}, and that the isotopic substitution of the hydrogens α to the iodomercuri group would contribute a factor k_{III}/k_V, then k_I/k_{II} would be ~1.14. This probably should be multiplied by a further factor of 1.035 arising from the pre-exponential ratio of reduced masses[2] to give a calculated value of ~1.18 for k_I/k_{II}. Although still small this is considerably larger than the value, 1.06, actually found. These results support the suggestion that quantitative changes in the transition state electronic structure accompany the introduction of an alkyl group on the carbon atom bearing the methoxy group. These changes probably involve the incorporation of more carbonium ion character at that position. On the other hand it is possible that the lack of quantitative correspondence is due to the fortuitous accumulation of mechanical factors[15] and/or experimental errors and is without significance.

Experimental

All the isotopic versions of 2-phenyl-2-methoxyethylmercuric iodide were prepared from the corresponding styrenes by Schaleger's method,[3] and each had m.p. ~30°. In each case, the styrene was prepared from the corresponding 1-phenylethanol by the method of Berstein, Bennett, and Fields.[16]

An ethereal solution of 2.06 g. (0.0492 mole) of lithium aluminum deuteride (Metal Hydrides, 99.5%) was added slowly from a dropping funnel to 35.3 g. (0.294 mole) of acetophenone dissolved in 200 ml. of dry ether to give 1-deuterio-1-phenylethanol after 2 hr. of refluxing followed by hydrolysis with an ethanol–water mixture. The usual precautions to exclude water were observed prior to the hydrolysis. An excess of acetophenone was used, and the usual order of the addition was reversed in order to minimize the possibility of deuterium substitution at the 2-carbon.

In a similar manner 2,2,2-trideuterio-1-phenylethanol was prepared from trideuterioacetophenone and lithium aluminum hydride. The trideuterioacetophenone was prepared by shaking acetophenone with three successive portions of sodium deuteroxide in excess deuterium oxide. Each shaking was continued until the infrared spectrum of the acetophenone showed no further change. The first shaking required about 1 hr. and each of the others about 0.5 hr.

The 1,2,2,2-tetradeuterio-1-phenylethanol was prepared from trideuterioacetophenone and lithium aluminum deuteride in a similar fashion.

The 1-phenylethanols were converted to styrenes without purification or weighing. The over-all yields of styrene were around 18% based on the lithium aluminum hydride or deuteride which was the limiting reagent in each case. The styrenes each showed only one peak in vapor phase chromatography.

To estimate isotopic purity, n.m.r. spectra of compounds III–VI were obtained in carbon tetrachloride solution. Each of these showed an aromatic band at τ ~2.7 p.p.m. and a sharp singlet at τ 6.65 p.p.m., attributed to the methoxy group. In addition III showed a band with the appearance of a triplet centering at τ 7.56 p.p.m., and a second triplet, with about half the intensity of the first, centering at 5.20 p.p.m. The former is attributed to the methylene group, the two protons being nonequivalent[17] and each signal being split by the methine proton. If the central lines are unresolved, the band has the appearance of a triplet. The smaller triplet is attributed to the methine proton. Again a quartet is predicted but a triplet would result if the central lines were unresolved. In the spectrum of IV the larger triplet becomes, roughly, a doublet, and the smaller triplet all but disappears. From the residual intensity of the smaller triplet a minimum isotopic purity of 85% can be estimated. In the spectrum of V no trace of the larger triplet can be found, and the methine band appears as a single peak. Assuming that a peak twice the height of the noise would have been detected a minimum isotopic purity of 90% is estimated. Neither methylene nor methine signal can be detected in the spectrum of VI and with the same assumption about detectability 90% isotopic purity is again estimated. The latter two values indicate that k_{III}/k_V and k_{III}/k_{VI} given in Table I are not appreciably in error due to isotopic impurity. However it is possible that k_{III}/k_{IV} may be in error by as much as a factor of 1.02 due to isotopic contamination. None of the conclusions discussed previously would be altered by such an error. The n.m.r. spectra were obtained on a Varian Model 4311 high resolution spectrometer operating at 56 Mc. Tetramethylsilane was used as an internal reference.[18]

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Derivatives of 6,8-Dihydroxyflavone

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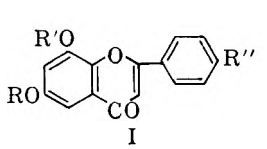
Conditions are described for the preparation of 2-hydroxy-3,5-dimethoxyacetophenone and from this, 6,8-dimethoxyflavone and -flavonol, their 4′-methyl ethers, and the corresponding hydroxy compounds. Under mild demethylating conditions, 6,8-dimethoxyflavone and its derivatives suffer selective cleavage of the 6-methoxyl group giving compounds whose structures have been established by synthesis.

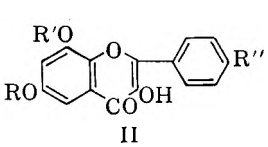
6,8-Dihydroxyflavone and its derivatives have proved unexpectedly difficult to synthesize because the preferred intermediate, 2-hydroxy-3,5-dimethoxyacetophenone, has been difficultly accessible. An account[1] of the preparation, in 4% yield, of 6,8-dimethoxyflavone by Mentzner's method[2] and a note[3] on the synthesis of that compound and its 4′-methyl ether by the present method have been published.

Since early attempts[4] to synthesize 2,5-dihydroxy-3-methoxyacetophenone resulted in poor yields, an alternative route to this compound was examined. 2-Hydroxy-3-methoxyacetophenone was coupled with diazotized sulfanilic acid and the resulting azo dye reduced to 5-amino-2-hydroxy-3-methoxyacetophenone. Attempts to complete the final stage of the synthesis, namely replacement of the amino group by hydroxyl, were not successful immediately. This route, therefore, was abandoned when it was found that the Elbs[5,6] persulfate oxidation of 2-hydroxy-3-methoxyacetophenone, under modified conditions, furnished the desired quinol in good yields. Partial methylation of the quinol with molar quantities of methyl sulfate then gave 2-hydroxy-3,5-dimethoxyacetophenone.

The last compound was condensed with benzaldehyde and with anisaldehyde to give the corresponding chalcones. Oxidative cyclization with selenium dioxide[7] then provided the flavones (I, R″ = H and OCH_3, R = R′ = CH_3) and treatment with alkaline hydrogen peroxide[8] afforded the flavonols (II, R = R′ = CH_3, R″ = H, and R = R′ = CH_3, R″ = OCH_3). On demethylation by hydrobromic acid these furnished the corresponding hydroxyflavones (I, R = R′ = R″ = H and R = R′ = H, R″ = OH) and hydroxyflavonols (II, R = R′ = R″ = H and R = R′ = H, R″ = OH). 3-Hydroxy-4,6,8-trimethoxyflavone proved unexpectedly difficult to demethylate in this way, but was smoothly converted to the tetrahydroxy compound by treatment with magnesium iodide.[9]



I



II

On heating with hydrobromic acid for much shorter periods than were necessary to achieve complete demethylation, 6,8-dimethoxyflavone and 3-hydroxy-6,8-dimethoxyflavone were found to yield monomethyl ethers and 4′,6,8-trimethoxyflavone a dimethyl ether. It seemed likely that these were 6-hydroxy compounds since the positive charge on the pyrone oxygen atom, arising either from direct protonation or from its conjugation with the protonated ring carbonyl group, would be expected to hinder the approach of hydroxonium ions to the 8-methoxyl group. The 6-methoxyl group, being unconjugated with the pyrone carbonyl, would, in contrast, be expected to cleave readily.[10] Similarly, the dihydroxy compound obtained from 4′,6,8-trimethoxyflavone under slightly more vigorous conditions was expected to be 4′,6-dihydroxy-8-methoxyflavone. These predictions were confirmed by synthesis of authentic 6-hydroxy-8-methoxyflavones from appropriate isopropylated intermediates.[11] 2,5-Dihydroxy-3-methoxyacetophenone was treated with isopropyl sulfate giving 2-hydroxy-3-methoxy-5-isopropoxyacetophenone, which on condensation with benzaldehyde, anisaldehyde, and with *p*-isopropoxybenzaldehyde yielded the corresponding chalcones. Dehydrogenation with selenium dioxide and oxidation with alkaline hydrogen peroxide furnished the isopropoxymethoxyflavones and -flavonols, which were then deisopropylated under mild conditions.

4′-Hydroxy-6,8-dimethoxyflavone, and -flavonol, required to complete the series, were prepared in the same way from 4-benzyloxy-2′-hydroxy-3′,5′-dimethoxychalcone with subsequent removal under acid conditions of the benzyl group.

Experimental

All melting points were determined on a Kofler block and are corrected.

2,5-Dihydroxy-3-methoxyacetophenone. (a).—The diazonium salt prepared from sulfanilic acid (0.28 g.) was added with shaking to an ice-cold suspension of 2-hydroxy-3-methoxyacetophenone[12] (0.2 g.) in 4% aqueous sodium hydroxide (5 ml.). After 1 hr., the azo dye was collected, dissolved in 4% aqueous sodium hydroxide, reduced by the addition of excess sodium hydrosulfite, and the solution neutralized with hydrochloric acid. After being saturated with ammonium sulfate, the pale yellow solution was exhaustively extracted with ether and the extract evaporated *in vacuo* to give a residue which on crystallization from benzene–petroleum ether (b.p. 80–100°) furnished 5-amino-2-hydroxy-3-methoxyacetophenone as yellow prisms (0.09 g.), m.p. 145.5–147°.

Anal. Calcd. for $C_9H_{11}O_3N$; C, 59.7; H, 6.1; N, 7.7. Found: C, 59.8; H, 6.1; N, 7.6.

(1) J. E. Gowan, S. P. M. Riogh, G. T. MacMahon, S. O'Cleirigh, E. M. Philbin, and T. S. Wheeler, *Chem. Ind.* (London), 1672 (1955); *Tetrahedron*, **2**, 116 (1958).

(2) C. Mentzner, D. Molho, and P. Vercier, *Compt. rend.*, **232**, 1488 (1951).

(3) T. H. Simpson, *Chem. Ind.* (London), 1672 (1955).

(4) W. Baker, N. C. Brown, and J. A. Scott, *J. Chem. Soc.*, 1922 (1939).

(5) K. Elbs, *J. prakt. Chem.*, **48**, 179 (1893).

(6) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).

(7) H. S. Mahal and K. Venkataraman, *ibid.*, 569 (1936).

(8) J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, **42B**, 1 (1934).

(9) A. Schonberg and R. Moubasher, *J. Chem. Soc.*, 462 (1944).

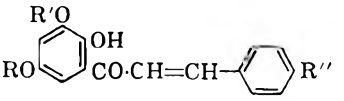
(10) T. H. Simpson and J. L. Beton, *ibid.*, 4065 (1954).

(11) T. H. Simpson, *Sci. Proc. Roy. Dublin Soc.*, **27**, 111 (1956).

(12) W. Baker and A. R. Smith, *J. Chem. Soc.*, 347 (1936).

TABLE I

CHALCONES

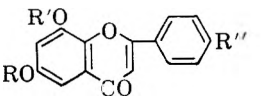


R	R′	R″	Crystalline form	M.p., °C.	Yield,[a] %	Molecular formula	—Calcd.— C	H	—Found— C	H
CH_3	CH_3	H	Garnet prisms	81–83	80	$C_{17}H_{16}O_4$	71.8	5.7	71.8	5.7
CH_3	CH_3	CH_3O	Garnet prisms	121.5–122.5	85	$C_{18}H_{18}O_5$	68.8	5.8	69.0	5.8
$(CH_3)_2CH$	CH_3	H	Red prisms	73–74	70	$C_{19}H_{20}O_4$	73.1	6.5	72.9	6.4
$(CH_3)_2CH$	CH_3	CH_3O	Red needles	112–113	70	$C_{20}H_{22}O_5$	70.2	6.5	70.3	6.5
$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Red needles	92–94	70	$C_{22}H_{26}O_5$	71.3	7.1	71.3	7.1
CH_3	CH_3	$C_6H_5CH_2O$	Red prisms	172–174	60	$C_{24}H_{22}O_5$	73.8	5.7	73.6	5.9

[a] Based on quantity of ketone.

TABLE II

FLAVONE DERIVATIVES



R	R′	R″	Crystalline form	M.p., °C.	Yield, %	Molecular formula	—Calcd.— C	H	OCH_3	—Found— C	H	OCH_3
CH_3	CH_3	H	Cream colored needles	148–149 and[a] 152–153 (dimorphic)	75	$C_{16}H_8O_2(OCH_3)_2$	72.3	5.0	21.9	72.3	5.1	22.0
CH_3	CH_3	CH_3O	Cream colored needles	187–187.5	80	$C_{16}H_7O_2(OCH_3)_3$	69.2	5.2	29.7	69.3	5.2	29.7
$(CH_3)_2CH$	CH_3	H	Colorless needles	150–151	70	$C_{19}H_{16}O_4$	73.5	5.9	...	73.6	5.8	...
$(CH_3)_2CH$	CH_3	CH_3O	Cream colored prisms	182–183	70	$C_{20}H_{20}O_5$	70.6	5.9	...	70.6	5.8	...
$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Colorless prisms	94–96	65	$C_{22}H_{24}O_5$	71.7	6.6	...	71.7	6.5	...
CH_3	CH_3	$C_6H_5CH_2O$	Yellow needles	183–185	70	$C_{24}H_{20}O_5$	74.2	5.2	...	74.3	5.3	...
H	H	H	Yellow needles	278 dec.[a]	80	$C_{15}H_{10}O_4$	70.9	4.0	...	71.0	4.2	...
CH_3CO	CH_3CO	H	Colorless needles	198–200[a]	..	$C_{16}H_{14}O_5$	67.5	4.2	...	67.4	4.2	...
H	H	HO	Yellow needles	>300 dec.	80	$C_{15}H_{10}O_5$	66.7	3.7	...	66.5	3.7	...
CH_3CO	CH_3CO	CH_3COO	Colorless needles	240–242	..	$C_{21}H_{16}O_8$	63.6	4.1	...	63.8	4.2	...
C_2H_5	C_2H_5	C_2H_5O	Colorless prisms	161–162	..	$C_{15}H_7O_2(OC_2H_5)_3$	72.2	6.3	38.1	71.1	6.3	38.8
H	CH_3	H	Pale yellow needles	244–245	65	$C_{16}H_9O_3OCH_3$	71.6	4.5	11.6	71.4	4.6	11.5
CH_3CO	CH_3	H	Colorless needles	190–192	..	$C_{18}H_{14}O_5$	69.7	4.6	...	69.8	4.7	...
H	CH_3	CH_3O	Yellow needles	257–259 dec.	60	$C_{16}H_9O_3(OCH_3)_2$	68.5	4.7	20.8	68.4	4.8	20.5
CH_3CO	CH_3	CH_3O	Colorless needles	206–209	..	$C_{19}H_{16}O_6$	67.1	4.8	...	67.0	4.9	...
H	CH_3	HO	Yellow needles	>288 dec.	60	$C_{15}H_9O_4OCH_3$	67.6	4.3	10.9	67.8	4.2	10.6
CH_3CO	CH_3	CH_3COO	Colorless needles	215–217	..	$C_{20}H_{16}O_7$	65.2	4.4	...	65.1	4.3	...
CH_3	CH_3	HO	Pale yellow prisms	199–200	85	$C_{16}H_9O_3(OCH_3)_2$	68.5	4.7	20.8	68.3	4.7	20.5
CH_3	CH_3	CH_3COO	Colorless needles	172–175	..	$C_{19}H_{16}O_6$	67.0	4.8	...	67.1	4.8	...

[a] See ref. 1.

Attempts to convert this compound to the corresponding quinol by diazotization and hydrolysis or to the intermediate quinone by oxidation were unsuccessful.

(b).—A saturated solution of potassium persulfate (18 g., 0.066 mole) at 0° was added during 2 hr. to an ice-cold suspension of 2-hydroxy-3-methoxyacetophenone (10 g., 0.06 mole) in 10% aqueous sodium hydroxide (60 ml., 0.15 mole) containing sodium sulfite (7.6 g.); stirring was continued and the temperature maintained at 0° for a further 18 hr. The solution was then neutralized by hydrochloric acid, precipitated starting ketone (1.2 g.) recovered, and filtrate extracted with ether (three 50-ml. portions). Benzene (300 ml.) and sodium sulfite (7 g.) were added to the aqueous liquor, the mixture made strongly acid by the addition of concentrated hydrochloric acid (100 ml.), and then heated under reflux for 20 min. After cooling, the benzene layer was separated and the aqueous layer extracted with ether (four 100-ml. portions). Evaporation of the combined benzene and ether extracts to low bulk and cooling furnished 2,5-dihydroxy-3-methoxyacetophenone in yellow prisms (2.8 g.), m.p. 173–176°, which after crystallization from benzene and from water had m.p. 172–174° (lit.[4] m.p. 172°). Its diacetate formed colorless plates, m.p. 127–128° (lit.[4] m.p. 127°), from methanol.

2-Hydroxy-3,5-dimethoxyacetophenone and 2-Hydroxy-3-methoxy-5-isopropoxyacetophenone.—A solution of the foregoing quinol (5 g.) and methyl sulfate (4.2 g.) in acetone (50 ml.) was refluxed with excess anhydrous potassium carbonate in an atmosphere of carbon dioxide. After 3 hr. the mixture was filtered, the combined filtrate and washings evaporated *in vacuo*, and the residue dissolved in ether (100 ml.). After washing with 2% aqueous sodium carbonate (three 20-ml. portions), the ether layer was extracted with aqueous sodium hydroxide (4%, six 150-ml. portions) and the extract acidified. 2-Hydroxy-3,5-dimethoxyacetophenone was obtained in yellow needles (2.9 g.), m.p. 84–86°, from ethanol.

Anal. Calcd. for $C_8H_6O_2(OCH_3)_2$: C, 61.2; H, 6.2; OCH_3, 31.6. Found: C, 61.4; H, 6.2; OCH_3, 31.3.

It gave an intense red ferric coloration in ethanol. Its **2,4-dinitrophenylhydrazone** formed red needles, m.p. 246–248°, from *n*-butyl alcohol.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.1; H, 4.3; N, 14.9. Found: C, 51.1; H, 4.2; N, 14.8.

Partial isopropylation of the same quinol (5 g.) with isopropyl sulfate (6 g.) was carried out in the same way and furnished 2-hydroxy-3-methoxy-5-isopropoxyacetophenone in yellow prisms (2.5 g.), m.p. 70–72°, from aqueous ethanol; it gave a red ethanolic ferric coloration.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.2.

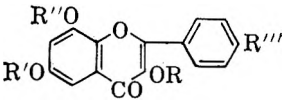
Its 2,4-dinitrophenylhydrazone formed red needles, m.p. 242–245°.

Anal. Calcd. for $C_{18}H_{20}O_7N_4$: C, 53.5; H, 5.0; N, 13.9. Found: C, 53.5; H, 4.8; N, 13.9.

Preparation of Chalcones.—Aqueous sodium hydroxide (3 g.) was added with shaking to a solution of one of the *o*-hydroxy ketones described before (1 g.) and an excess of the appropriate aldehyde, *viz.*, benzaldehyde (1.5 g.), anisaldehyde (1.5), *p*-isopropoxybenzaldehyde (2–3 g.), or *p*-benzyloxybenzaldehyde (3 g.) in ethanol (10 ml.). After 1 hr., the reaction product was diluted with water, acidified, and extracted with ether. The extract was then washed in succession with 2% aqueous sodium hydrogen carbonate, 25% aqueous sodium hydrogen sulfite, and then water. Evaporation of the ether furnished the chalcone which

TABLE III

FLAVONOL DERIVATIVES



R	R′	R″	R‴	Crystalline form	M.p., °C.	Yield %	Molecular formula	Calcd. C	Calcd. H	Calcd. OCH_3	Found C	Found H	Found OCH_3
H	CH_3	CH_3	H	Cream colored prisms	198–200	66	$C_{16}H_8O_3(OCH_3)_2$	68.5	4.7	20.8	68.4	4.7	21.1
CH_3CO	CH_3	CH_3	H	Colorless needles	194–196	..	$C_{19}H_{16}O_6$	67.1	4.8	...	67.0	4.8	...
CH_3	CH_3	CH_3	H	Colorless plates	165–166	..	$C_{15}H_7O_2(OCH_3)_3$	69.2	5.2	29.8	69.4	5.4	29.9
H	CH_3	CH_3	CH_3O	Cream colored prisms	218–220	75	$C_{15}H_7O_3(OCH_3)_3$	65.9	4.9	27.8	65.8	4.7	28.0
CH_3CO	CH_3	CH_3	CH_3O	Colorless needles	119–122	..	$C_{20}H_{18}O_7$	64.9	4.9	...	64.8	4.8	...
CH_3	CH_3	CH_3	CH_3O	Colorless prisms	164–165 and 167–168 (dimorphic)	..	$C_{15}H_6O_2(OCH_3)_4$	66.7	5.3	36.3	66.7	5.2	36.4
H	$(CH_3)_2CH$	CH_3	H	Cream colored needles	183–184	60	$C_{18}H_{18}O_5$	69.9	5.6	...	69.7	5.5	...
CH_3CO	$(CH_3)_2CH$	CH_3	H	Colorless prisms	205–206	..	$C_{21}H_{20}O_6$	68.5	5.5	...	68.5	5.5	...
H	$(CH_3)_2CH$	CH_3	CH_3O	Cream colored prisms	163–164	65	$C_{20}H_{20}O_6$	67.4	5.7	...	67.4	5.7	...
CH_3CO	$(CH_3)_2CH$	CH_3	CH_3O	Colorless prisms	178–180	..	$C_{22}H_{22}O_7$	66.3	5.6	...	66.6	5.6	...
H	$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Pale yellow needles	152–155 and 160–161 (dimorphic)	60	$C_{22}H_{24}O_6$	68.7	6.3	...	68.7	6.2	...
CH_3CO	$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Colorless needles	155–156	..	$C_{24}H_{26}O_7$	67.6	6.2	...	67.7	6.2	...
H	CH_3	CH_3	$C_6H_5CH_2O$	Yellow needles	198–200	65	$C_{24}H_{20}O_6$	71.3	5.0	...	71.5	4.8	...
CH_3CO	CH_3	CH_3	$C_6H_5CH_2O$	Colorless prisms	191–193	..	$C_{26}H_{22}O_7$	69.9	5.0	...	70.1	5.2	...
H	H	H	H	Yellow needles	257–260	85	$C_{15}H_{10}O_5$	66.7	3.7	...	66.7	3.9	...
CH_3CO	CH_3CO	CH_3CO	H	Colorless needles	181–183	..	$C_{21}H_{16}O_8$	63.6	4.1	...	63.7	4.2	...
H	H	H	HO	Pale yellow needles	>300 dec.	55	$C_{15}H_{10}O_6$	62.9	3.5	...	62.9	3.7	...
CH_3CO	CH_3CO	CH_3CO	CH_3COO	Colorless needles	211–213	..	$C_{23}H_{18}O_{10}$	60.8	4.0	...	60.9	4.1	...
H	H	CH_3	H	Colorless needles	258–262 dec.	65	$C_{15}H_8O_4.O.CH_3$	67.6	4.3	10.9	67.7	4.2	10.7
CH_3CO	CH_3CO	CH_3	H	Colorless needles	211–212	..	$C_{20}H_{16}O_7$	65.2	4.4	...	65.1	4.4	...
H	H	CH_3	CH_3	Pale yellow needles	258–264 dec.	65	$C_{15}H_8O_4(OCH_3)_2$	65.0	4.5	19.7	64.9	4.3	20.1
CH_3CO	CH_3CO	CH_3	CH_3	Colorless prisms	176 and 194.5 (dimorphic)	..	$C_{21}H_{16}O_8$	63.3	4.6	...	63.3	4.6	...
H	H	CH_3	HO	Pale yellow needles	>300° dec.	65	$C_{15}H_8O_6OCH_3$	64.0	4.0	10.3	64.0	4.1	10.4
CH_3CO	CH_3CO	CH_3	CH_3COO	Colorless needles	219–222	..	$C_{22}H_{18}O_9$	62.0	4.3	...	62.0	4.4	...
H	CH_3	CH_3	HO	Pale yellow needles	260 dec.	80	$C_{16}H_8O_4(OCH_3)_2$	65.0	4.5	19.7	65.0	4.4	19.3
CH_3CO	CH_3	CH_3	CH_3COO	Colorless needles	188–191	..	$C_{21}H_{18}O_8$	63.3	4.6	...	63.5	4.8	...

was purified by crystallization from ethanol, in the case of methyl ethers, or in the case of isopropyl compounds, petroleum ether (80–100°). Melting points and crystalline forms of the chalcones together with the results of microanalyses are reported in Table I.

Oxidation of Chalcones with Selenium Dioxide.—A solution of the appropriate chalcone (1 g.) and excess selenium dioxide (resublimed, 3 g.) in *n*-pentyl alcohol (25 ml.) was heated under reflux for 18 hr., filtered, the residue washed repeatedly with boiling ethanol, and the combined filtrate and washings distilled in steam to remove the pentanol. The remaining solid was dissolved in chloroform, dried, and chromatographed on a column of alumina (Spence, grade "O") using chloroform as the eluent). Final purification of the flavone was achieved by crystallization from ethanol and from petroleum ether (b.p. 80–100°).

Analytical data, melting points, etc., of flavones prepared by this method are listed in the first section of Table II.

Oxidation of Chalcones with Alkaline Hydrogen Peroxide.—The following general method was used for the preparation of flavonols from chalcones. Aqueous sodium hydroxide (4%, 30 ml.) and hydrogen peroxide (100 vol., 10 ml.) were added in succession to a solution of the appropriate chalcone (200 mg.) in hot ethanol (15 ml.). After 15 min., the pale yellow solution was acidified and the precipitated flavonol then purified by crystallization from ethanol. Melting points, analytical data, etc., are listed in the first section of Table III. Acetates were prepared by the acetic anhydride–pyridine method and were crystallized from ethanol; methyl ethers were prepared by reaction with methyl sulfate in aqueous ethanolic sodium carbonate. All the flavonols gave intense red-brown colorations with ferric chloride in ethanol.

Complete Demethylation of Flavones and Flavonols.—A solution of the methoxy compound (200 mg.) in aqueous hydrobromic acid (48% w./w., 80 ml.) was heated under reflux for 5 hr., diluted with water, and partially neutralized with sodium hydroxide. The precipitated hydroxy compound was filtered, washed with water until neutral, and purified by crystallization from aqueous acetic acid and from aqueous ethanol.

3-Hydroxy-4′,6,8-trimethoxyflavone furnished only a poor yield of the desired tetrahydroxy compound, contaminated with much intractable resin when it was demethylated by the previous method; therefore, the following procedure was used. A solution of magnesium iodide, prepared from iodine (500 mg.) and excess magnesium in anhydrous ether (50 ml.), was added to 3-hydroxy-4′,6,8-trimethoxyflavone (50 mg.) in anhydrous benzene (20 ml.), the solvents were evaporated *in vacuo*, and the residue heated to 180° for 2 hr. The complex was then decomposed with dilute sulfuric acid and the precipitate collected and dissolved in boiling water. After being thrice extracted with boiling benzene, the aqueous solution was cooled, depositing 3,4′,6,8-tetrahydroxyflavone.

All the hydroxyflavonols prepared by these methods gave dark brown colorations with ferric chloride in ethanol; hydroxyflavones gave negative ferric reactions. Melting points, analytical results, etc., of these compounds and of their acetates, prepared by the pyridine–acetic anhydride method and crystallized from ethanol, are listed in the second section of Tables II and III.

Partial Demethylation of Flavones and Flavonols. (a) **6-Hydroxy-8-methoxyflavone.**—A solution of 6,8-dimethoxyflavone (170 mg.) in acetic acid (3.5 ml.) and hydrobromic acid (48% w./w., 25 ml.) was refluxed for 12 min., diluted with water, treated with sodium hydroxide, and extracted with ether to remove unchanged starting material. Acidification furnished a precipitate from which a small quantity of dihydroxyflavone was obtained by crystallization from aqueous ethanol. Chromatographic examination of the residue (85 mg.) on "Separa" paper using the upper phase of benzene–pyridine–water (100:0.6:100) as irrigant, showed it to contain two hydroxymethoxyflavones, one in relatively small concentration. Two crystallizations from benzene furnished pure 6-hydroxy-8-methoxyflavone (45 mg.).

(b) **6-Hydroxy-4,8-dimethoxyflavone.**—A solution of 4′,6,8-trimethoxyflavone (150 mg.) in acetic acid (4 ml.) and hydrobromic acid (48% w./w., 50 ml.) was refluxed for 20 min., diluted with water, and brought to pH 5.0 with sodium hydroxide. The resulting precipitate was dissolved in boiling aqueous acetic acid (50%, 50 ml.), the solution thrice extracted with boiling petroleum ether (b.p. 100–120°, 20 ml.), and the raffinate cooled, depositing needles (90 mg.). Crystallization from benzene–petroleum ether and from aqueous ethanol furnished 6-hydroxy-4′,8-dimethoxyflavone (65 mg.).

(c) **4′,6-Dihydroxy-8-methoxyflavone.**—A solution of the

trimethoxyflavone in the same quantities of acetic and hydrobromic acid as in the last experiment was refluxed for 40 min., diluted with water, neutralized, and the resulting precipitate dissolved in aqueous acetic acid (50%, 50 ml.) and extracted with boiling benzene (three 20-ml. portions). The cooled aqueous liquors deposited a solid which, after trituration with boiling benzene and crystallization from aqueous acetic acid, afforded 4′,6-dihydroxy-8-methoxyflavone.

(d) **3,6-Dihydroxy-8-methoxyflavone.**—3-Hydroxy-6,8-methoxyflavone (100 mg.) was partially demethylated in boiling acetic (5 ml.) and hydrobromic acids (48% w./w., 40 ml.) during 15 min., the product isolated as before, and dissolved in boiling aqueous acetic acid (50%, 75 ml.). After extraction with boiling petroleum ether (100–120°, three 20-ml. portions), the aqueous liquors were heated with charcoal. The yellow needles obtained on cooling were crystallized from benzene–petroleum ether and then from aqueous ethanol yielding 3,6-dihydroxy-8-methoxyflavone (24 mg.).

The melting points of these compounds were undepressed on admixture with the appropriate authentic specimen obtained from the corresponding isopropoxymethoxyflavone. All four compounds were readily soluble in aqueous sodium hydroxide but only the flavonol gave a ferric coloration (dark brown in ethanol). Analytical data, etc., of these compounds and their acetates, crystallized from ethanol or aqueous ethanol, are summarized in the third sections of Tables II and III.

Deisopropylation of Methoxyisopropoxyflavones.—The following general method of effecting selective cleavage of the isopropyl groups of isopropoxymethoxy compounds was employed. To a solution of the isopropoxymethoxyflavone or -flavonol (150 mg.) in boiling acetic acid (2 ml.), boiling hydrobromic acid (48% w./w., 10 ml.) was added; the mixture was heated for a further 3 min. and poured into water (100 ml.). The resulting solid was collected, washed with water, and freed from starting material either (if a flavone) by dissolving in aqueous sodium hydroxide and extracting uncleaved ethers with benzene or (if a flavonol) by dissolving in boiling aqueous acetic acid (1:1, 180 ml.) and extracting these with boiling petroleum ether (b.p. 100–120°, three 2-ml. portions). Purification from demethylated compounds was then effected by crystallization from aqueous acetic acid or aqueous methanol. The characteristics of hydroxymethoxyflavones and -flavonols prepared in this way, and of their acetates are listed in the third sections of Tables II and III.

4′-Hydroxy-6,8-dimethoxy- and 3,4′-Dihydroxy-6,8-dimethoxyflavones.—The corresponding 4-benzyl ethers (150 mg.) were dissolved in acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.), heated in the steam bath for 1 hr., and evaporated *in vacuo*. Crystallization of the residue from aqueous ethanol furnished the 4′-hydroxyflavones; melting points, analytical data, etc., of these compounds and of their acetates are recorded in the third sections of Tables II and III.

Acknowledgment.—The work described in this paper forms a part of the program of the Torry Research Station of the Department of Scientific and Industrial Research.

The Δ^4-Ethylene Ketals of Testosterone and Testosterone Acetate[1]

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Ketalization of testosterone acetate with ethylene glycol by conventional methods with a low concentration of *p*-toluenesulfonic acid catalyst produced a mixture of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate and the well known Δ^5-ketal. Under similar conditions, analogous results were obtained with testosterone. The structures of these new isomeric ketals have been demonstrated by both chemical and physical methods. The Δ^4-ketal of testosterone acetate has been converted by acid catalysis to its Δ^5-isomer.

During the preparation of the ethylene glycol ketal of testosterone acetate (3,3-ethylenedioxyandrost-5-en-17β-ol acetate) as an intermediate for other work, a compound having markedly different physical properties was isolated in fair yield (34%), in addition to the desired product. The analytical data of the new compound were correct for the desired Δ^5-ketal, but the compounds differed in melting point (159–161° *vs.* 202–204° for the known[2] ketal) and in optical rotation (+80.0° *vs.* −52.1° for the known ketal). Neither compound absorbed in the ultraviolet region of the spectrum. A comparison of the infrared spectra showed only minor differences, the most notable of which was the appearance of a weak absorption band at 6.04–6.05 μ in the spectrum[3] of the isomeric compound; a less well defined weak band appeared in the spectrum of the known ketal just below 6.00 μ. These observations led to the tentative conclusion that the isomeric ketal (II, see Fig. 1) possessed a double bond in position 4,5 of the steroid nucleus, in contrast to the 5,6-double bond of the known compound.

Saponification of the acetoxy ketal II led to a hydroxy ketal III which was isomeric with the known Δ^5-ketal[2] of testosterone. Differing physical properties were evident here as with the 17β-acetoxy compounds; there was a different melting point (225–232° *vs.* 185–187° for the known Δ^5-ketal) and a difference in optical rotation (+95.1° *vs.* −45.5° for the Δ^5-isomer). In addition, the infrared spectrum of the new hydroxy ketal displayed a weak absorption band at 6.04 μ in contrast to the 5.98-μ band[3] of the known Δ^5-compound[2] V.

By azeotropic ketalization of testosterone (IV) under similar conditions the Δ^4-ketal of testosterone III was prepared in 30% yield, along with the known Δ^5-ketal V (26% yield). Compound III was identical with that obtained by saponification of the Δ^4-ketal of testosterone acetate and could be converted to the latter by acetylation (see Fig. 1).

Of particular interest were the molar rotational differences between the members of each pair of isomeric compounds.

	ΔM_D
M_D of Δ^4-17β-Acetoxy ketal II (+300) *minus* M_D of Δ^5-17β-Acetoxy ketal VI (−195)	= 495
M_D of Δ^4-17β-Hydroxy ketal III (+320) *minus* M_D of Δ^5-17β-Hydroxy ketal V (−151)	= 471

(1) Abstracted in part from the Ph.D. dissertation of J. W. D., Rensselaer Polytechnic Institute, January, 1962.

(2) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(3) G. Roberts, B. S. Gallagher, and R. N. Jones, "Infrared Absorption Spectra of Steroids," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1958, p. 11. Δ^5-Steroids are reported to absorb in the 5.97–6.00-μ region, and Δ^4-compounds at *ca.* 6.04 μ.

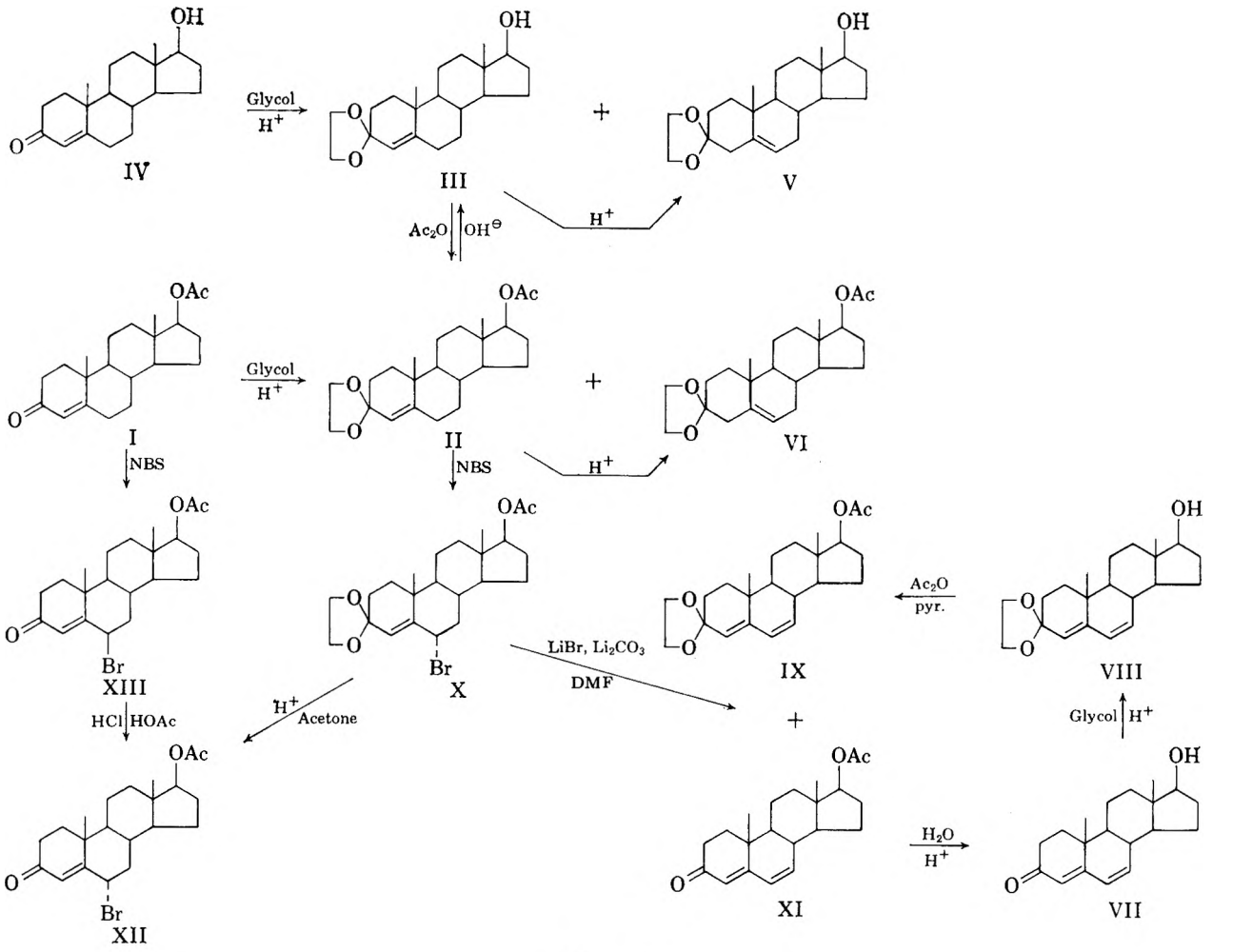

Figure 1

The predicted[4] difference (ΔM_D) between the molar rotations of two isomeric steroids unsaturated between positions 4,5, and 5,6 is 492. This close correlation supported the conclusion that the new steroidal ketals were indeed Δ⁴-isomers of their known Δ⁵-counterparts.

A recent communication[5] reports the preparation and yields of a series of nine steroidal Δ⁴-3-ethylene ketals by substitution of weaker acids (adipic and oxalic) for the *p*-toluenesulfonic acid customarily employed as catalyst. Δ⁴-3-Ketals of testosterone and of 6-dehydrotestosterone (see following) were among those reported; although physical constants and experimental conditions were not described, the broad generality of Δ⁴-3-ketal preparation was amply demonstrated by the wide variety of Δ⁴-3-keto steroids which were similarly ketalized in that study. It is of interest that in most cases Brown, Lenhard, and Bernstein found that adipic acid catalyzed the formation of Δ⁴-ketals only, and that catalysis by the stronger oxalic acid led to the generation of a mixture of Δ⁴- and Δ⁵-ketals; congruently, our products from catalysis with *small* amounts of the much stronger *p*-toluenesulfonic acid were also mixtures of Δ⁴- and Δ⁵- ketals.

Attempts in this laboratory to epoxidize the Δ⁴-ketal in order to establish the location of the double bond in a manner analogous to the scheme of Fernholz and Stavely[6] were unsuccessful. Commercial 40% peracetic acid contains appreciable amounts of mineral acid which hydrolyzed the ketal despite buffering with sodium acetate. Monoperphthalic acid did not effect epoxidation, probably due to steric hindrance by the dioxolane ring to approach of the reagent to the 4,5-double bond.

The structure proof employed by Antonucci, *et al.*,[2] for the Δ⁵-ketal, involving allylic bromination with N-bromosuccinimide, dehydrohalogenation, acid hydrolysis, and identification of the resulting dienone as androsta-5,7-dien-17β-ol-3-one, was then applied. To provide an authentic sample of 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol acetate (IX), the expected product of the application of a similar reaction sequence to the Δ⁴-ketal II, androsta-4,6-dien-17β-ol[7] (VII) was ketalized with glycol and *p*-toluenesulfonic acid by azeotropic distillation in benzene[8] to give 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol (VIII) in 30% yield. Evidence that the 4,6-diene structure was not isomerized during ketalization was provided by the ultraviolet spectrum of VIII, which displayed characteristic[9] ab-

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 178.

(5) J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 310 (1962).

(6) E. Fernholz and H. E. Stavely, Abstracts of Papers, 102nd National Meeting of the American Chemical Society, 1941, p. 39M.

(7) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4354 (1950).

(8) In an earlier report [S. Bernstein, W. S. Allen, M. Heller, R. H. Lenhard, L. I. Feldman, and R. H. Blank, *J. Org. Chem.*, **24**, 286 (1959)] it was stated that the Δ⁴·⁶-3-keto moiety is unreactive under these conditions. G. J. Fonken, *ibid.*, **26**, 2549 (1961), has, however, described the preparation of the Δ⁴·⁶-3,3-ethylenedioxy derivatives of Δ⁴·⁶-cholestadien-3-one and of Δ⁴·⁶·²²-ergostatrien-3-one by standard methods.

(9) L. Dorfman, *Chem. Rev.*, **53**, 55 (1953).

sorption for the 4,6-dien-3-alkoxy structure at 234, 239, and 248 mμ. Acetylation of VIII then provided the desired 17β-acetoxy compound IX.[10]

Bromination of the Δ⁴-ketal II with N-bromosuccinimide in carbon tetrachloride afforded a monobromo ketal, isolated in 60% yield, whose analysis and infrared spectrum agreed with its formulation (later demonstrated) as 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate (X). When the total crude product from the bromination of II was heated in a boiling solution of 4% *s*-collidine in xylene, only a trace of collidine hydrobromide was produced. When the process was repeated in boiling *s*-collidine, only 38% of the material was dehydrobrominated, based on the collidine hydrobromide isolated; in addition, 52% of the starting bromo ketal was recovered. As an alternative, the dehydrohalogenation conditions of Joly and co-workers[11] were employed. The total crude bromination product of II was heated with lithium bromide and lithium carbonate in dimethylformamide at 100° and the crude product (in 60% yield) was shown by ultraviolet analysis to be a mixture of the 4,6-diene-3-ketal IX (27%) and the 4,6-dien-3-one XI (63%). Hydrolysis of this mixture with dilute methanolic hydrochloric acid afforded a 48% over-all yield of androsta-4,6-dien-17β-ol (VII). The location of the bromine substituent in X was thus shown to be at C-6; consequently, the double bond of the new ketal must be in the 4,5-position.

Cleavage of X under mild conditions, in acetone at room temperature with *p*-toluenesulfonic acid, afforded a bromo ketone XII isomeric with the known[7] 6β-bromotestosterone acetate. The 6α-bromo epimer has not been reported in the literature; however, both its ultraviolet spectrum and optical rotation fall into the pattern established by the properties of other 6-halogenated Δ⁴-3-ones. In a recent summary of the ultraviolet spectra of 6-substituted Δ⁴-3-keto steroids, Ringold and Bowers[12] concluded that 6α-bromo compounds exhibit hypsochromic shifts of 3 to 4 mμ in the ultraviolet compared to the parent Δ⁴-3-ketones and the 6β-bromo epimers show bathochromic shifts of the order of 6 to 8 mμ. Fieser and Fieser[13] have compared the optical rotations of epimeric pairs of 6-chloro- and 6-bromocholestenones. Between these closely analogous compounds, dextrorotatory changes of 45° and 47° are found, respectively, on going from the 6β- to the 6α-epimers. Therefore, the new bromo ketone XII was formulated as 6α-bromotestosterone acetate on the basis of its optical rotation and ultraviolet spectrum. The properties of the two bromo ketones are summarized in Table I.

When 6β-bromotestosterone acetate (XIII) was exposed to the reagents and conditions employed in the acetonolysis of the bromo ketal X, little change in its properties was observed, indicating that little or no epimerization of the 6β-bromine had occurred. Exposure to the epimerization conditions[14] of Bowers and co-workers (hydrogen chloride in glacial acetic acid at room temperature) converted it to 6α-bromotestosterone acetate in good yield.

TABLE I

Compound	M.p.,[a] °C.	$[\alpha]^{25}D$[b]	λ_{max} mμ (ε)[c]
6α-Bromotestosterone acetate (XII)	145–146 (dec.)	+57.6°	237 (13,600)
6β-Bromotestosterone acetate[d] (XIII)	147–148 (dec.)	−13.0°	248 (13,300)
Testosterone acetate (I)	140–142	+96°	241 (16,000)

[a] Uncorrected. [b] In chloroform solution. [c] In ethanol solution. [d] This was a sample prepared in this laboratory by the method of ref. 7, where constants reported were m.p. 140–142°, $[\alpha]^{20}D$ −16°, λ_{max} 248 mμ (ε 15,500).

From the foregoing observation it is inferred that during mild acetonolysis of the bromo ketal X to 6α-bromotestosterone acetate (XII), no epimerization of the bromine substituent at C-6 occurred. Consequently, bromination of the Δ⁴-ketal II with N-bromosuccinimide must have afforded the (equatorial) 6α-bromo ketal directly; in contrast, N-bromosuccinimide bromination of testosterone acetate appears to yield only the (axial) 6β-epimer XIII.

Exposure of the pure bromo ketal X to boiling *s*-collidine for three hours did not effect substantial dehydrohalogenation and 80% of the starting material was recovered. This lack of reactivity is presumably due to the absence of a suitably oriented hydrogen atom on C-7; there is no hydrogen *trans* and coplanar to the equatorial bromine on C-6 to provide the basis for an E2 elimination reaction under the influence of the nucleophile, *s*-collidine.

In a brief series of ketalization experiments with testosterone acetate the concentration of catalyst (*p*-toluenesulfonic acid) was varied, with the other components and the duration (seven hours) held constant. An ultraviolet absorption assay of the crude product was used to determine the extent of reaction. Tripling of the catalyst concentration (from 0.00037 *M* to 0.0011 *M*) was found to increase the yield of total ketals from 49% to 76%. The proportions of Δ⁴- and Δ⁵-isomers produced were not determined in these experiments. Other experiments showed that employment of different quantities of ethylene glycol, which existed as a separate phase during the reaction, as expected had no appreciable effect on the yield.

In preparative experiments with testosterone acetate a 0.0011 *M* catalyst concentration and 0.043 *M* steroid concentration appeared to be optimum for Δ⁴-ketal production. With testosterone, preparation of the Δ⁴-ketal was effected best when both of these concentrations were doubled. In the ketalization of the less reactive androsta-4,6-dien-17β-ol a somewhat higher concentration of catalyst was employed, 0.042 *M* steroid and 0.003 *M* catalyst.

A most interesting observation was that the Δ⁴-ketal II could be converted to its Δ⁵-isomer VI in boiling benzene by a tenth-molar quantity of *p*-toluenesulfonic acid. The crude yield was 45% and no other crystalline product was obtained. Similar results were obtained with the Δ⁴-ketal of testosterone (III). The fact that the use of a low catalyst concentration favors formation of the Δ⁴-ketal, coupled with the demon-

(10) The Δ⁴- and Δ⁴·⁶-ketals were found to be unusually sensitive to hydrolysis; storage in a vacuum desiccator over potassium hydroxide is desirable. Interestingly, the 17β-hydroxy-Δ⁴-ketals were observed to be more resistant to accidental hydrolysis than their acetylated counterparts. Largely for this reason, ketalization of the 17β-hydroxy compound followed by acetylation was found to be more satisfactory for preparative purposes.

(11) R. Joly, J. Warnant, G. Nomine, and D. Berlin, *Bull. soc. chim France*, 366 (1958).

(12) H. J. Ringold and A. Bowers, *Experientia*, **17**, 65 (1961).

(13) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 291.

(14) A. Bowers, E. Denot, M. B. Sanchez, and H. J. Ringold, *Tetrahedron*, **7**, 153 (1959).

strated isomerization of the ketal to its Δ⁵-isomer under what are essentially the usual conditions for the preparation of the Δ⁵-ketal, has led to the hypothesis that the Δ⁴-compound is an intermediate in the formation of the Δ⁵-product usually isolated.

The mechanism of formation of the unsaturated ketals is still uncertain. Brown, Lenhard, and Bernstein[5] advanced a reasonable explanation for the formation of both the α,β- and β,γ-unsaturated compounds through 1,2-addition of the hydroxyl function to either of the intermediate dienol ethers A or B, respectively (see Fig. 2).

An alternative explanation may be advanced, based partly on Djerassi and Gorman's mechanism.[15] The precursor of the Δ²,⁴-enol ether A can be represented as E (see Fig. 2). Displacement, rather than elimination at this point, would lead to the protonated ketal F.[16] Simple loss of a proton would give C, the Δ⁴-ketal. Deprotonation by attack of a base on an allylic proton at C-6 (represented by G) would afford B and then D, the Δ⁵-ketal, by 1,2-addition. This alternative course leading to the Δ⁵-ketal may well be greatly assisted by the presence of larger amounts of catalyst. The scheme outlined also provides a rationale for the demonstrated isomerization of the Δ⁴-ketal structure to its Δ⁵-isomer; by reprotonation of the Δ⁴-ketal, the intermediate F is formed, which can then lose a proton by the alternate path leading eventually to the Δ⁵-ketal D. Further experimentation will be necessary to verify these speculations.

Experimental

Melting points were determined in capillaries and are uncorrected. Ultraviolet spectra were measured with solutions in ethanol and infrared spectra were determined with potassium bromide pellets (1% by weight). Optical rotations were measured with 1% solutions in chloroform.

3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—Testosterone acetate (I, 5.0 g., 16 mmoles, m.p. 140–142°) was ketalized by azeotropic distillation[2] for 4 hr. in 375 ml. benzene with 80 mg. (0.42 mmole) of *p*-toluenesulfonic acid monohydrate and 23 ml. of ethylene glycol. Recrystallization of the crude solid product from a mixture of acetone and methanol afforded 1.91 g. of needle like crystals of the Δ⁴-ketal II, m.p. 152–155° (33.7%). The compound showed strong ether absorption (10.55 μ) and acetate carbonyl absorption (5.78 μ) in the infrared, plus a weak band at 6.04 μ attributed to the 4,5-double bond. An analytical sample, prepared by several recrystallizations from *n*-hexane containing a trace of pyridine, had m.p. 159–161°, $[\alpha]^{25}D$ +80.0°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.69; H, 9.30.

Concentration of the recrystallization liquors led to the crystallization of 2.0 g. (35.3%) of the known Δ⁵-isomer VI, m.p. 202–204°, $[\alpha]^{25}D$ −51°; lit.[2] m.p. 203–205°, $[\alpha]^{29}D$ −52.1°.

Saponification of 3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—Saponification of II (1.00 g., 2.67 mmoles) in refluxing aqueous ethanolic potassium hydroxide for 1 hr. afforded 0.90 g. of 3,3-ethylenedioxyandrost-4-en-17β-ol (III), m.p. 218–229°. Two recrystallizations from acetone containing a trace of pyridine gave the analytical sample, m.p. 224–230°, $[\alpha]^{25}D$ +96.4°. The compound did not absorb in the ultraviolet; in the infrared spectrum, a hydroxyl band appeared at 2.90 μ, plus a band at 6.04 μ attributed to the Δ⁴-olefinic bond; ketal ether bands remained intact.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.57; H, 9.68.

(15) C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).

(16) Such a displacement was envisioned by Djerassi and Gorman in the formation of dithiolanes from α,β-unsaturated ketones in order to explain the fact that the double bond remains at the 4,5-position in these compounds.

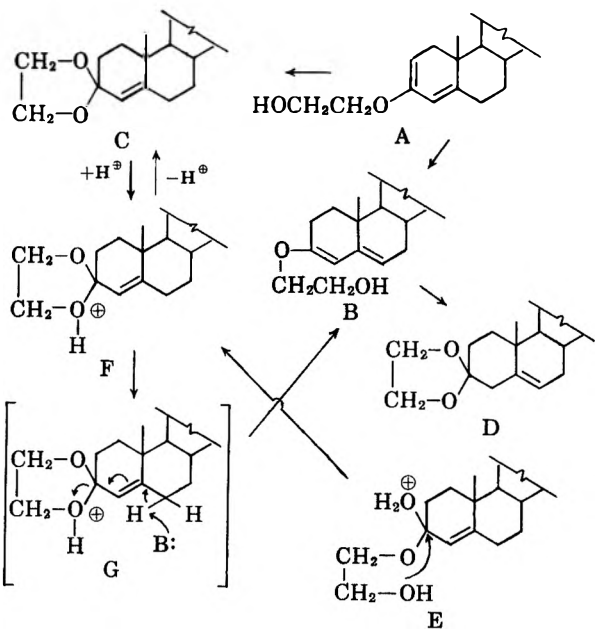

Figure 2

3,3-Ethylenedioxyandrost-4-en-17β-ol (III).—Testosterone (30.0 g., 104 mmoles) was ketalized by azeotropic distillation in 1.2 l. of benzene for 5 hr. with 0.5 g. (2.63 mmoles) of *p*-toluenesulfonic acid monohydrate and 130 ml. of ethylene glycol. The dried crude product had an ultraviolet absorption of λ_{max} 241 mμ (ε 6400), indicating that 40% of the starting ketone remained unconverted to ketal. Careful fractional crystallization of the total crude product from acetone containing a trace of pyridine gave 6.31 g. of the Δ⁴-ketal III in five crops of crystals, all melting in the range 210–230°. The yield was 30.4% based on the conversion indicated by the ultraviolet spectrum of the total product, or 18.2% over-all. Several recrystallizations from acetone provided the analytical sample, m.p. 225–232°, $[\alpha]^{25}D$ +95.1°. The infrared spectrum was identical with that of the material obtained by saponification of 17β-acetoxy compound II.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.84.

From the mother liquors was obtained 5.32 g. of the Δ⁵-isomer V, m.p. 175–183° (15.4% over-all yield, or 25.6% of the total ketals). Recrystallization from methanol–*n*-hexane furnished a pure sample, m.p. 185.5–188°, $[\alpha]^{25}D$ −44.0°; lit.[2] m.p. 185–188°, $[\alpha]^{25}D$ −45.5°.

Acetylation of 3,3-Ethylenedioxyandrost-4-en-17β-ol (III).—A solution of 10.0 g. (30 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol in 50 ml. of pyridine and 20 ml. of acetic anhydride was heated to 100° for 1 hr., then left at room temperature overnight. Dilution of the reaction solution with 2 l. of cold water gave a white crystalline precipitate which after air drying weighed 11.30 g. (a quantitative yield) and had m.p. 153–162°. Recrystallization from *n*-hexane containing a trace of pyridine gave 9.72 g. of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II), m.p. 158–160.5°; plus a second crop, 1.07 g., m.p. 155–159°.

The melting point was undepressed when mixed with a sample of the Δ⁴-ketal obtained by ketalization of testosterone acetate and the infrared spectra were identical.

Attempted Epoxidation of 3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—To a solution of 1.0 g. (2.7 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate in 70 ml. of anhydrous ether was added a molar equivalent of monoperphthalic acid[17] as a solution in anhydrous ether (1.47 ml. of a 1.82 *M* solution). The solution was held at 5° for 2 days, then at room temperature for a day; a starch–potassium iodide test for peracid was then negative. The solution was diluted with 50 ml. of ether and was washed with 25 ml. of 2 *N* sodium hydroxide followed by three 25-ml. portions of water. Concentration of the ether solution to a small volume by boiling afforded 0.85 g. of white crystalline solid, m.p. 148–155°. An infrared spectrum of this material showed that it was essentially unchanged from starting material.

(17) E. E. Royals and L. L. Harrell, *J. Am. Chem. Soc.*, **77**, 3405 (1955).

3,3-Ethylenedioxyandrosta-4,6-dien-17β-ol (VIII).—Androsta-4,6-dien-17β-ol-3-one (VII, 23.0 g., 80 mmoles, m.p. 203–205°) was ketalized by azeotropic distillation in 1.9 l. of benzene for 24 hr. with 1.16 g. (6.1 mmoles) of *p*-toluenesulfonic acid monohydrate and 116 ml. of ethylene glycol. The crude product was noncrystalline; column chromatography on Florisil afforded the ketal VIII as white needles (7.95 g., 30.0%), eluted with 20% ether in *n*-pentane. Further elution of the column with ether allowed the recovery of 8.5 g. of starting material.

One recrystallization from ether containing a drop of pyridine gave 5.96 g. of slightly impure ketal, m.p. 178–181°. Several recrystallizations from a mixture of ether and hexane plus a trace of pyridine gave the analytical sample, m.p. 181.2–183.0°, $[\alpha]^{25}D$ +88.9°. The infrared spectrum was consistent with the assigned structure, and ultraviolet absorption was observed at λ_{max} 239 mμ (ε 25,200), 234 (sh) (23,800), and 248 (sh) (15,700).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.00; H, 8.87.

3,3-Ethylenedioxyandrosta-4,6-dien-17β-ol Acetate (IX).—A solution of 7.00 g. (21.2 mmoles) of 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol in 10 ml. of pyridine and 5 ml. of acetic anhydride was heated at 100° for 30 min. and then cooled in ice. The crystals that separated were collected by suction filtration and washed with cold ether and *n*-hexane. After drying, the product weighed 4.28 g. (54.3%) and had m.p. 160–162.5°. Recrystallization from *n*-hexane afforded an analytical sample, m.p. 163–164.5°, $[\alpha]^{25}D$ +61.1°. With the exception of acetate absorption bands now present in the infrared spectrum, the ultraviolet and infrared spectra were identical with those of the 17β-hydroxy ketal VIII.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.45; H, 8.33.

6α-Bromo-3,3-ethylenedioxyandrost-4-en-17β-ol Acetate (X).—A mixture of 2.0 g. (5.34 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II) and 0.96 g. (5.40 mmoles) of N-bromosuccinimide in 100 ml. of dry carbon tetrachloride was refluxed for 3 min. while being irradiated with an incandescent bulb; the solution then gave a negative starch–potassium iodide test. Filtration and evaporation of the filtrate gave an oil which crystallized readily. Recrystallization of the crude product from ether gave the bromo ketal acetate X as three crops of crystals totaling 1.45 g. (59.9% of theory). Two recrystallizations from ether provided analytically pure material, m.p. 161–162° dec., $[\alpha]^{25}D$ −72.6°. A melting point determined in an evacuated Pyrex capillary was unchanged from one determined in an open capillary.

Anal. Calcd. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.34; Br, 17.63. Found: C, 60.92; H, 7.46; Br, 17.88.

Dehydrohalogenation of Bromo Ketal Acetate X with Lithium Bromide and Lithium Carbonate in Dimethylformamide.—The entire crude product from the N-bromosuccinimide bromination of 3.75 g. (10 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate was dissolved in 55 ml. of dry dimethylformamide. Lithium carbonate (2.68 g., 40 mmoles) and lithium bromide (3.47 g., 40 mmoles) were added. (Both salts had been dried *in vacuo* at 100°.) The yellow mixture was heated at 100° and stirred mechanically for 17 hr. After cooling to room temperature, the reaction mixture was diluted with 1 l. of cold water and stirred for 1 hr. The product was extracted with six 100-ml. portions of methylene dichloride which were combined and dried over sodium sulfate. Evaporation of the filtered extract gave 15 ml. of a dimethylformamide solution of the product. This solution was diluted with 400 ml. of water and the oily precipitate was extracted with ether in three 250-ml. portions. The combined ether extract was dried over sodium sulfate, filtered, and concentrated by boiling; *n*-pentane was added to the warm ether solution until crystallization began. The mixture was cooled in ice and filtered, affording 1.84 g., m.p. 122–132°. A second crop, 0.22 g., m.p. 122–145°, was obtained from the filtrate. Analysis of the ultraviolet spectrum of the total crude product (63% of theory) showed it to be a mixture of 27% of 3,3-ethylenedioxyandrost-4,6-dien-17β-ol acetate (characteristic absorption at 235, 238, and 247 mμ) and 63% of androsta-4,6-dien-17β-ol-3-one acetate (characteristic absorption at 283 mμ). Recrystallization from aqueous methanol containing a few drops of 2 *N* hydrochloric acid resulted not only in hydrolysis of the minor ketal component but also in hydrolysis of the 17β-acetoxyl function. There was obtained 1.38 g. (48.1%) of slightly impure androsta-4,6-dien-17β-ol-3-one (VII), m.p. 180–190°. A mixture melting point with authentic material (m.p. 202–204°) was undepressed; further recrystallization of the impure material gave the pure compound, identical in all respects with an authentic sample.

Attempted Dehydrohalogenation of X with *s*-Collidine.—The total crude bromo ketal derived from the N-bromosuccinimide bromination of 10 mmoles of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate was dissolved in a mixture of 50 ml. of dry xylene and 2.0 ml. (1.83 g., 15 mmoles) of *s*-collidine (b.p. 169–171°). The solution was heated under reflux for 30 min. and then cooled to room temperature. It was evident from the very small quantity of collidine hydrobromide which had precipitated that dehydrohalogenation was far from complete. Distillation at reduced pressure was employed to remove most of the xylene, after which 35 ml. of *s*-collidine was added to the residue. The solution was distilled at atmospheric pressure through a 3-in. Vigreux column until the vapor temperature had reached 156°. The fractionating column was replaced by a reflux condenser and the collidine solution was boiled for 30 min. After cooling to room temperature and dilution with 100 ml. of ether, the mixture was filtered to collect precipitated collidine hydrobromide, which after drying amounted to 0.76 g., or 37.6%. The ethereal filtrate was evaporated, affording a residual collidine solution that was diluted with 600 ml. of cold water. The sticky solid which precipitated was collected by filtration and recrystallized from a mixture of ether and *n*-pentane. There was obtained 2.37 g. of needlelike crystals in three crops, each melting in the vicinity of 160° with decomposition. An infrared spectrum of the major fraction was identical with that of authentic 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate (X) and a bromine analysis provided confirmation.

Anal. Calcd. for $C_{23}H_{33}BrO_4$: Br, 17.7. Found: Br, 18.1.

The undehydrohalogenated bromo ketal constituted 52.3% of the starting material. The filtrate gave only dark oily material which could not be induced to crystallize.

When a solution of 500 mg. of pure X in 10 ml. of *s*-collidine was heated under reflux for 3 hr. and was then worked up as indicated earlier, there was isolated 0.54 g. of crude product, m.p. 199° dec. This compound was probably a collidine complex of bromo compound, for on recrystallization from aqueous ethanol there was recovered 400 mg. (80%) of the starting bromo ketal, identified by its melting point, optical rotation, and the identity of its infrared spectrum with that of an authentic sample of X.

Acetonolysis of 6α-Bromo-3,3-ethylenedioxyandrost-4-en-17β-ol Acetate (X).—A solution of 500 mg. (1.1 mmoles) of 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate and 50 mg. of *p*-toluenesulfonic acid monohydrate in 20 ml. of dry acetone was left at room temperature for 16 hr. After dilution with 20 ml. of ether plus 20 ml. of *n*-hexane, the solution was washed with 20 ml. of dilute sodium bicarbonate solution, two 20-ml. portions of water, and then with 20 ml. of saturated brine. The ether–hexane solution was dried briefly over anhydrous sodium sulfate and was then filtered and concentrated by boiling until crystallization began. Three crops of platelike crystals were obtained, totaling 360 mg., or 80% of the theoretical yield of bromo ketone. Recrystallization from ether–*n*-pentane afforded 275 mg. of pure 6α-bromotestosterone acetate (XII), m.p. 145–146° dec., $[\alpha]^{25}D$ +57.6°. Ultraviolet absorption was λ_{max} 237 mμ (ε 13,600). A mixture melting point with authentic 6α-bromotestosterone acetate (see following text) was undepressed and the infrared spectra were identical.

Attempted Epimerization of 6β-Bromotestosterone Acetate[7] under Mild Conditions.—Conditions identical to those employed for the acetonolysis of the bromo ketal X were used. A solution of 1.00 g. (2.44 mmoles) of 6β-bromotestosterone acetate and 0.10 g. of *p*-toluenesulfonic acid monohydrate in 40 ml. of acetone was left at room temperature for 16 hr. The solution was diluted with 40 ml. of ether and 40 ml. of *n*-hexane and was then washed with 40 ml. of dilute sodium bicarbonate, two 40-ml. portions of water, and 40 ml. of saturated brine. After brief drying over anhydrous sodium sulfate, the ether–hexane solution was filtered and concentrated by boiling until crystallization began from the hot solution. Needle-like crystals (700 mg.) were obtained, m.p. 119.5–123° dec. A mixture melting point with starting material (m.p. 147–148° dec.) was intermediate, m.p. 136–138.5°. Without further purification, the product was examined in the ultraviolet: λ_{max} 244 mμ (ε 13,000). Its optical rotation was $[\alpha]^{25}D$ −1.9°. The extent of change from the properties of pure 6β-bromotestosterone acetate ($[\alpha]^{25}D$ −13° and λ_{max} 248 mμ (ε 13,300)) indicated that epimerization of bromo ketone occurred to only a minor extent under the same conditions as were employed for acetonolysis of the bromo ketal X.

6α-Bromotestosterone Acetate (XIII).—Bromination of testosterone acetate in carbon tetrachloride solution with a molar equivalent of N-bromosuccinimide under strong irradiation with an incandescent bulb gave 6β-bromotestosterone acetate, m.p. 147–148° dec., $[\alpha]^{25}D$ −13.0°, λ_{max} 248 mμ (ε 13,300). The yield of purified product was 56.8% and the physical properties agreed with those reported[7] for the compound. A portion was then epimerized to the 6α-bromo (equatorial) epimer by the procedure of Bowers and co-workers.[14]

Dry hydrogen chloride was bubbled through a solution of 1.00 g. (2.44 mmoles) of 6β-bromotestosterone acetate in 100 ml. of glacial acetic acid for 25 min. at room temperature. After standing for 30 min. longer, the solution was diluted with 2 l. of cold water to afford a solid precipitate. The crude product was collected on a filter and washed with water, then air dried. The slightly sticky solid was dissolved in ether and the solution was dried over anhydrous potassium carbonate. After filtration, the ether solution was diluted with *n*-pentane and concentrated by boiling until the product crystallized as plates, m.p. 133–135° dec. One recrystallization from ether–*n*-hexane afforded pure 6α-bromotestosterone acetate XII, m.p. 147–148° dec., $[\alpha]^{25}D$ +54.8°. Ultraviolet absorption was at λ_{max} 237 mμ (ε 13,600).

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.33; H, 7.18; Br, 19.48.

Ketalization of Testosterone Acetate with Differing Low Concentrations of Acid Catalyst.—Testosterone acetate (5.0 g., 15.1 mmoles) was ketalized azeotropically in benzene solution (350 ml.) with 20 ml. of ethylene glycol and 25 mg. of *p*-toluenesulfonic acid. The reaction was carried out by heating at reflux under a water trap for 7 hr. The mixture was then cooled to room temperature and washed with dilute sodium bicarbonate and several times with water. Evaporation of the benzene solution to dryness under reduced pressure gave a solid crystalline residue which was examined for ultraviolet absorption.

The experiment was repeated with 50 mg. of acid catalyst, then with 75 mg. The three experiments represented catalyst concentrations of 0.00037 *M*, 0.00074 *M*, and 0.00111 *M*, respectively. The crude product of each reaction absorbed at 241 mμ in the ultraviolet, indicative of unchanged testosterone acetate. Calculations showed the extent of reaction in each case to be (a) 0.00037 *M* catalyst, 49% conversion to ketal; (b) 0.00074 *M* catalyst, 65% conversion to ketal; and (c) 0.00111 *M* catalyst, 75% conversion to ketal.

Isomerization of Testosterone Acetate Δ^4-Ketal II to Its Δ^5-Isomer VI.—A solution of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II, 1.00 g., 2.6 mmoles) and 50 mg. (0.26 mmole) of *p*-toluenesulfonic acid monohydrate in 100 ml. of dry benzene was heated under reflux for 3 hr., with the condensate returning through a Dean–Stark water separator. After cooling to room temperature, the solution was washed with dilute sodium bicarbonate, then three times with water. After brief drying over sodium sulfate, the benzene solution was distilled to dryness under reduced pressure to afford a solid residue which was recrystallized from a mixture of acetone and *n*-hexane, 0.45 g., m.p. 180–189° (a 45% yield). No further crystalline material could be obtained from the filtrate. One additional recrystallization from acetone containing a trace of pyridine gave pure 3,3-ethylenedioxyandrost-5-en-17β-ol acetate, m.p. 201–204°, $[\alpha]^{25}D$ −50.9°; lit.[2] m.p. 203–205°, $[\alpha]^{29}D$ −52.1°. A mixture melting point with authentic material was undepressed and a comparison of infrared spectra showed no differences.

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The Base-Catalyzed Self-Condensation of 2-Ethyl-2-hexenal. III. Structure of Isomeric Glycols, $C_{16}H_{30}O_2$[1]

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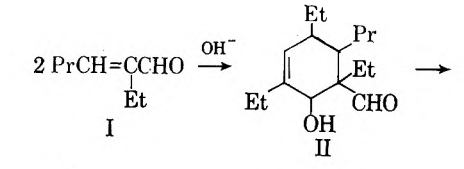
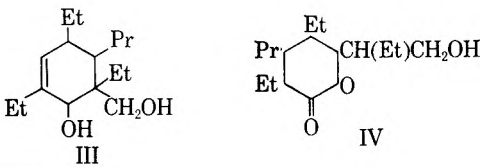
The self-condensation of 2-ethyl-2-hexenal by heating under reflux with aqueous sodium hydroxide produces four glycol diastereoisomers, $C_{16}H_{30}O_2$ (III) (25% total yield), and previously described[4] lactones, $C_{16}H_{30}O_3$ (IV) and $C_{12}H_{22}O_2$ (XIV). The glycols have all been shown to be 6-hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ols by degradation (two routes) to known 3-propyl-2,4,6-triethylphenol (VIII). They are each produced from the corresponding aldol (II) in a crossed Cannizzaro reaction by oxidation of butanal and 2-ethyl-2-hexenal.

In the previous papers of this series[3,4] the self-condensation of 2-ethyl-1-hexenal (I) was reported to produce three C_{16} products: an aldol, $C_{16}H_{28}O_2$ (II),

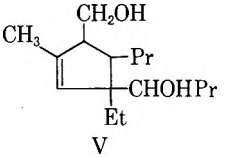


I II



III IV

a glycol, $C_{16}H_{30}O_2$ (III, 32% yield), and a lactone, $C_{16}H_{30}O_3$ (IV) in the presence of aqueous methanolic potassium hydroxide at 25°. Lithium aluminum hydride reduction of II gave III, obtained as a liquid. Publishing simultaneously and independently, Pummerer and Smidt[5] also described the self-condensation of I, employing aqueous sodium hydroxide at reflux temperature (110°). They reported the formation of two diastereoisomeric glycols, $C_{16}H_{30}O_2$ (22% total yield), one of m.p. 62° and one a liquid, and to both they assigned a five-membered ring structure (V). Since it seemed unlikely to us that the difference in reaction conditions in the two experiments[4,5] was suf-



V

(1) Presented at the 135th National American Chemical Society Meeting, Boston, Mass., April, 1959.

(2) Chemistry Division, Research Department, U. S. Naval Ordnance Test Station, China Lake, Calif.

(3) A. T. Nielsen, *J. Am. Chem. Soc.*, **79**, 2518 (1957).

(4) A. T. Nielsen, *ibid.*, **79**, 2524 (1957).

(5) R. Pummerer and J. Smidt, *Ann.*, **610**, 192 (1957).

TABLE I

6-METHYLOL-5-PROPYL-2,4,6-TRIETHYL-2-CYCLOHEXEN-1-OL DIASTEREOISOMERS (III)

M.p., °C.	Distribution[a] at 110°, % ± *ca.* 3	Anal. Found, %[b] C	H	Bis-3,5-dinitrobenzoate, m.p., °C.	Anal. Found %[c] C	H	N
B.p. 134–135[d] (0.4 mm.)	55	75.49	12.12	183.5–183.5[e]	56.65	5.61	8.70
62–62.5[f]	30	75.46	12.95	159–160[g]	56.13	5.41	8.67
90–91	10	75.6	12.9	153–154[g]	56.11	5.33	8.50
112–113	5	75.29	12.93	...[h]			

[a] Isomer distribution in glycol mixture obtained after 20–96-hr. reflux of 2-ethyl-2-hexenal with aqueous sodium hydroxide. [b] Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. [c] Calcd. for $C_{30}H_{34}N_4O_{12}$: C, 56.07; H, 5.33; N, 8.72. [d] Bis-*p*-nitrophenylurethan, m.p. 76.5–78.5°. [e] Rectangular prisms; reported m.p. 178° (R. H. Hall and K. H. W. Tuerck, British Patent 608,985 (September 23, 1948); *Chem. Abstr.*, **44**, 4493 (1950). [f] Bis-*p*-nitrophenylurethan, m.p. 208–210° (prisms from nitromethane). Calcd. for $C_{30}H_{38}N_4O_8$: C, 61.84; H, 6.57; N, 9.62. Found: C, 61.6; H, 6.73; N, 9.67. Attempts to prepare a crystalline bis-*p*-nitrophenylurethan of the 90° isomer were unsuccessful. [g] Crystals of the 62° glycol bis-3,5-dinitrobenzoate were flat and hexagonal while those of the 90° derivative were rhombic prisms. The melting point of a mixture of these two derivatives was 133–139°. [h] See ref. 6a.

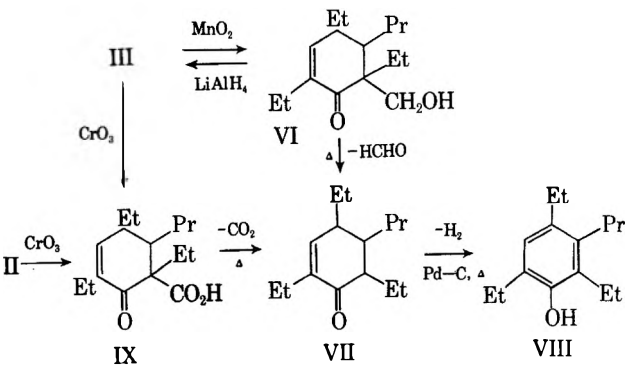
ficient to produce glycols having the same molecular formula, but different structures, the previous experiments were carefully re-examined. In the present paper new evidence is presented affirming 6-hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol structures (III) for all isomeric glycols, $C_{16}H_{30}O_2$, obtained from I.

The procedure of Pummerer and Smidt[5] was repeated and found to yield not two, but four isomeric glycols, $C_{16}H_{30}O_2$ (25% total yield). Crystallization from petroleum ether was an efficient method of isolating the crystalline glycols and an improved yield (*ca.* 30% of the total) of the 62° isomer was realized. In addition, smaller amounts of isomers not previously described were obtained, one of m.p. 90–91° (*ca.* 10% of the total) and one of m.p. 112–113° (*ca.* 5%). The liquid isomer was the major component of this mixture (*ca.* 55%). Results are summarized in Table I. Re-examination of liquid glycol samples which we had obtained earlier[4] by condensation of 2-ethyl-2-hexenal at 25° or by lithium aluminum hydride reduction of II revealed 0–6% crystalline isomers. Evidently the isomer distribution depends on reaction conditions; much more of the crystalline isomers are produced by the vigorous conditions of Pummerer and Smidt.

The four glycol samples are diastereoisomers, not polymorphs. They cannot be directly interconverted by physical or chemical means and each forms a distinct bis-3,5-dinitrobenzoate derivative (Table I).[6] Their infrared spectra are similar (strong OH stretching band at 3500 cm.$^{-1}$ and a weak C=C stretching band at 1640 cm.$^{-1}$). Small but distinct differences in the spectra are observed in the region 700–1500 cm.$^{-1}$; these affirm, to a rough degree, the isomer distribution determined by crystallization.

Assignment of structure III to the glycol (principally liquid isomer) obtained in our previous work[4] rested on preparation of the same compound from II by lithium aluminum hydride reduction (bis-*p*-nitrophenylurethan derivatives identical). The structure II had been established rigorously by two unrelated degradation schemes.[3]

Each of the four glycols was oxidized with active manganese dioxide catalyst[7] to a ketol (VI, $C_{16}H_{28}O_2$) having an α,β-unsaturated carbonyl group ($\epsilon_{max}^{240\ m\mu}$ 9000). The ketols (VI) readily lost formaldehyde on heating to form an α,β-unsaturated ketone (VII, $C_{15}H_{26}O$; $\epsilon_{max}^{241\ m\mu}$ 7800).



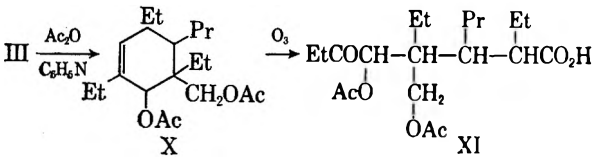
Formation of VI and VII is consistent with an allylic secondary hydroxyl group in III. Lithium aluminum hydride reduction of the ketols (VI) regenerated the glycols (III), thus establishing the position of the double bond (a detailed study of this reaction is in progress).[6b] Dehydrogenation of VII by heating with palladium–charcoal catalyst led to 3-propyl-2,4,6-triethylphenol (VIII), identical with an authentic sample synthesized by an alternate route[3] (phenylurethan derivatives identical). Ketone VII also was prepared from III by chromic acid oxidation (the pure 60° isomer or the mixture of four isomers obtained by the procedure of Pummerer and Smidt[5] gave the same result). The intermediate β-keto acid (IX) was not isolated, but decarboxylated *in situ* to VII, which was then dehydrogenated to VIII (ketol VI also was produced by the chromic acid oxidation since formate is a product). Chromic acid oxidation of aldol II had previously been shown to produce VIII through the following sequence: II → IX → VII → VIII.[3]

Structure V arrived at by Pummerer and Smidt does not agree with our results and it becomes of interest to re-examine their data in terms of structure III. Their experimental findings can easily be reconciled with III except for an apparent discrepancy which rests in assignment of methyl ketone structures to two ketocarboxylic acids obtained by degradation of the glycol diacetate, $C_{20}H_{34}O_4$ (X). Cleavage of X with ozone pro-

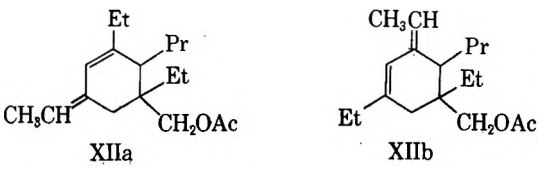
(6)(a) The 112° isomer appeared to be much less reactive than the other isomers and could not be converted into a bis-3,5-dinitrobenzoate derivative. (b) Chemical differences between the isomers have been noted in experiments in progress leading to establishment of stereochemistry; results will appear in a forthcoming publication. The maximum number of isomers possible is believed to be four since stereochemistry at C-4 and C-5 appears to be the same in all.

(7) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

duced a keto acid, $C_{20}H_{34}O_7$ (XI), which gave a positive iodoform test and was assigned a methyl ketone structure. However, Lieben's iodoform test is not reliable in distinguishing between methyl and ethyl ketones.[8] On the basis of structure III, keto acid XI would be formulated as an ethyl ketone.



The second ketocarboxylic acid giving a positive iodoform test was reported to have formula, $C_{14}H_{24}O_5$, and was obtained by ozonolysis of a liquid diene monoacetate, XII (λ_{max} 239.5 mμ, ϵ_{max} 17,400; present work) prepared by potassium acid sulfate-catalyzed dehydroacetoxylation of X.[9] The conversion X → XII is subject to rearrangements; if no ring contraction occurs,[10] structures XIIa or XIIb are probable (expected[11] λ_{max} 242 mμ, ϵ_{max} >15,000). A 1,3-cyclohexadiene structure is incompatible with the ultraviolet spectrum (expected[11] λ_{max} 263 mμ, ϵ_{max} <10,000). The observed formation of acetaldehyde on ozonolysis[5] is in agreement with the presence of an ethylidene group. The alcohol (XIII) derived from XII by saponification is primary, loses formaldehyde on prolonged heating, and produces α-ethyl-β-propylsuccinic, propionic, and acetic acids on permanganate oxidation.[5] A keto acid derived



from XIIa, XIIb, or XIIc[10] by ozonolysis would be formulated as an ethyl ketone, $C_{15}H_{26}O_5$.[8,9,12]

The identity of the reducing agents in the Cannizzaro reaction leading to III from I now has been clearly established. Aldol isomers (II) are reduced directly to III isomers,[13] but not by II itself (as stated by Pummerer and Smidt[5]) for the following reasons. (1) No III is produced from II alone under conditions whereby I yields III.[4] (2) No C_{16} carboxylic acid (such as one obtained by oxidizing II) was found to be a significant reaction product. (3) The total mole-equivalents of butyric and 2-ethyl-2-hexenoic acids produced account for 90% of the acid formed in the reaction. The reducing agents in the crossed Cannizzaro reaction, based on the number of equivalents of acid produced are butanal (69% of the total reduction), 2-ethyl-2-hexenal (21.5%), and unknown high molecular weight material (9.5%). [About 10% of the high molecular weight material produced a distillable methyl ester when treated with diazomethane; the amount of C_{16} acid (if any) is estimated to be less than 2% of the total carboxylic acid produced.] In addition to glycol III other alcohols formed were butanol (0.3% yield) and 2-ethyl-2-hexen-1-ol (1%). Table II summarizes the material balance of alcohol and carboxylic acid products involved in the Cannizzaro reaction (38.5 hr. at 110°).

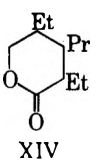
TABLE II

YIELDS OF CANNIZZARO PRODUCTS FROM 2-ETHYL-2-HEXENAL (I)

	Yield, %	Mole-equivalents from 10 moles of I	
Alcohols[a]			
1-Butanol	0.3	0.05	
2-Ethyl-2-hexen-1-ol	1.0	0.09	1.38 total
Glycols (III)	25	1.24	
Acids			
Butyric	4.8	0.96	
2-Ethyl-2-hexenoic	1.5	0.30	1.39 total
Unidentified[b]	(7.6[c])	0.13	

[a] Yield of undistillable neutral residue was 2% by weight. The amount of Cannizzaro derived alcohol in this residue was not determined; it cannot exceed 0.1 mole-equivalent, but is probably much less than this figure. [b] Undistillable acid residue, "neut. equiv.," 730. [c] Weight per cent yield (grams produced from 100 g. of I.

In the present study two lactones (IV and XIV) were obtained from I by the procedure of Pummerer and Smidt in yields of 30% and 9%, respectively.

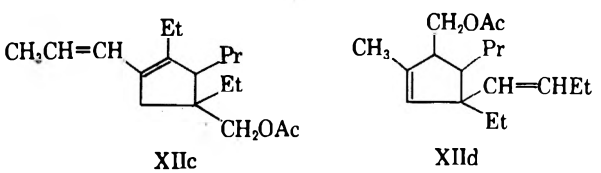


Evidence establishing these structures has been presented.[8,4,14] The amount of IV produced, relative to XIV, decreases as reaction conditions become more vigorous (higher temperature, higher base concentration). Yields of IV and XIV, respectively, under various conditions are 25°, 16 hr. (56 and 0%)[4]; 110°, 38.5 hr. (30 and 9%); 160–200°, 21 hr. (0 and 36%).[14] The values at 25° are with aqueous methanolic potassium hydroxide (0.5 mole-equivalent), the others with

(8) Several workers have observed that ethyl ketones give a positive iodoform test. The reaction has been studied. (a) A. Fry, I. Ookuni, G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Org. Chem.*, **27**, 1914 (1962); (b) C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 1548 (1957); (c) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **71**, 1496 (1949); *cf.* other references cited in these papers.

(9) The elemental analysis of the methyl ester of the ketocarboxylic acid obtained by ozonolysis of XII corresponds to a formula $C_{14}H_{24}O_5$ for the acid; however, the saponification equivalent of the ester is in very close agreement with the keto acid formula, $C_{15}H_{26}O_5$.[5]

(10) Contraction to a five-membered ring such as XIIc cannot be ruled out, nor can the formation of mixtures of conjugated dienes. However, the unconjugated structure XIId, assigned by Pummerer and Smidt,[5] is in disagreement with the observed ultraviolet spectrum.



(11) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Co., New York, N. Y., 1949, pp. 184–198.

(12) Additional data accumulated by Pummerer and Smidt,[5] including degradation of III and XII to various hydrocarbons, $C_{16}H_{28}$ and $C_{16}H_{26}$, appear to be less informative and need not be considered. None of these data would appear to be in disagreement with structure III.

(13) The glycol isomers are believed to form from the corresponding aldol isomers (II), not by base-catalyzed epimerization of III (only possible at C-1). Equilibration of II with its acyclic precursor would lead to a mixture of II diastereoisomers epimeric at C-1 and C-6.

(14) M. Häusermann, *Helv. Chim. Acta*, **34**, 1482 (1951). Other products reported were 1-butanol (8.3%), 2-ethyl-1-hexanol (2.1%), butyric acid (5.1%), 2-ethyl-2-hexenoic acid (2.5%), and a liquid glycol, $C_{16}H_{30}O_2$ (8.4%).

aqueous sodium hydroxide (0.72 mole-equivalent at 110° and 1.0 mole-equivalent at 160–200°). With more vigorous reaction conditions XIV evidently forms at the expense of IV in agreement with the mechanism[4] of the intramolecular formation of these compounds from their common precursor, II.

Experimental[15]

Self-Condensation of 2-Ethyl-2-hexenal (Neutral Products).—The procedure of Pummerer and Smidt[5] was used with slight modifications. To a solution of 250 g. (6.25 moles) of sodium hydroxide in 750 ml. of water was added 1100 g. (8.7 moles) of purified,[3] freshly distilled 2-ethyl-2-hexenal[16] during 4.5 hr., with vigorous stirring (temperature, 67°). The mixture was then refluxed (110° within the liquid), with stirring, for 38.5 hr. (nitrogen atmosphere). The mixture was separated into neutral and acidic products using the procedure previously described. The isolation of acidic products is described subsequently.

The neutral portion was distilled to yield the following fractions: (1) 8 ml., b.p. 60–90° (29 mm.); (2) 18.2 g., b.p. 90–123° (29 mm.), mainly 2-ethyl-2-hexen-1-ol; (3) 44 ml., b.p. 86–142° (1.8 mm.); (4) 296 g., b.p. 145–151° (1.5 mm.), crude glycol mixture; and (5) 22.5 g. of residue. Redistillation of fraction 1 at 740 mm. gave 3 g. of 1-butanol, b.p. 118–120°, and 2.4 g. of 3-heptanone, b.p. 146–151° ($n^{12}D$ 1.4115; 2,4-dinitrophenylhydrazone, m.p. 82–83°, alone, and when mixed with an authentic sample). The possibility that the 3-heptanone was an impurity in the 2-ethyl-2-hexenal employed cannot be discounted.

2-Ethyl-2-hexen-1-ol.—Redistillation of fraction 2 (above) gave 11.6 g., b.p. 95–97° (27 mm.), $n^{11}D$ 1.4490, of 2-ethyl-2-hexen-1-ol (1% yield). (Found: C, 74.36; H, 12.74.) Quantitative bromination by direct titration with bromine in acetic acid indicated 1.03 double bonds (assuming mol. wt., 128.2). The α-naphthylurethan derivative melted at 80–80.5°, alone, and when mixed with an authentic sample (see following). The infrared spectrum was identical with the authentic sample.

An authentic sample of 2-ethyl-2-hexen-1-ol was prepared as follows. To a solution of 10 g. (0.264 mole) of lithium aluminum hydride in 400 ml. of dry ether was added 70.0 g. (0.555 mole) of purified 2-ethyl-2-hexenal during 4 hr., with refluxing and stirring continued for 1 hr. after addition of the aldehyde was complete. After standing at room temperature for 12 hr. and decomposing the reaction mixture with dilute hydrochloric acid in the usual manner, the product was separated by extraction with ether and the extracts dried with magnesium sulfate. Distillation gave 61.5 g. (87%) of the alcohol, b.p. 94–96° (26 mm.), $n^{26}D$ 1.4488. A redistilled, analytical sample had b.p. 93–93.5° (24 mm.), $n^{25}D$ 1.4489; infrared bands at (cm.$^{-1}$) 3400 (OH) and 1670 (C=C).

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.04; H, 12.67.

The **α-naphthylurethan** derivative was obtained as needles from petroleum ether (b.p. 60–70°), m.p. 80–80.5° (79% yield).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 77.05; H, 7.86; N, 4.83.

6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol Isomers (III).—Fraction 4, from the condensation described before, was redistilled[17] to yield 275 g. (25% yield) of viscous glycol mixture, b.p. 146–150° (1.5 mm.), $n^{26}D$ 1.4960. Fractional crystallization from 350 ml. of petroleum ether (b.p. 60–70°) at −15° gave 52.3 g., m.p. 55–60°, and 18.5 g., m.p. 47–55°, after one week. Recrystallization from the same solvent gave feathery needles, m.p. 62–62.5° (42 g.). Samples of glycol obtained by self-condensation of 2-ethyl-2-hexenal for 19 hr. (24% yield) and 96 hr. (25% yield), under the same conditions, gave essentially the same amount of each isomer.

From the sample of mixed glycols (250 g., b.p. 137–142°, 0.5 mm., 25.2% yield) obtained in a 96-hr. run there was isolated by crystallization from 600 ml. of petroleum ether (−15°, 1 week) 69 g., m.p. 45–60°. The filtrate was concentrated to *ca.* one-half its volume and chilled again to −15° to yield, by fractional crystallization, 23.8 g., m.p. 85–90°, and 7.5 g., m.p. 100–105°, after 12 days. Recrystallization of these latter fractions from hexane gave pure samples of glycols, m.p. 90–91° and 112–113°, respectively (*cf.* Table I). The mother liquors were diluted with ether, washed several times with *N* sodium hydroxide solution and water,[17] dried with magnesium sulfate, and distilled to yield 130.5 g., b.p. 155–160° (3 mm.), of glycol from which an additional 8.1 g. of crystals, m.p. 45–59°, was obtained by crystallization from cold hexane (20 days, −15°). A sample of liquid glycol, from which no additional crystals could be obtained, had b.p. 134–135° (0.4 mm.), $n^{25}D$ 1.4960. Analytical data for the four isomers are given in Table I. The isomers could not be interconverted by heating with acid or basic catalysts under a variety of conditions.

A sample of C_{16} glycol (21.1 g.) obtained in 74% yield by lithium aluminum hydride reduction of 2-hydroxy-6-propyl-1,3,5-triethyl-3-cyclohexene-1-carboxaldehyde (II)[3] was crystallized from hexane at −15° to yield 1.6 g. (5.7% yield from II), m.p. 90–111°; no 60° isomer was obtained. Recrystallization gave 1.12 g., m.p. 110–112°. The remaining liquid glycol, $n^{22}D$ 1.4957, from which no additional crystals could be obtained had the same infrared spectrum as the previous liquid glycol from the condensation and formed the same bis-*p*-nitrophenylurethan and bis-3,5-dinitrobenzoate derivatives (Table I).

A sample of C_{16} glycol obtained by self-condensation of 2-ethyl-2-hexenal at 25° (4-hr. reaction time) was dissolved in petroleum ether and stored at −15° for 11 months; seeding with crystalline isomers produced no crystals during this time. Similarly, a sample (3 g.) obtained by a 7-hr. reaction time at 25° produced 0.04 g. (1.3%), m.p. 87–91°, as the only crystalline product.

The infrared spectra of the solid glycol isomers were determined in potassium bromide; that of the liquid, neat. All showed strong OH stretching absorption at 3500 cm.$^{-1}$ and weak, broad C=C absorption at 1640 cm.$^{-1}$. No carbonyl absorption was present. Small, but significant differences in the spectra of the four isomers were evident in the region 700–1500 cm.$^{-1}$. A band of medium intensity which appears at 1080–1090 cm.$^{-1}$ in each of the crystalline isomers is absent in the liquid isomer. A synthetic mixture of isomers prepared to agree closely in composition with the amounts isolated in a particular run (55% liquid, 30% 62°, 10% 90°, and 5% 112°) had the same infrared spectrum as the distilled uncrystallized mixture obtained from the condensation.

The **bis-3,5-dinitrobenzoate** derivatives listed in Table I were prepared by heating one mole-equivalent of glycol with two mole-equivalents of 3,5-dinitrobenzoyl chloride in dry pyridine solution under reflux for 20–40 hr. The derivatives were isolated by pouring the reaction mixture into ice-cold *N* hydrochloric acid and recrystallizing the precipitated product from ethanol. Several attempts to prepare a crystalline bis-3,5-dinitrobenzoate derivative of the 112° isomer by a variety of procedures were unsuccessful.

Self-Condensation of 2-Ethyl-2-hexenal (Acidic Products).—Distillation of the acidic portion of the reaction mixture (from 1100 g. of 2-ethyl-2-hexenal—condensation described earlier) gave the following principal fractions: (1) 48.3 g., b.p. 72–89° (28 mm.) mainly butyric acid; (2) 132 g., b.p. 95–114° (0.5–1.9 mm.), mainly a mixture of 2-ethyl-2-hexenoic acid and XIV; (3) 352 g., b.p. 171–178° (1.5–2.0 mm.), of crude 3-propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioic acid 1,5-lactone (IV) (30% yield); and (4) 84 g. of brown, semisolid, undistillable residue.

Butyric Acid.—In addition to the butyric acid obtained in fraction 1, preceding, some also was isolated from the aqueous portion of the reaction mixture. (Previously,[4] the aqueous part had not been investigated for acidic material. In this run about 24% of the total free acid was found in the water.) The combined aqueous solution from the previous condensation reaction was acidified with sulfuric acid and steam-distilled until essentially no more acid was found in the distillate (total volume, 61 l.; total of 0.288 gram-equivalent of acid present by direct titration). The distillate was made slightly alkaline with sodium hydroxide and concentrated to a volume of 200 ml. Acidification of this concentrate with sulfuric acid followed by continuous extraction with ether for 31 hr. led to the isolation of 18.9 g. (0.213 mole) of butyric acid, b.p. 77–79° (26 mm.). The total butyric acid

(15) Melting points were determined on a Kofler hot stage and are uncorrected. Ultraviolet spectra were measured in 95% ethanol; infrared spectra of liquids were determined neat.

(16) A generous supply of 2-ethyl-2-hexenal was supplied by the Carbide and Carbon Chemicals Corp., South Charleston, W. Va.

(17) Acidic and/or peroxide impurities often accumulate in samples of the glycols stored in the presence of air and cause decomposition (primarily dehydration) on subsequent distillation. These impurities may be removed by several washings of an ether solution of the sample with *N* sodium hydroxide solution.

yield from 8.7 moles of I is 0.83 mole, including both previously distilled samples (67.2 g., combined, 0.765 mole, neut. equiv., 88.4, corrected for traces of neutral impurity) and 6.1 g. of miscellaneous foreruns and residues (*cf.* Table II).

2-Ethyl-2-hexenoic Acid.—Fraction 2 was extracted with saturated sodium bicarbonate solution to remove 2-ethyl-2-hexenoic acid. Distillation gave, as one fraction, 22.6 g. (0.16 mole), b.p. 95–99° (1 mm.), $n^{25}D$ 1.445, of 2-ethyl-2-hexenoic acid; neut. equiv., 143.8 (calculated for $C_8H_{14}O_2$, 142.2); infrared spectrum identical with authentic sample. The total yield of 2-ethyl-2-hexenoic acid from 8.7 moles of I is 0.26 mole including the previous purified sample and 14 g. (0.1 mole) of miscellaneous foreruns and residues (*cf.* Table II).

2,4-Diethyl-3-propyl-1,5-pentanolactone (XIV).—The material not removed by the sodium bicarbonate extraction of fraction 2 was isolated and distilled, yielding 79 g. (9%), b.p. 111–117° (1.9 mm.), $n^{25}D$ 1.466, of lactone XIV as the main product. The infrared spectrum was identical with that of an authentic sample, previously obtained.[3]

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; mol. wt., 198.3. Found: C, 72.91; H, 10.74; sapon. equiv., 204.

Acid Residue.—The 84 g. of viscous acid residue was found to contain a total of 0.115 gram-equivalent of acidic material (neut. equiv., 730). Separation of this sample into neutral and carboxylic acid fractions by extraction with sodium bicarbonate solution gave 53 g. of viscous acid mixture (neut. equiv., 470) and 27 g. of neutral residue. Treatment of 39.6 g. of the acidic material, dissolved in ether, with excess diazomethane gave 5.3 g., b.p. 124–127° (1 mm.), 4.0 g., b.p. 135–172° (0.7 mm.), and 30.4 g. of undistillable residue. None of the previous substances was investigated further. The distilled material (9.3 g.) would represent *ca.* 0.03 mole, assuming mol. wt., 282.

6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-one (VI).—Glycol III, isomer, m.p. 88–90°, (5.0 g.), manganese dioxide catalyst[7] (30 g.), and 60 ml. of cyclohexane were mixed and the mixture shaken continuously at room temperature for 89 hr. The mixture was filtered and washed with cyclohexane to yield 4.86 g. of colorless oil after removal of solvent. Distillation gave 4.0 g. (80%) of ketol VI, b.p. 117–118° (0.5 mm.), $n^{25}D$ 1.491; infrared bands at 3500 and 1650 cm.$^{-1}$ (C=O, conjugated) in chloroform solvent; ultraviolet spectrum, λ_{max} 240 mμ (ϵ_{max} 9000). Oxidation of the other three glycol isomers also gave ketols, $C_{16}H_{28}O_2$, having similar properties.[6b]

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.12; H, 11.4.

The ketol derived from the 90° glycol isomer was dissolved in ether (10 ml.) and added to a solution of 1.0 g. of lithium aluminum hydride in 50 ml. of ether and the mixture was refluxed for 22 hr. Decomposition in the usual manner with dilute hydrochloric acid led ultimately to 0.71 g. of glycol, m.p. 88–89°, after crystallization from hexane. Reduction in a similar manner of ketols derived from the other glycol isomers also led to regenerated glycols.[6b]

5-Propyl-2,4,6-triethyl-2-cyclohexen-1-one (VII). A. By Demethylolation of VI.—A 1.05-g. sample of ketol VI (derived from liquid glycol isomer) was heated for 15 min. with a flame in a stream of nitrogen. The exit gases were passed through Johnson's reagent to produce formaldehyde 2,4-dinitrophenylhydrazone (0.09 g.), m.p. 160–165°. During the heating, gas evolution was noted and the loss in weight was 0.13 g. (calculated loss of weight due to formaldehyde evolution, 0.123 g.). The residue (0.90 g.) was distilled to yield 0.6 g. of ketone VII, b.p. 85–90° (0.25 mm.), $n^{24}D$ 1.4770, and 0.3 g. of residue; infrared band (chloroform) at 1660 cm.$^{-1}$ (conjugated C=O); ultraviolet, λ_{max} 241 mμ, ϵ_{max} 7630 (lit.[3] λ_{max} 242 mμ, ϵ_{max} 5600). This procedure yields the purest sample of VII.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.28; H, 12.13.

B. By Oxidation of III.—A 12.7-g. (0.05 mole) sample of glycol III (isomer, m.p. 61–62°) was oxidized with chromic oxide in aqueous acetic acid using a slight modification of the procedure developed earlier[3] for oxidation of aldol II. The decarboxylation at 70° gave a 20% yield of carbon dioxide; the liquid glycol mixture gave the same result. Addition of mercuric oxide and additional heating did not increase the yield of carbon dioxide.

The reaction mixture was made alkaline with sodium hydroxide and steam-distilled to yield 4.6 g. (41%) of ketone VII, b.p. 96–105° (0.8 mm.); redistillation gave 3.3 g., b.p. 90–92° (0.7 mm.), $n^{27}D$ 1.4790. A similar oxidation of the liquid glycol mixture gave a 43% yield of VII, b.p. 87–88° (0.5 mm.), $n^{26}D$ 1.4770 (Found: C, 80.20; H, 11.82); infrared bands at 1670 (C=O) and 1625 (C=C) cm.$^{-1}$; ultraviolet, λ_{max} 241 mμ, ϵ_{max} 7800.

The aqueous alkaline residue was acidified with sulfuric acid and heated with mercuric oxide and the liberated carbon dioxide collected as previously[3] to assay formic acid; yields were 21% and 24% from the 62° and liquid glycol mixture, respectively. The combined yields of carbon dioxide and formic acid (41–44%) correspond closely to the yield of VI (41–43%).

2,4,6-Triethyl-3-propylphenol (VIII) was prepared from ketone VII (obtained by chromic acid oxidation of III, m.p. 62°) by dehydrogenation with palladium–charcoal catalyst as previously described.[3] From 6.0 g. of ketone was isolated 2.0 g., b.p. 90–91° (0.45 mm.), $n^{25}D$ 1.4975, and 1.2 g., b.p. 91–93° (0.45 mm.), $n^{25}D$ 1.5070; λ_{max} 283.5, ϵ_{max} 1780; reported[3] for authentic sample, b.p. 96–98° (0.4 mm.), $n^{25}D$ 1.519, λ_{max} 282 mμ, ϵ_{max} 2040; infrared spectrum identical with the authentic sample except for some slight carbonyl absorption at 1678 cm.$^{-1}$. The **phenylurethan** derivative melted at 123–124° (lit.[5] m.p. 122–122.5°) and when mixed with an authentic sample the melting point was not depressed.

6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol Diacetate (X).—The procedure of Pummerer and Smidt[5] was followed to yield the diacetate X from the liquid glycol isomer, 78–79% yield, b.p. 136–138° (0.95 mm.), $n^{22}D$ 1.4733 (lit.[5] $n^{20}D$ 1.4745); strong acetate band at 1750 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.04; H, 10.13.

Dehydroacetoxylation of diacetate X to the diene monoacetate (XII) was accomplished by the procedure of Pummerer and Smidt.[5] A 39.0-g. sample of X was mixed with 55.6 g. of freshly melted and powdered potassium acid sulfate and heated in an oil bath maintained at 86–96° for 3 hr. The mixture was distilled under reduced pressure to remove the acetic acid (2-hr. heating at bath temperature of 92°). There was obtained 6.4 g. (0.925 mole-equivalent) of acetic acid distillate (neut. equiv., 61). The residue was diluted with water, extracted with ether, and the combined extracts washed several times with water and dried; removal of the ether gave 28.7 g. of orange oil. Distillation under nitrogen gave 22.4 g. (70% yield) of dienemonoacetate, b.p. 100–106° (0.4 mm.), $n^{25}D$ 1.489; infrared bands, 1740 (C=O, ester) and 1640 (C=C) cm.$^{-1}$; ultraviolet, λ_{max} 239.5 mμ, ϵ_{max} 17,400.

The Base-Catalyzed Self-Condensation of α,β-Unsaturated Ketones. Structure of Heilbron's Styryl Alkyl Ketone Dimers[1]

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The crystalline dimers obtained by base-catalyzed self-condensation of certain styryl alkyl ketones have been shown to be 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones. They are not 1,3-dialkanoyl-2,4-diarylcyclobutanes, as suggested previously by other workers. Three such dimers have been dehydrogenated to 4-alkanoyl-2-alkyl-3,5-diarylphenols and the latter substances cleaved to 2-alkyl-3,5-diarylphenols and alkanoic acids. 2-Ethyl-3,5-diphenylphenol obtained by this reaction sequence was identical with a sample prepared by an independent synthesis. Dimers have been obtained in 13–22% yield from ketones of the type ArCH=CH-$COCH_2R$ where R may be any alkyl group other than methyl and Ar is a phenyl group, unsubstituted or one having electron-releasing groups in the *para* (preferably) or *meta*, but not *ortho* position.

In a previous report[3] it was concluded that the base-catalyzed self-condensation of α,β-unsaturated ketones, $RCH_2CH{=}CHCOCH_2R'$, proceeds initially as a Michael condensation, in all known examples of this reaction, to form as the primary product an acyclic monoolefinic 1,5- or 1,7-diketone. As the final product, four structural types (A–D) were recognized: (A) an acyclic monoolefinic diketone, (B) a cyclic saturated diketone, (C) a cyclic monoolefinic ketol, and (D) a cyclic diolefinic monoketone. Products B–D arise from A by Michael or aldol condensations. Numerous reported examples of these various possibilities are now known.[3,4] In the present study the self-condensation of a group of styryl alkyl ketones to cyclic saturated diketones (product type B) has been examined and the structures of the products established. Throughout the following discussion the term monomer is applied to the styryl alkyl ketones, and dimer to the derived cyclic saturated diketones.

The base-catalyzed self-condensation of certain styryl alkyl ketones ($ArCH{=}CHCOCH_2R$) to form dimeric saturated diketones was first recognized by Heilbron and co-workers,[5–7] who prepared many such compounds. These workers also noted the existence of certain dimers of this type which earlier had been described as monomers by others.[8–11] Since the publication of Heilbron's work, only one other report has appeared describing this reaction.[12] None of the reports describes structure elucidation studies on the dimers.

Studies of reaction conditions were made by Heilbron[5–7] and have been extended by us. The condensation is generally conducted with one mole-equivalent each of aromatic aldehyde and methyl ketone for *in situ* formation of the styryl alkyl ketone monomer, which then self-condenses. Although the pure styryl alkyl ketones may be employed, this procedure usually offers no advantage. Sodium hydroxide catalyst (*ca.* 0.2 mole-equivalent) in *ca.* 97% ethanol (3% water) solvent and a reaction time of two to ten days at room temperature, or four to six hours at reflux temperature, were employed in the present work. Water solvent favors monomer formation.[5–7] (In the preparation of styryl propyl ketone dimer 87% ethanolic sodium hydroxide led to 14.5% yield of dimer, whereas ethanolic sodium ethoxide gave a 17.4% yield.) The reaction is not catalyzed by ultraviolet light or heat in the absence of base. Yields are generally low (13–22%) but the reaction is very easily adapted to large-scale preparations—the dimer crystallizes from the reaction solution and is recovered by simple filtration. Usually a single recrystallization from ethanol or ethanol–ethyl acetate produces a pure product. In the condensation of 4-dimethylaminobenzaldehyde with 2-octanone at room temperature (twenty-two hours, 0.4 mole-equivalent of sodium hydroxide) the product which crystallized from the reaction mixture was the monomer, 4-dimethylaminostyryl hexyl ketone (52% yield); by heating the monomer in ethanolic sodium hydroxide solution (50–78°, twenty-four hours), the dimer V was produced in 17.9% yield. Table I summarizes examples of the present study; yields, seldom mentioned in Heilbron's work, are recorded.

Properties of the various styryl alkyl ketone dimers are entirely similar. They are all colorless and relatively much higher melting than the corresponding monomers. Their solubility in most organic solvents is somewhat low. They may be crystallized from hot ethanol or ethanol–ethyl acetate, often in the form of very long, fine needles. Their infrared spectra reveal no hydroxyl or olefinic stretching bands; strong carbonyl absorption is found, usually two bands near 1700 and 1720 $cm.^{-1}$ in potassium bromide, but only one near 1720 $cm.^{-1}$ in carbon tetrachloride solution. The ultraviolet spectra indicate two unconjugated, independently absorbing aryl groups per molecule; in ethanol λ_{max} near 259 mμ (ϵ_{max} 400–600). The compounds do not decolorize potassium permanganate in acetone solution. It is evident that they are saturated diketones as originally suggested by Heilbron.[5–7]

Although the number of different examples of the dimerization reaction previously reported is large (*ca.* twenty-two)[5–7,9,12] no chemical evidence previously has been presented which establishes the structure of any one. Heilbron[6,7] noted the similarity in certain chemi-

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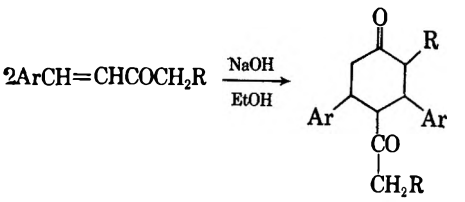
TABLE I

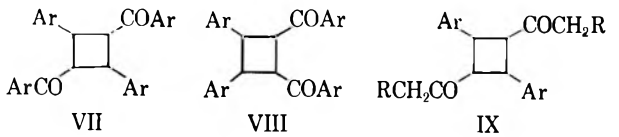
SYNTHESIS OF STYRYL ALKYL KETONE DIMERS



Dimer	Ar	R	Yield, %[a]	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. Mol. wt.	Found C	Found H	Found Mol. wt.
I	C_6H_5	Ethyl	14.5[b]	198–199[c]	$C_{24}H_{28}O_2$	82.72	8.10	348.5	82.80	8.29	319
II	C_6H_5	Isopropyl	22.4[d]	205–206[d]	$C_{26}H_{32}O_2$	82.93	8.57	376.5	82.76	8.03	412
III	C_6H_5	Octyl	13.9	116–118[e]	$C_{36}H_{52}O_2$	84.32	10.22	512.8	84.74	10.36	484
IV	4-$CH_3C_6H_4$	Butyl	20.2	165–167[f]	$C_{30}H_{40}O_2$	83.28	9.32	432.6	83.06	9.54	465
V	4-$(CH_3)_2NC_6H_4$	Pentyl	17.9	185–186[f]	$C_{34}H_{50}N_2O_2$[g]	78.51	9.72	518.8	78.56	9.54	492
VI	4-*i*-PrC_6H_4	Hexyl	12.6	161–162[f]	$C_{38}H_{56}O_2$	83.77	10.36	544.8	84.02	10.38	538

[a] Yields of pure recrystallized material. [b] Yield, 17.4% with sodium ethoxide in ethanol, m.p. 196–197°. [c] Reported m.p. 194–195°.[6b] [d] Reported 13.6% yield[6b]; m.p. 202°,[6b] 209°.[12] [e] Reported m.p. 116°.[6a,11] [f] New compounds. [g] Calcd.: N, 5.40. Found: N, 5.21.

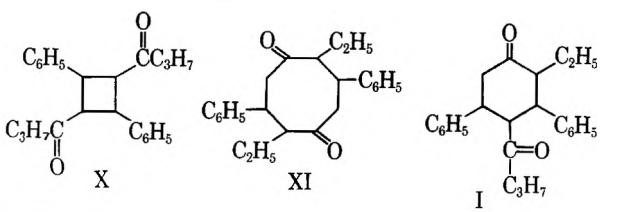
cal and physical properties between his dimers and those obtained by Stobbe[13,14] by photodimerization of chalcones (ArCH=CHCOAr). Stobbe's "truxillic" ketones (VII) are produced by prolonged exposure of chalcones to ultraviolet illumination. They form monocarbonyl derivatives (with difficulty) in contrast to the isomeric 1,2-diaroyl "truxinic" ketones (VIII), which have relatively lower melting points and readily form biscarbonyl

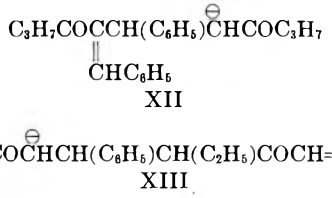


Ar = Aryl; R = Alkyl

derivatives. Heilbron's dimers were described as saturated and relatively inert, forming monoximes with difficulty, and they were arbitrarily assigned the cyclobutane ("truxillic" type) structure (IX). Despite lack of evidence supporting structure IX, the notion has persisted that the dimers are cyclobutane derivatives,[12,15] although an observation has been made that this structure is probably incorrect.[16]

Styryl propyl ketone dimer (I), the simplest known example,[6b,8] was selected for detailed structure elucidation studies. By considering the base-catalyzed dimerization of the monomer to proceed by two successive Michael additions to a cyclic saturated diketone (product type B, discussed previously), three possible structures could be considered (X, XI, and I). These products would arise through anions (XII and XIII) of two possible intermediate acyclic monoolefinic 1,5-diketones.





Anion XII would seem an unlikely intermediate since its formation would require either prior abstraction of an unreactive vinyl proton from the monomer, or reaction through an anion of a ketol ($C_3H_7COCHCHOHC_6H_5$). It could lead to X or I, but formation of a cyclobutane ring (X) is not favored in Michael condensations.[17] To produce an anion leading to XI would require prior prototropic rearrangement of XIII to place the negative charge on the starred carbon atom. However, XIII is formed directly in the initial Michael condensation of two monomers and could lead directly to the favored six-membered ring product (I) in the second, intramolecular, Michael condensation.

Chemical evidence establishing structure I for styryl propyl ketone dimer was obtained in the following manner. Heating I with palladium-on-charcoal catalyst gave a ketone phenol, $C_{24}H_{24}O_2$, m.p. 172–173°. Strong hydroxyl stretching absorption was present at 3450 cm.$^{-1}$; carbonyl absorption was shifted to 1670 cm.$^{-1}$ (potassium bromide) in the dehydrogenated product. The ultraviolet spectrum was changed from one resembling benzene (in I) to one having a single intense band at 239 mμ (ε 21,500, ethanol). These data support a phenol structure, having an alkanoyl group attached to the aromatic ring, such as compound XIV. Heating the ketone phenol with a catalytic amount of camphorsulfonic acid[18] led to an oily product (not purified) having hydroxyl absorption in the infrared, strong carbonyl absorption at 1740 cm.$^{-1}$ (ester), and practically no absorption near 1670 cm.$^{-1}$. This mixture is believed to be principally ester XVII and phenol XX. It was treated with hot aqueous ethanolic sodium hydroxide solution to yield 3,5-diphenyl-2-ethylphenol (XX), m.p. 82–83° (λ_{max}^{EtOH} 238

(13) H. Stobbe and A. Hensel, *Ber.*, **59**, 2254 (1926).

(14) H. Stobbe and K. Bremer, *J. prakt. Chem.*, **123**, 1 (1929).

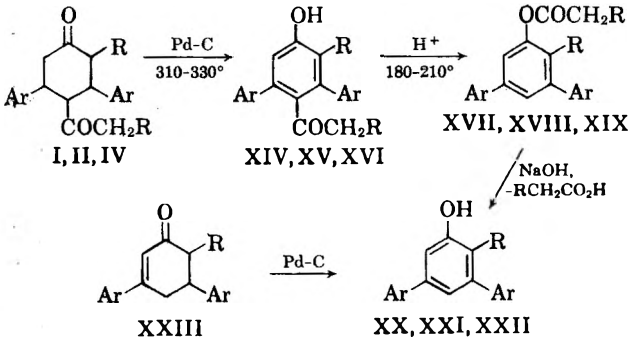
(15) R. A. Raphael in "Chemistry of Carbon Compounds," Vol. IIA; E. H. Rodd, Ed., Elsevier, 1953, pp. 48, 57.

(16) E. R. H. Jones and H. P. Koch, *J. Chem. Soc.*, 393 (1942).

(17) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 248 (1959).

(18) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928).

mμ, ε 25,300), and butyric acid (identified as its *p*-phenylphenacyl ester). The acid-catalyzed treatment evidently led to a retrograde Fries rearrangement of XIV which produced ester XVII. An authentic sample of XX was synthesized from the known 3,5-diphenyl-



I, XIV, XVII, XX, XXIII. R = Et, Ar = C_6H_5
II, XV, XVIII, XXI. R = *i*-Pr, Ar = C_6H_5
IV, XVI, XIX, XXII. R = Bu, Ar = 4-$CH_3C_6H_4$

6-ethyl-2-cyclohexen-1-one (XXIII)[19] by heating with palladium on charcoal; it was identical with the sample obtained from I.

Preceding degradation sequence also was successful with styryl isobutyl ketone dimer (II)[20] and 4-methylstyryl amyl ketone dimer (IV), leading to ketone phenols XV and XVI, respectively. Heating these substances with camphorsulfonic acid, followed by saponification of the intermediate esters XVIII and XIX, led to phenols XXI and XXII, respectively (the latter compound was a liquid and not characterized). In each saponification reaction the respective aliphatic acid was isolated and identified as its *p*-phenylphenacyl ester. From XIX hexanoic acid itself was isolated. The amount of steam volatile organic acid (isovaleric) obtained by saponification of XVIII was 0.95 mole-equivalent. It is believed reasonable to conclude that other styryl alkyl ketone dimers which have physical and chemical properties like I are also 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones.

The scope of the dimerization reaction has been examined with respect to structure of alkyl (R) and aryl (Ar) groups in the styryl ketone monomer, ArCH=CHCOCH$_2$R. Heilbron determined that the reaction failed with styryl isopropyl and styryl *t*-butyl ketones and thus established the necessity of an RCH$_2$ group.[6,21] All monomers with alkyl or arylalkyl substituents RCH$_2$ which have been examined undergo the reaction, including those with R = *n*-alkyl from ethyl through octyl,[6] isopropyl,[6] 2-methylbutyl,[9] benzyl,[7,22] and β-phenylethyl,[7,22] but not methyl.[6,23] The reaction fails when R = hydrogen.[5] It should be noted that R cannot be aryl, for in the condensation of aldehydes with benzyl methyl ketone condensation occurs on the methylene group.[7]

The position and type of ring substituent in the phenyl group of the styryl alkyl ketone monomer affect the dimerization reaction. Successful dimerizations have been realized with phenyl substituents hydrogen, *p*-methyl and *p*-isopropyl reacting at room temperature, and with *p*-dimethylamino, *p*-methoxy, *p*-chloro, 3,4-dimethoxy, and 3,4-methylenedioxy reacting at refluxing ethanol temperature (but not at room temperature). Failures have been reported for *o*-chloro, *o*-methyl, *o*-hydroxy, *m*-chloro, *m*-methoxy, *m*-nitro, and *p*-nitro substituents. The *ortho* substituents prevent the reaction and *para* substitution, relative to *meta*, appears to facilitate it. The effects of ring substitution on certain other Michael reactions fall closely into this pattern of reactivity; *e.g.*, addition of ethyl acetoacetate to various unsymmetrically substituted dibenzylideneacetones, and diethyl malonate to ring substituted benzylidene methyl ketones.[24] For these various Michael reactions, *p*-phenyl substituents affect the yield, to a rough approximation, in the order: CH_3, *i*-Pr > H > $(CH_3)_2N$ > OH > CH_3O, Cl > NO_2. This order reflects the position of equilibrium, not the rate of Michael addition. Although it follows closely Taft's σ_I values,[25] it is difficult to attach significance to this observation until more is learned of the effects of ring substituents on the forward and reverse Michael reaction. The reaction would be expected to resemble cyanohydrin formation of aromatic aldehydes where electron-withdrawing groups enhance the rate.[26] On the other hand, it should be noted that the effect of ring substituents on the cyanohydrin equilibrium is not profound in degree,[26] and (by comparison) somewhat different reaction constants (ρ) for the forward and/or reverse Michael addition could produce the equilibrium order we observed.

Experimental[27]

4-Butanoyl-3,5-diphenyl-2-ethylcyclohexan-1-one [Styryl Propyl Ketone Dimer (I)].—The procedure of Heilbron and Irving[6b] was used with slight modifications. Benzaldehyde (106 g., 1 mole) and 2-pentanone (86 g., 1 mole) were dissolved in 500 ml. of absolute ethanol. A 10% solution of sodium hydroxide (75 ml.) was added all at once and the mixture was stirred for a few moments. The temperature rose rapidly to 40° and within 20 min. had reached a maximum of 49°. After about 40 min. crystals were noted in the orange solution. The mixture was stored in the dark at room temperature for 6 days before filtering the product and washing with ethanol; the crude product weighed 34.4 g., m.p. 180–193°. The filtrate was chilled and the second crop of crystals was recrystallized from a mixture of ethyl acetate and ethanol to yield 5.0 g., m.p. 193–194°. Recrystallization of the first crop from the same solvent mixture gave 20.0 g., m.p. 198–199°. The total yield of recrystallized material, 25 g., was 14.5%.

The product failed to decolorize potassium permanganate in acetone solution. The ultraviolet absorption spectrum revealed several sharp maxima of low intensity (ϵ_{max} in parentheses): 243

(19) W. Dieckmann, *Ber.*, **46**, 2703 (1912).

(20) The dimer II has been isolated in three isomeric forms[12] (m.p. 205°, 170°, and 140°) shown in our work to be diastereoisomers. The stereochemistry of these substances will be discussed in a forthcoming publication.

(21) Phenyl *n*-alkyl ketones undergo normal Michael addition to chalcone, whereas isobutyrophenone does not; *cf.* D. B. Andrews and R. Connor *J. Am. Chem. Soc.*, **57**, 895 (1935).

(22) A number of monomers of the type, ArCH=CHCO(CH$_2$)$_n$C$_6$H$_5$ (*n* = 2,3), have been prepared in *ca.* 50% aqueous ethanolic sodium hydroxide [*Cf.* M. Clark and J. D. A. Johnson, *J. Chem. Soc.*, 126 (1962)]; no evidence of dimers was found. On the other hand, Heilbron[7] found dimers to form from this monomer type when Ar = C$_6$H$_5$ by reaction in *ethanolic* sodium hydroxide. This difference in results confirms the importance of solvent in the reaction.[5-7]

(23) Crystalline products have been obtained by condensation of benzaldehyde and 2-methoxybenzaldehyde with 2-butanone (product formulas $C_{28}H_{28}O_2$ and $C_{24}H_{26}O_3$, respectively). Preliminary evidence indicates their structures to be of a different type from I (unpublished results, this laboratory); *cf.* ref. 5 and C. V. Gheorghiu and B. Arwentiew, *Bull. soc. chim. France*, (4) **47**, 195 (1930).

(24) Ref. 17, p. 219 and pp. 300–327.

(25) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

(26) J. W. Baker and H. B. Hopkins, *J. Chem. Soc.*, 1089 (1949).

(27) Melting points were determined on a Kofler block and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol. Infrared spectra of liquids were determined neat unless otherwise stated.

(285), 248 (354), 253 (469), 258 (596), 265 (555), and 268 mμ (445), and a broad band at 288 mμ (372). The infrared spectrum (potassium bromide) revealed no absorption near 3500 cm.$^{-1}$ but split carbonyl bands (1690 and 1720 cm.$^{-1}$); in carbon tetrachloride solution a single carbonyl band appeared at 1720 cm.$^{-1}$. The other dimers prepared (Table I) were found to have very similar ultraviolet and infrared spectra.

The preparation of I was repeated using sodium ethoxide catalyst (0.2 mole) in 500 ml. of absolute ethanol and a room temperature reaction time of 65 hr. The crude product (40.0 g.) was recrystallized from ethanol to give 30.2 g. (17.4% yield), m.p. 196–197°.

Preparation of Styryl Alkyl Ketone Dimers.—The first procedure described, used for preparing I, was employed for the preparation of other dimers, except that the solvent was *ca.* 97% ethanol rather than 87% [one mole each of aldehyde and ketone were dissolved in 680 ml. of absolute ethanol and 30 ml. of 25% sodium hydroxide solution (aqueous) was added]. The following aldehydes and ketones were condensed at room temperature (reaction times listed in parentheses): benzaldehyde with methyl isobutyl ketone to form II (10 days); *p*-tolualdehyde and 2-heptanone to form IV (12 days); cuminaldehyde with 2-nonanone to form VI (6 days). In these reactions there was an initial rapid exothermic reaction with a temperature rise to *ca.* 40–50°, followed by cooling to room temperature within *ca.* 3 hr. The reaction time selected was somewhat arbitrary and often longer than necessary, since almost all of the crystalline product appeared to form within 1–2 days. Benzaldehyde and 2-undecanone were condensed to form III by initially heating on the steam bath for 4 hr., then allowing to stand at room temperature for 42 hr. The products were recrystallized from ethanol or ethyl acetate or mixtures of these solvents. The preparation of one other dimer (V) is described subsequently. Yields, melting points, elemental analyses, and molecular weights of pure, recrystallized products are summarized in Table I. Reactions, separately, of 4-nitro- and 3-nitrobenzaldehyde with 2-decanone resulted in the formation of dark tarry material from which no crystalline product could be isolated.

4-Dimethylaminostyryl Hexyl Ketone.—To a solution of 74.6 g. (0.5 mole) of 4-dimethylaminobenzaldehyde and 64.1 g. (0.5 mole) of 2-octanone in 340 ml. of absolute ethanol was added 30 ml. of a 25% aqueous sodium hydroxide solution. The aldehyde slowly dissolved as the mixture was agitated and the temperature rose from 22° to 27°. The dark solution on standing at room temperature for 22 hr. deposited yellow crystals which were removed by filtration; yield 86.8 g., m.p. 71–72°. Recrystallization from ethanol gave large yellow needles, 67.6 g. (52% yield), m.p. 77–78°; a second recrystallization from ethanol did not raise the melting point. Infrared bands at 1660 (C=O) and 1640 (C=C) cm.$^{-1}$ (Nujol mull).

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.40; mol. wt., 259.4. Found: C, 78.83; H, 9.42; N, 5.34; mol. wt., 290, 308.

4-Hexanoyl-3,5-bis(4-dimethylaminophenyl)-2-pentylcyclohexan-1-one [4-Dimethylaminostyryl Hexyl Ketone Dimer (V)].—A mixture of 81.8 g. of 4-dimethylaminostyryl hexyl ketone, 300 ml. of absolute ethanol, and 25 ml. of 25% aqueous sodium hydroxide solution was heated to 50–55° to obtain a solution and maintained at this temperature for 17 hr. and at 75–78° for an additional 7 hr. After cooling to room temperature and allowing to stand 24 hr. the mixture was filtered to yield 19.7 g. of crystals, m.p. 173–179°. Recrystallization from ethanol–ethyl acetate gave 14.6 g. (17.9%) of needles, m.p. 184–186°; recrystallization gave 13.9 g., m.p. 185–186°; properties are summarized in Table I.

Attempted Photodimerization of Styryl Isobutyl Ketone.—Styryl isobutyl ketone was prepared by the procedure of Metayer.[12] A 94-g. sample (0.5 mole) was placed in a quartz flask and irradiated for 96.5 hr. using a high-energy ultraviolet lamp while the liquid was stirred continuously. Distillation gave 86.9 g. (92.5%) of recovered ketone and a small amount of dark liquid residue which failed to crystallize.

4-Butanoyl-3,5-diphenyl-2-ethylphenol (XIV).—A 2-g. sample of styryl propyl ketone dimer (I) and 0.3 g. of 10% palladium-on-charcoal catalyst were thoroughly mixed in a test tube and heated (nitrogen atmosphere) with a flame for 30 min. (temp., 310–320° in the liquid). After cooling to room temperature, the volatile materials which had condensed on the walls of the test tube were removed by rinsing out with cold chloroform. The solid residue remaining was extracted with boiling chloroform and filtered and the filtrate concentrated to dryness. From three such runs there was obtained 4.6 g. of a brown solid which was crystallized from benzene to yield 0.95 g., m.p. 168–171°, and 0.25 g., m.p. 152–162°, of crude phenol in successive crops; total yield, 1.20 g. (20%). Recrystallization from benzene gave small prisms, m.p. 172–173°; infrared spectrum (potassium bromide), strong OH stretching band (3500 cm.$^{-1}$) and conjugated carbonyl at 1670 cm.$^{-1}$; ultraviolet spectrum, λ_{max} 239 mμ (ε 21,500) and shoulder at 290 mμ (ε 4000). No color change was noted when the phenol was added to ethanolic ferric chloride solution.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.64; H, 7.19.

3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)phenol (XV).—The procedure used for preparing XIV was employed with styryl isobutyl ketone dimer (II), m.p. 205–206°; temp., 310–320°, 15-min. heating. From three 2-g. batches there was obtained 5.44 g. of yellow solid which was crystallized first from ethanol to yield 1.88 g. of recovered dimer, m.p. 198–207°. The mother liquor was concentrated to dryness and the residue crystallized from benzene to yield 1.38 g. (23%) of phenol XV, m.p. 193–200°; recrystallization gave small rhombic crystals, m.p. 202–203°. Infrared bands at 3500 (OH) and 1670 (conjugated C=O) cm.$^{-1}$ (potassium bromide); ultraviolet spectrum showed shoulders near 240 mμ (ε 23,000) and 290 mμ (ε 4000). No change in color in ferric chloride solution was observed.

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 84.13; H, 8.20.

2-Butyl-3,5-bis(4-methylphenyl)-4-hexanoylphenol (XVI).—The procedure used for preparing XIV was employed with 4-methylstyryl amyl ketone dimer (IV); temp., 320–330°, 20-min. heating. The crude residue (5.15 g.) was crystallized first from ethanol to yield 0.83 g. of recovered dimer, m.p. 160–164°. The mother liquor was concentrated to dryness and the residue crystallized from heptane to yield 1.65 g. (28%) of phenol XVI, m.p. 101–105°. Two recrystallizations from hexane gave 1.2 g., m.p. 105.5–107°; further recrystallization gave prisms, m.p. 106–108°; infrared bands at 3500 (OH) and 1670 cm.$^{-1}$ (conjugated C=O) (potassium bromide); ultraviolet spectrum, broad maximum near 237 mμ (ε 28,000) and shoulder at 290 mμ (ε 4950). No color was produced in ethanolic ferric chloride solution.

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.07; H, 8.47. Found: C, 83.57; H, 8.07.

Deacylation of 4-Butanoyl-3,5-diphenyl-2-ethylphenol to 3,5-Diphenyl-2-ethylphenol (XX).—A mixture of 0.344 g. (1 mmole) of ketophenol XIV, 0.094 g. (1 mmole) of phenol, and 4.5 mg. of camphorsulfonic acid was heated in a test tube immersed in an oil bath at 180° for 1 hr. The residue was distilled to yield 0.15 g., b.p. 160–180° (700 mm.), $n^{25}D$ 1.5221, believed to be a mixture of phenol (major constituent) and phenyl butyrate [infrared bands at 3600 cm.$^{-1}$ (OH) and 1730 cm.$^{-1}$ (ester C=O)]. The residue remaining (0.31 g.) revealed strong infrared bands at 3600 cm.$^{-1}$ (OH) and 1750 cm.$^{-1}$ (ester C=O); practically none of the carbonyl absorption of the starting material at 1670 cm.$^{-1}$ was evident and the material is believed to be a mixture of 3,5-diphenyl-2-ethylphenol (XX) and its butyrate ester (XVII). The entire residue (0.31 g.) was treated with 10 ml. of water, 10 ml. of ethanol, and 10 g. of sodium hydroxide and the mixture refluxed for 18.5 hr. The mixture was diluted with water and extracted with ether; the combined extracts were dried and concentrated to leave 0.28 g. of residue. Crystallization from hexane gave 0.066 g. of **3,5-diphenyl-2-ethylphenol (XX)**, m.p. 82–83°; when mixed with an authentic sample (preparation is described later, m.p. 83–83°), the melting point was not depressed; the infrared and ultraviolet spectra of the two samples were identical. The deacylation could be carried out effectively with camphorsulfonic acid alone (phenol absent) with similar results (mixture of XX and its butyrate ester produced). Aluminum chloride was much less effective as a reagent for this reaction. An attempt to separate the 3,5-diphenyl-2-ethylphenyl butyrate from the mixture by distillation was ineffective since the distillate was contaminated with the phenol (XX); ester XVII could not be crystallized.

The aqueous alkaline portion remaining from this saponification was made acidic with sulfuric acid, diluted with water, and distilled; 3.4 l. of distillate was collected. The distillate was neutralized with sodium hydroxide solution, concentrated to

a volume of 10 ml., and then treated with 0.2 g. of *p*-phenylphenacyl bromide and 10 ml. of ethanol. After refluxing 1.3 hr. and cooling, the mixture was filtered to yield 0.24 g. of crude *p*-phenylphenacyl butyrate, m.p. 60–80°; recrystallization from dilute ethanol gave prisms, m.p. 80–81°; when mixed with a authentic sample (m.p. 78–80°), the melting point was not depressed.

Deacylation of 3,5-Diphenyl-2-isopropyl-4-(3-methylbutanoyl)-phenol to 3,5-Diphenyl-2-isopropylphenol (XXI).—A 0.5-g. sample of ketophenol XV and 5 mg. of camphorsulfonic acid were heated at 205° for 4 hr. The residue, which had an isovaleric acid odor, was dissolved in ether and washed with sodium bicarbonate solution; the ether solution was dried and concentrated to dryness. The residue (0.42 g.) had hydroxyl (3600 cm.$^{-1}$) and carbonyl (1750 cm.$^{-1}$, ester) absorption and is believed to contain principally the phenol XXI and its isovalerate ester (XVIII). A 0.36-g. portion of the residue was saponified by refluxing for 24 hr. with a mixture of 10 g. of sodium hydroxide, 10 ml. of water, and 10 ml. of ethanol. There was obtained 0.30 g. of crude phenol XXI which was crystallized from hexane to yield 0.21 g., m.p. 112–115°. Recrystallization gave colorless prisms of **3,5-diphenyl-2-isopropylphenol (XXI)**, m.p. 114–115°; infrared band (potassium bromide) at 3500 cm.$^{-1}$ (OH) (carbonyl absent).

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.54; H, 6.94.

The aqueous alkaline portions (including the sodium bicarbonate extracts) were combined, acidified with sulfuric acid, diluted with water, and distilled. The first 1200 ml. of distillate contained 0.00119 equivalent of acid (by direct titration with 0.1 *N* sodium hydroxide) and the next fraction (700 ml.) contained 0.0008 equivalent; total, 0.00127 equivalent (94.5%) of isovaleric acid. The neutralized distillate was concentrated and the *p*-phenylphenacyl ester prepared; 0.16 g., m.p. 76–77°, was obtained; the melting point was not depressed when the material was mixed with an authentic sample (m.p. 73–75°).

Deacylation of 2-Butyl-3,5-bis(4-methylphenyl)-4-hexanoylphenol.—A 0.5-g. sample of the ketophenol XVI and 5 mg. of camphorsulfonic acid were heated at 200–210° for 3.5 hr. The residue was saponified by the procedure described previously; reflux time, 24 hr. The product, believed to be mainly 2-butyl-3,5-bis(4-methylphenyl)phenol (XXII), was obtained as an oil which failed to crystallize from hexane on chilling to −15°.

The aqueous alkaline portion was concentrated to near dryness and diluted with water to a volume of 25 ml. The solution was acidified with sulfuric acid and extracted with ether. After drying the solution and removing the ether the residue was distilled to yield 0.08 g. of hexanoic acid, b.p. 185° (690 mm.), $n^{25}D$ 1.4165, neut. equiv., 120 (calcd. 116.2). The *p*-phenylphenacyl ester was prepared, m.p. 63–64°; when mixed with an authentic sample, m.p. 63–64°, the melting point was not depressed.

3,5-Diphenyl-2-ethylphenol (XX) from 3,5-Diphenyl-6-ethyl-2-cyclohexen-1-one (XXIII).—A 1.0-g. sample of 3,5-diphenyl-6-ethyl-2-cyclohexen-1-one (XXIII) (prepared by the procedure of Dieckmann[19]) was mixed with 0.3 g. of 10% palladium-on-charcoal catalyst and the mixture heated gently with a flame for 15 min. (until bubbling ceased). The combined product of two such runs was extracted with boiling chloroform several times and the extracts were filtered. Concentration of the filtrate gave 1.43 g. of orange oil which was crystallized from hexane to yield 0.45 g. of crude XX, m.p. 76–81°; two recrystallizations from hexane raised the melting point to 82–83° (colorless prisms); infrared bands (Nujol) at 3500 and 3600 cm.$^{-1}$ (hydroxyl); carbonyl absorption was absent; λ_{max} 238 mμ (ε 25,300), shoulders at 260 mμ (ε 15,600) and 300 mμ (ε 4400).

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 88.06; H, 6.68.

Reactions of Enamines with Electrophilic Sulfur Compounds

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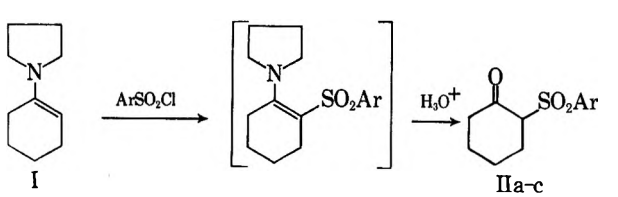
The reaction of 1-pyrrolidinocyclohexene and arylsulfonyl chlorides led, on hydrolysis, to 2-arylsulfonylcyclohexanones. With *o*-, *m*-, or *p*-nitrobenzenesulfenyl chloride, 2-mono- and 2,6-bis(*o*-, *m*-, and *p*-nitrophenylsulfenyl)cyclohexanones were obtained. Intermediate bisnitrophenylsulfenyl enamines were isolated. Only monosubstitution products were obtained from 1-pyrrolidinocyclohexene and *m*- or *p*-nitrophenyl disulfides and from 6-methyl-1-pyrrolidinocyclohexene and *o*-nitrobenzenesulfenyl chloride. From propane-1,3-dithiol-di-*p*-toluenesulfonate and 1-pyrrolidinocyclohexene, the 1,2-cyclohexanedione mono-1,3-propanedithiol ketal was obtained.

Since the initial work of Stork and his collaborators on the alkylation and acylation of enamines,[1] this class of compounds has gained increasing recognition as reactive intermediates in organic synthesis. While previous interest focused mainly on the use of enamines in the formation of carbon to carbon bonds, this report describes some reactions of enamines with electrophilic sulfur derivatives.

A few other studies in this area were indicated recently. Thus the reaction of 1-piperidinopropene with benzenesulfonyl chloride gave 2-benzenesulfonyl-1-piperidinopropene,[2] but alkylsulfonyl chlorides and enamines led to 3-aminotrimethylene sulfones.[2,3] These may arise either from cyclization of initially formed α-sulfonylimmonium intermediates, postulated in analogy to precursors of arylsulfonyl enamines, or from addition of a sulfur analog of ketene to the enamines. A third example is the reaction of sulfur dichloride with the bispyrrolidine enamine of bicyclo[3.3.1]nonane-2,6-dione which gave 2-thiaadamantane-4,8-dione on hydrolysis.[4]

We have found that the pyrrolidine enamine of cyclohexanone I reacts with *p*-acetamidobenzenesulfonyl chloride, *p*-nitrobenzenesulfonyl chloride, and *p*-toluenesulfonyl chloride[5] to give the corresponding arylsulfonyl ketones IIa–c on hydrolysis.



I IIa-c

a, Ar = *p*-acetamidophenyl
b, Ar = *p*-nitrophenyl
c, Ar = *p*-tolyl

(1)(a) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); (b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

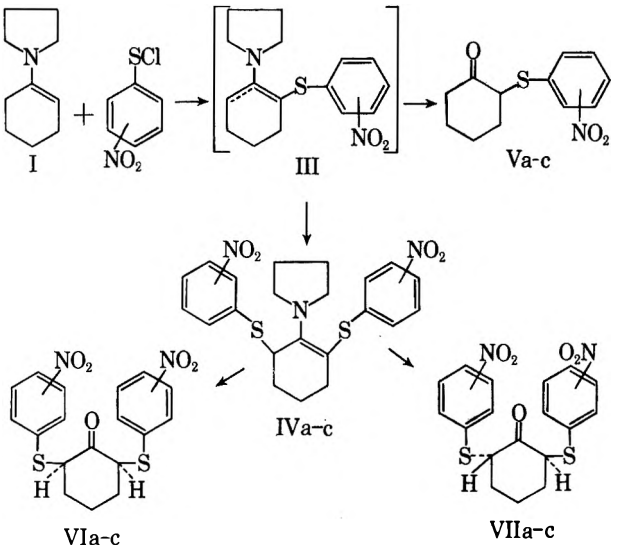
(2) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962).

(3) G. Stork and I. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962).

(4) H. Stetter, H. Held, and A. Schulte-Oestrich, *Ber.*, **95**, 1687 (1962).

(5) Also indicated by G. Stork, Abstracts, 16th National Organic Symposium, June, 1959, pp. 44–52.

In addition to the sulfone IIa, the reaction mixture from *p*-acetamidobenzenesulfonyl chloride and 1-pyrrolidinocyclohexene gave a small amount of 2-*p*-acetamidobenzenesulfenylcyclohexanone and, similarly, the reaction with *p*-nitrobenzenesulfonyl chloride yielded also the bis-*p*-nitrobenzenesulfenyl enamine IVa and 2-*p*-nitrobenzenesulfenylcyclohexanone Va. These products presumably arose from the corresponding sulfenyl chlorides.[6]

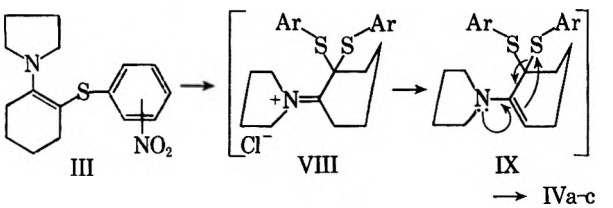


a, *p*-nitrophenyl
b, *o*-nitrophenyl
c, *m*-nitrophenyl

Indeed, reaction of *o*-nitrobenzenesulfenyl chloride and 1-pyrrolidinocyclohexene yielded, after hydrolysis, a mixture of the bis-*o*-nitrobenzenesulfenyl enamine IVb, the α-sulfenyl ketone Vb, and the epimeric α,α'-disulfenyl ketones VIb and VIIb. A separable mixture of the disulfenyl ketones VIb and VIIb also was obtained on acid hydrolysis of the purified disulfenyl enamine IVb. Analogous results were found in the reaction of *m*-nitrobenzenesulfenyl chloride with 1-pyrrolidinocyclohexene where the disulfenyl ketones VIc and VIIc and the monosulfenyl ketone Vc were isolated. The epimeric 2,6-diarylsulfenylcyclohexanones VIa,b,c and VIIb,c could be divided into two groups on the basis of their infrared carbonyl absorptions at 1720–1725 and 1700–1710 cm.$^{-1}$, respectively. The monosubstituted arylsulfenylcyclohexanones Va–c showed carbonyl absorption at 1705–1710 cm.$^{-1}$. (Empirical comparison of differences in absorption near 815 and 730 cm.$^{-1}$, however, could suggest a reversed grouping of the *m*-nitrophenyl pair, VIc and VIIc.) Stereochemical assignments of the epimeric groups were based on nuclear magnetic resonance spectra of the 2,6-di-*m*-nitrobenzenesulfenylcyclohexanone pair, VIc and VIIc, which alone was sufficiently soluble in suitable solvents. The compound showing axial protons α to the carbonyl group at higher field (5.9 τ *vs.* 5.5 τ) and some separation of methylene protons into axial and equatorial groups (about 8.1 and 7.6 τ *vs.* about 7.8 τ) was assigned the *cis* configuration VIc, which would be expected to be more rigid than the *trans* epimer VIIc where protons are averaged in a rapid interchange of two equivalent conformers.

Each of the nitrobenzenesulfenyl chlorides on reaction with 1-pyrrolidinocyclohexene formed predominantly the 2,6-disubstitution product, thus displaying a reaction course which is contrary to the cumulative experience of enamine chemistry, where one has always found a preference for the formation of monosubstitution products. The preferential formation of 2,6-disubstitution products with one equivalent or less of the electrophile indicates a higher nucleophilic reactivity of an α-carbon in an initially produced monosubstituted enamine intermediate III as compared with the starting enamine I. While this relationship is not readily rationalized for a 6-substituted 1-pyrrolidinocyclohexene, the direct precursor of the products IVa,b,c, it could be expected for the thioether substituted enamine, where negative charge density at the α-carbon might be increased due to stabilization of a more polarized enamine by the adjacent sulfur substituent. A 2,2-disubstituted immonium chloride intermediate VIII, formed from III, would undergo loss of a proton in the basic reaction medium to give the 2,2-disubstituted enamine IX, which could rearrange to the 2,6-disubstituted products IVa–c.

Some analogy to this new rearrangement can be seen in the transformation of 2-bromo-2-methylcholestan-3-one to the 4-bromo ketone.[7] In the present case the driving force of the rearrangement should arise from the formation of the conjugated nitrophenylsulfenyl enamine system as well as from a relief of steric compression in the α,α-disubstituted enamine where overlap of the unshared nitrogen electrons and the double bond requires a structure with steric repulsion between a sulfur substituent and one methylene group of the pyrrolidine ring.

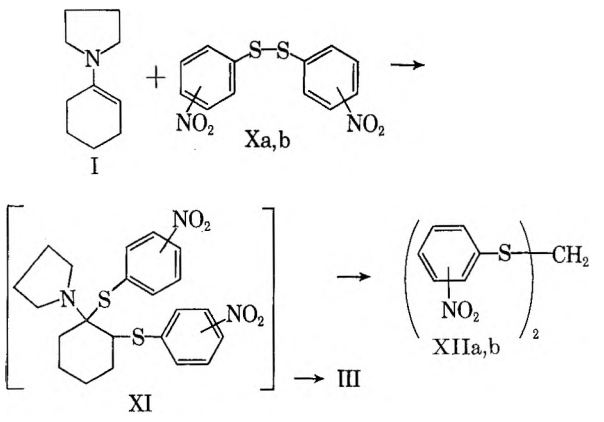


In contrast to the reactions with nitrobenzenesulfenyl chlorides, the addition of *p*- and *m*-nitrobenzenedisulfides Xa,b to 1-pyrrolidinocyclohexene and hydrolysis led mostly to monosubstituted ketones. This reaction course may be due to the formation of the dithioether intermediates XIa,b and a reflection of the higher nucleophilicity of aryl sulfide ions as compared with chloride ion. The reversibly formed adducts XIa,b can eliminate aryl sulfide ion, which is then removed from the reaction mixture by slow reaction with the solvent methylene dichloride, thus forming the thioacetals XIIa,b. (See p. 2126, Col. 1.)

A monosubstituted enamine XIV was the only isolated reaction product from the addition of *o*-nitrobenzenesulfenyl chloride to 6-methyl-1-pyrrolidinocyclohexene XIII. Here lack of further reaction can be explained by a higher energy of an immonium salt-like transition state arising from the substituted enamine XIV as compared with the unsubstituted enamine XIII. The presence of an alkyl substituent

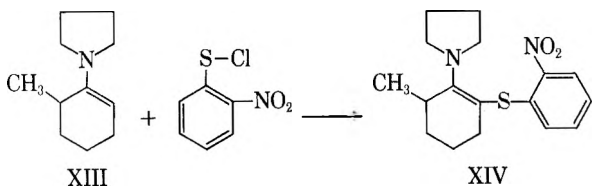
(6) While sulfenyl chlorides appear to be contaminants in the commercial sulfonyl chlorides, they also may have been generated in the reaction mixtures since the sulfenyl products were found, albeit in somewhat smaller yield, even when *p*-nitrobenzenesulfonyl chloride of analytical purity was used.

(7) C. Djerassi, N. Finch, and R. Mauli, *J. Am. Chem. Soc.*, **81**, 4997 (1959).



a, *p*-nitrophenyl
b, *m*-nitrophenyl

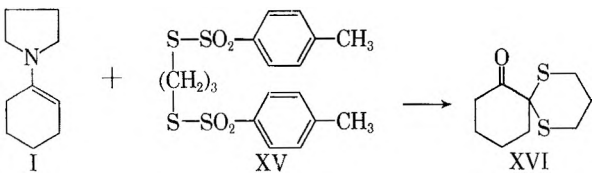
at C-6 should hinder electrophilic attack at C-2 of 1-pyrrolidinocyclohexene[8] in a quasi chair or boat conformation due to steric strain arising from either (a) 1,3-diaxial repulsion of the approaching electrophile by the substituent[9] or (b) coplanarity of the substituent and an α-methylene group of the heterocycle in the transition state. Because of the simultaneous high steric requirements of the methyl and sulfur substituents, electrophilic attack on enamine XIV would lead to a transition state with a twisted ring conformation where overlap stabilization between nitrogen, double bond, and the thioaryl system is reduced.



The predominant formation of disubstitution products from the reactions of pyrrolidinocyclohexene with arylsulfenyl halides and monosubstitution products with aryl disulfides as well as the monosubstitution reaction of 6-methyl-1-pyrrolidinocyclohexene with *o*-nitrobenzenesulfenyl chloride also could be explained in another way on the basis of previous observations in enamine chemistry.

It has been found[1] that an excess of very reactive electrophiles can lead to disubstitution products whereas less reactive, more discriminant electrophiles will give rise to monosubstitution products. In the present experiments this would require destructive removal of a part of the enamine, but not of the sulfenyl chloride, before the apparently instantaneous electrophilic attack is possible. Since product yields were far from quantitative, such a reaction course must be considered, but it should be recalled that disubstitution products were isolated predominantly even when the sulfenyl chloride was introduced as a minor impurity in the reaction of *p*-nitrobenzenesulfonyl chloride.

Finally, it was of interest to see if a 2,2-dithiosubstituted cyclohexanone could be obtained from 1-pyrrolidinocyclohexene and thus to find some support for the postulated 2,2-disubstituted immonium intermediate VIII. This was achieved by a reaction of 1-pyrrolidinocyclohexene I with the di-*p*-toluenesulfonate of propane 1,3-dithiol XV. This reaction, which clearly favored disubstitution on the same carbon, led, after hydrolysis, to the α-thioketal ketone XVI. Structural assignment was confirmed by an n.m.r. spectrum which showed two nonequivalent axial and equatorial protons of the α-methylene ketone (6.9 and 6.7 τ). This last reaction has been of value in some natural product work of this laboratory where the introduction of a thioketal blocking group was desired.[10]



Experimental

2-(4-Acetamidobenzenesulfonyl)cyclohexanone (IIa).—A solution of 38.6 g. (0.165 mole) of *p*-acetamidobenzenesulfonyl chloride and 16.2 g. (0.165 mole) of triethylamine in 1 l. of methylene chloride was cooled in ice and 25.0 g. (0.165 mole) of 1-pyrrolidinocyclohexene added under nitrogen. After 18 hr. at room temperature the solvent was removed under vacuum, an excess of dilute hydrochloric acid and enough methanol to maintain a homogeneous solution were added, and the solution stirred 90 min. at room temperature. Addition of water, extraction with methylene chloride, concentration, and crystallization from ethyl acetate gave 15.9 g. of sulfone (33% yield), m.p. 184–185°, after recrystallization.

Anal. Calcd. for $C_{14}H_{17}NO_4S$: C, 56.90; H, 5.80; N, 4.74; CH_3CO, 14.6. Found: C, 56.84; H, 5.83; N, 4.75; CH_3CO, 14.6 (by 4-hr. reflux in sulfuric acid).

Chromatography of the concentrated ethyl acetate filtrate on alumina (Woelm, neutral, activity II) gave 0.80 g. of material, m.p. 98–135°, eluted with 1:1 benzene–methylene chloride in the initial fractions and 1.8 g. (3.7% additional yield) of the sulfone. Recrystallization of the less polar material from benzene and cyclohexane produced 0.20 g., m.p. 122–124°, of 2-*p*-acetamidobenzenesulfenylcyclohexanone.

Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.84; H, 6.51; N, 5.32. Found: C, 64.01; H, 6.54; N, 5.24.

2-(4-Methylbenzenesulfonyl)cyclohexanone (IIc).—At 30°, a solution of 25.2 g. (0.13 mole) of *p*-toluenesulfonyl chloride in 300 ml. of methylene chloride was added to 20.0 g. (0.13 mole) of 1-pyrrolidinocyclohexene and 13.4 g. (0.13 mole) of triethylamine, in 100 ml. of methylene chloride. After 18 hr. 2.5 g. of triethylamine hydrochloride was filtered off, the reaction mixture concentrated under vacuum, dissolved in 500 ml. of benzene, and an additional 11.7 g. of triethylamine hydrochloride removed. After concentration under vacuum the residue was heated for 15 min. on a steam bath with an excess of dilute hydrochloric acid. Extraction of the cooled solution with methylene chloride, concentration, solution in hot cyclohexane, concentration, and trituration with hot ligroin gave 9.9 g. of crystals, m.p. 63–70°, and 13.1 g. of oil. Repeated recrystallization from ligroin produced 5.4 g., m.p. 76–78° (lit.[11] m.p. 76–80°), and 4.0 g., m.p. 65–75°. Distillation of the oil from a jacketed flask at bath temp. 130–200° (0.001 mm.) gave 8.3 g. of gummy crystals. All fractions (total crude, 17.7 g., 54% yield) had almost identical infrared spectra and each gave a 2,4-dinitrophenylhydrazone, m.p. 204–205°, recrystallized from methylene chloride and ethanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_6S$: C, 52.78; H, 4.66; N, 12.96. Found: C, 53.05; H, 4.65; N, 13.05.

In an alternative procedure the total reaction product after hydrolysis was chromatographed on alumina (Woelm, neutral, activity II) and 7.2 g. (21% yield) of the crystalline sulfone eluted with 5:1 petroleum ether–benzene, together with 5.0 g. of the oily material and 0.75 g. of pyrrolidine *p*-toluenesulfonamide,

(8) Such hindrance is found in the alkylation of analogous enamines; *cf.* ref. 1.

(9) W. R. W. Williamson, *Tetrahedron*, **3**, 314 (1958).

(10) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(11) J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 3468 (1956).

more rapidly eluted than the sulfone, m.p. 120–121° (lit.[12] m.p. 121°).

2-(4-Nitrobenzenesulfonyl)cyclohexanone (IIb), 2-(4-Nitrobenzenesulfenyl)cyclohexanone (Va), and 2,6-Di(4-nitrobenzenesulfenyl)-1-pyrrolidinocyclohexene (IVa).—A solution of 22.2 g. (0.10 mole) of *p*-nitrobenzenesulfonyl chloride (Eastman, recrystallized three times from cyclohexane, m.p. 77–79°. *Anal.* Calcd. for $C_6H_4ClNO_4S$: C, 32.52; H, 1.82. Found: C, 32.50, H, 1.95.) in 150 ml. of chloroform was added, with cooling, to 10.1 g. (0.10 mole) of triethylamine and 15.1 g. (0.10 mole) of 1-pyrrolidinocyclohexene in 150 ml. of chloroform, under nitrogen. After 18 hr. at room temperature the solvent was removed under vacuum, the residue taken up in 250 ml. of benzene, and 12.0 g. of triethylamine hydrochloride filtered off. Concentration under vacuum, addition of 200 ml. of methanol, filtration, and recrystallization from methanol gave 1.2 g. of IVa, m.p. 178–179°.

Anal. Calcd. for $C_{22}H_{23}N_3O_4S_2$: C, 57.77; H, 5.07; N, 9.19; S, 14.02. Found: C, 57.84; H, 5.18; N, 8.67; S, 13.92.

To the methanolic solution 23 ml. of 10% hydrochloric acid was added and, after 30 min. at room temperature, the solution was poured into water and extracted with methylene chloride. Concentration under vacuum and chromatography on 220 g. of Florisil gave 0.2 g., m.p. 91–93°, of crude Va, eluted with 1:2 petroleum ether–benzene; 2.5 g., m.p. 80–112°, of a mixture of IIb and Va in four fractions eluted with 1:2 petroleum ether–benzene; and 3.7 g., m.p. 113–120°, of crude IIb, eluted in ten fractions with benzene. Recrystallization of the crude Va from methanol, then from cyclohexane gave a sample with m.p. 97–98°, infrared, ν_{max} 1710 cm.$^{-1}$ (C=O) in potassium bromide.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.38; H, 5.22; N, 5.58; S, 12.77. Found: C, 57.70; H, 5.27; N, 5.57; S, 12.88.

Recrystallization of crude IIb from methanol gave 2.4 g. of sulfone, m.p. 120–121°; 0.8 g., m.p. 113–115°; and 0.5 g., m.p. 105–110° (mixtures of IIb and Va).

Anal. Calcd. for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.95. Found: C, 50.89; H, 4.60; N, 5.14.

In another experiment with unrecrystallized *p*-nitrobenzenesulfonyl chloride 3.0 g. of IVa was obtained. Chromatography of the acid hydrolysis mixture on 170 g. of alumina (Woelm, neutral, activity II) gave 1.0 g. of Va and 1.5 g. of IIb and 2.9 g. of a mixture, m.p. 76–83°, all eluted with 1:9 petroleum ether–benzene.

2,6-Di(4-nitrobenzenesulfenyl)cyclohexanone (VIa).—A suspension of 0.30 g. (0.64 mmole) of 2,6-di(4-nitrobenzenesulfenyl)-1-pyrrolidinocyclohexene in 25 ml. of methanol and 15 ml. of 3% hydrochloric acid was digested until all orange material had been converted to a white precipitate. Filtration and recrystallization from ethyl acetate and heptane gave 0.22 g. (83% yield), m.p. 128–132°; recrystallized from ethyl acetate to m.p. 134–135°, infrared, ν_{max} 1725 cm.$^{-1}$ (C=O) in potassium bromide.

Anal. Calcd. for $C_{18}H_{16}N_2O_5S_2$: C, 53.48; H, 3.99; N, 6.93; S, 15.86. Found: C, 53.56; H, 3.93; N, 6.90; S, 16.06.

2-(2-Nitrobenzenesulfenyl)cyclohexanone (Vb), *cis*- and *trans*-2,6-Di(2-nitrobenzenesulfenyl)cyclohexanone (VIb and VIIb), and 2,6-Di(2-nitrobenzenesulfenyl)-1-pyrrolidinocyclohexene (IVb).—To a stirred, cooled solution of 15.1 g. (0.10 mole) of 1-pyrrolidinocyclohexene and 10.1 g. (0.10 mole) of triethylamine in 100 ml. of methylene chloride, was added dropwise 19.0 g. (0.10 mole) of *o*-nitrobenzenesulfenyl chloride in 100 ml. of methylene chloride. After 20 hr. at room temperature the solution was shaken for 10 min. with an excess of dilute hydrochloric acid, washed with water, concentrated under vacuum, and triturated with methanol, thus giving 17.6 g. of a mixture of red and yellow crystalline materials. Several fractional recrystallizations gave 3.2 g. (8% yield) of yellow VIb, m.p. 180–181°, infrared, ν_{max} 1720 cm.$^{-1}$ (C=O) in potassium bromide, from dimethylformamide or dioxane; 0.7 g. (2% yield) of yellow VIIb, m.p. 153–154°, infrared, ν_{max} 1710 cm.$^{-1}$ (C=O) in potassium bromide, from methylene chloride and ethanol; 5.3 g. (12% yield) of IVb, red, m.p. 173–174°, from benzene; 1.0 g. (4% yield) of Vb, m.p. 113–114°, infrared, ν_{max} 1710 cm.$^{-1}$ (C=O) in potassium bromide, from cyclohexane.

Anal. Calcd. for $C_{12}H_{13}NO_3S$ (Vb): C, 57.38; H, 5.22; N, 5.58. Found: C, 57.44; H, 5.27; N, 5.66.

Anal. Calcd. for $C_{18}H_{16}N_2O_5S_2$ (VIb): C, 53.48; H, 3.99; N, 6.93; S, 15.86. Found: C, 53.17; H, 4.07; N, 7.04; S, 15.82.

Anal. Calcd. for $C_{18}H_{16}N_2O_5S_2$ (VIIb): C, 53.48; H, 3.99; N, 6.93. Found: C, 53.68; H, 4.11; N, 6.91.

Anal. Calcd. for $C_{22}H_{23}N_3O_4S_2$ (IVb): C, 57.77; H, 5.07; N, 9.19; S, 14.02. Found: C, 58.53; H, 5.17; N, 8.44; S, 13.86.

In a second experiment trituration of the crude reaction product with methanol gave 17.4 g. of red solid, 1.0 g. of brown solid on partial concentration, and 4.6 g. of residue on complete concentration of the methanol washings. Digestion of the major crop in 100 ml. of methanol and an excess of dilute hydrochloric acid until no red solid remained, cooling in ice, and filtration gave 11.1 g. of material. Treatment with hot benzene produced 3.9 g. (10% yield) of insoluble VIb. Concentration and crystallization from tetrahydrofuran gave 4.9 g. (12% yield) of VIIb. Concentration of the tetrahydrofuran and crystallization from cyclohexane led to 3.1 g. (12% yield) of Vb.

Hydrolysis of 2,6-Di(2-nitrobenzenesulfenyl)-1-pyrrolidinocyclohexene (IVb).—A suspension of 0.30 g. (0.65 mmole) in 30 ml. of methanol and 5 ml. of 3% hydrochloric acid was digested for 15 min. when all of the red solid had been converted to the yellow product. Filtration and recrystallization from dimethylformamide furnished 0.22 g. (83% yield) of a mixture of VIb and VIIb, m.p. 155–170°. Recrystallization from 80 ml. of benzene gave 0.1 g. of VIb, m.p. 181°.

Equilibration of *cis*- and *trans*-2,6-Di(2-nitrobenzenesulfenyl)-cyclohexanone (VIb and VIIb).—Heating of 0.10 g. of either VIb, m.p. 181°, or VIIb, m.p. 153°, in 5 ml. of dimethylformamide and 2 drops of 10% hydrochloric acid for 10 min. on a steam bath, cooling, addition of 1 ml. of water, and filtration gave 0.090 g. of a mixture of isomers, m.p. 165–167°, with identical infrared spectra and mixture melting points.

2-(3-Nitrobenzenesulfenyl)cyclohexanone (Vc) and *cis*- and *trans*-2,6-Di(3-nitrobenzenesulfenyl)cyclohexanone (VIc and VIIc).—To a stirred, ice-cooled solution of 7.5 g. (0.05 mole) of 1-pyrrolidinocyclohexene in 50 ml. of methylene chloride and 5.0 g. (0.05 mole) of triethylamine was added slowly 9.5 g. (0.05 mole) of *m*-nitrobenzenesulfenyl chloride[13] in 50 ml. of methylene chloride. After stirring for 24 hr. at room temperature, the reaction mixture was concentrated to dryness under vacuum, the residue taken up in 60 ml. of benzene, and 7.0 g. of triethylamine hydrochloride separated by filtration. Concentration under vacuum, solution in methylene chloride, thorough extraction with 1% hydrochloric acid, and concentration under vacuum left a gum which was separated into 3.0 g. of an insoluble mixture of 2,6-disubstituted cyclohexanone epimers (VIc and VIIc), and material soluble in hot cyclohexanone and 100 ml. of cold methanol. Chromatography of the methanol and cyclohexane concentrates on 90 g. of Florisil gave 3.3 g. (26% yield) of gummy 2-substituted ketone (Vc) eluted with 1.2 l. of 1:1 petroleum ether–benzene. Recrystallization of this material from cyclohexane gave 2.4 g. m.p. 56–57°, infrared, ν_{max} 1705 cm.$^{-1}$ (C=O) in potassium bromide.

Anal. Calcd. for: $C_{12}H_{13}NO_3S$: C, 57.38; H, 5.22; N, 5.58. Found: C, 57.63; H, 5.14; N, 5.73.

From the mother liquors 0.75 g. of the corresponding dinitrophenylhydrazone derivative was obtained, m.p. 178–180°, after recrystallization from ethanol.

Anal. Calcd. for: $C_{18}H_{17}N_5O_6S$: C, 50.15; H, 3.99; N, 16.23. Found: C, 50.32; H, 4.02; N, 15.95.

With 600 ml. of benzene 0.35 g. of epimeric 2,6-disubstitution products (VIc and VIIc) was eluted (total 3.35 g., 33% yield). Fractional crystallization of portions of the epimeric mixture from carbon tetrachloride followed by ethyl acetate gave the more soluble *trans* epimer (VIIc), m.p. 143–144°, infrared, ν_{max} 1700 cm.$^{-1}$ (C=O) in potassium bromide.

Anal. Calcd. for: $C_{18}H_{16}N_2O_5S_2$: C, 53.48; H, 3.99; N, 6.93. Found: C, 53.61; H, 4.11; N, 6.93.

The less soluble *cis* epimer (VIc), m.p. 145–146°, infrared, ν_{max} 1720 cm.$^{-1}$ (C=O) in potassium bromide was isolated in smaller amount with the approximate ratio of epimers 2:1.

Anal. Calcd. for $C_{18}H_{16}N_2O_5S_2$: C, 53.48; H, 3.99; N, 6.93. Found: C, 53.72; H, 4.25; N, 6.95.

6-Methyl-2-(2-nitrobenzenesulfenyl)-1-pyrrolidinocyclohexene (XIV).—A solution of one equivalent of *o*-nitrobenzenesulfenyl chloride in methylene chloride was added to 8.2 g. (0.05 mole) of 6-methyl-1-pyrrolidinocyclohexene and triethylamine, with the reaction conducted and worked up as described before. Trituration of the benzene concentrate with 50 ml. of methanol gave 6.1

(12) A. Müller and A. Sauerwald, *Monatsh.*, **48**, 155 (1927).

(13) H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).

g. of red crystalline product, m.p. 90–91°, which could be recrystallized from ligroin without change in melting point.

Anal. Calcd. for $C_{17}H_{22}N_2O_2S$: C, 64.11; H, 6.96; N, 8.80. Found: C, 64.36; H, 7.06; N, 8.64.

Chromatography of mother liquors material in benzene on florisil gave 0.20 g. of methylene-di-*o*-nitrobenzenesulfide (XIIc), m.p. 175–177° (lit.[14] m.p. 170°).

Anal. Calcd. for $C_{13}H_{10}N_2O_4S_2$: C, 48.45; H, 3.13; N, 8.69; S, 19.90. Found: C, 48.52; H, 3.07; N, 8.63; S, 19.87.

Reaction of 1-Pyrrolidinocyclohexene (I) with *m*- and *p*-Nitrobenzene Disulfides (Xa,b).—To a solution of 7.5 g. (0.05 mole) of enamine and 5.0 g. (0.05 mole) of triethylamine in 50 ml. of methylene chloride was added 7.7 g. (0.025 mole) of (a) *p*-nitrobenzene disulfide or (b) *m*-nitrobenzene disulfide with 180 ml. of methylene chloride, slowly with stirring and cooling in ice. After standing at room temperature for 20 hr., the solvent was removed under vacuum and the residue triturated with cyclohexane to give the following compounds.

(a) 1.4 g. of methylene-di-*p*-nitrobenzene sulfide (XIIa), m.p. 181–182° (lit.[15] m.p. 179°), recrystallized from benzene.

Anal. Calcd. for $C_{13}H_{10}N_2O_4S_2$: C, 48.45; H, 3.13; N, 8.69; S, 19.90. Found: C, 48.75; H, 3.11; N, 8.70; S, 19.82.

(b) 7.7 g. of solid which could be separated by methanol into soluble amine hydrosulfide and 4.3 g. of insoluble methylene-di-*m*-nitrobenzene sulfide (XIIb), m.p. 140–141°, recrystallized from ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2O_4S_2$: C, 48.45; H, 3.13; N, 8.69; S, 19.90. Found: C, 48.62; H, 3.11; N, 9.43; S, 19.79.

Concentration of cyclohexane filtrates, solution in methylene chloride, washing with dilute hydrochloric acid, concentration, and crystallization from cyclohexane gave (a) 2.1 g. (33% yield), m.p. 97–98°, of Va and (b) 5.0 g. (79% yield), m.p. 56–57°, of Vc. In another experiment 7.7 g. (0.025 m.) of *p*-nitrophenyl disulfide and 180 ml. of methylene chloride were added slowly to 3.8 g. (0.025 mole) of enamine and 5.0 g. (0.050 mole) of triethylamine in 50 ml. of methylene chloride with cooling in ice. After 20 hr. at room temperature the concentrated reaction mixture yielded 2.9 g. of methylene-di-*p*-nitrobenzene sulfide (XIIa), 1.7 g. of water-soluble amine hydrosulfide material and 1.3 g. of 2,6-di(4-nitrobenzenesulfenyl)-2-pyrrolidinocyclohexene (IVa), crystallized from 100 ml. of methanol and 20 ml. of ether. Concentration of the mother liquors, and hydrolysis of the residue with excess 1% hydrochloric acid at room temperature for 2 hr. gave 4.0 g. of 2-(4-nitrobenzenesulfenyl)cyclohexanone (Va), 63% yield, after recrystallization from hexane.

1,5-Dithiaspiro[5.5]undecan-1-one (XVI).—A solution of 9.0 g. (0.021 mole) of propane-1,3-dithiol-di-*p*-toluenesulfonate, 4.0 g. (0.068 mole) of triethylamine, and 3.2 g. (0.021 mole) of enamine in 50 ml. of dry dioxane was stirred under nitrogen for 3 hr. and then refluxed 20 hr. After concentration under vacuum, solution in ether, washing with dilute hydrochloric acid, and reconcentration, the crude product was passed over Florisil in 1:1 benzene–petroleum ether. Distillation at 120–180° (0.001 mm.) gave 1.85 g. of oily product which could be purified further by preparative thin layer chromatography on Merck Alumina G with 3:1 cyclohexane–benzene as solvent and redistillation at 140° (0.001 mm.) to give 1.20 g. (28% yield) of product, m.p. 53–54°, from petroleum ether; infrared, ν_{max} 1690 cm.$^{-1}$ (C=O) in potassium bromide.

Anal. Calcd. for $C_9H_{14}S_2O$: C, 53.43; H, 6.98. Found: C, 53.45; H, 7.01.

A dinitrophenylhydrazone, m.p. 154–155°, crystallized from ethanol.

Anal. Calcd. for $C_{15}H_{18}N_4O_4S_2$: C, 47.10; H, 4.74; N, 14.65. Found: C, 47.36; H, 4.96; N, 14.41.

A semicarbazone crystallized from ethanol, m.p. 235–236°.

Anal. Calcd. for $C_{10}H_{18}N_3OS_2$: C, 46.10 H, 6.97; N, 16.13. Found: C, 45.88; H, 6.55; N, 16.26.

Acknowledgment.—The author is greatly indebted to Mr. L. Dorfman and associates of CIBA, Summit, New Jersey, for n.m.r. spectra. Mr. G. Warner provided the *m*-nitrobenzenesulfenyl chloride and gave assistance in some initial experiments and Mr. J. Nelson provided the propane-1,3-dithiol-di-*p*-toluenesulfonate. Professor E. Eliel helpfully discussed some of the n.m.r. spectra. Microanalyses were given by Mr. G. I. Robertson. The work was supported by National Science Foundation grant G.P. 225.

(14) D. G. Foster and E. E. Reid, *J. Am. Chem. Soc.*, **46**, 1936 (1924).
(15) W. R. Waldron and E. E. Reid, *ibid.*, **45**, 2399 (1923).

Michael Additions of Nitroform. II. The Nitrite Elimination Reaction[1]

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In absolute methanol, potassium trinitromethide adds to methyl acrylate, acrylonitrile, and acrylamide to yield the potassium salts of methyl 4,4-dinitro-2-butenoate, 4,4-dinitro-2-butenenitrile, and 4,4-dinitro-2-butenamide. With acrylamide as the augend, a second product, potassium 4,4-dinitro-2-hydroxybutyramide, was formed. Proofs of structure of these new dinitromethyl derivatives are described.

In the first paper in this series,[2] it was reported that the reaction of nitroform with methyl acrylate (I, Y = $COOCH_3$) or methyl vinyl ketone (I, Y = $COCH_3$) yielded, in addition to the Michael adducts II methyl 4,4-dinitro-2-hydroxypimelate (III, Y = $COOCH_3$) and 5,5-dinitro-2-hydroxy-2,8-nonanedione (III, Y = $COCH_3$). In the case of the augend methyl acrylate, a second nitrite elimination product, the potassium salt of methyl 4,4-dinitro-2-butenoate (IV, Y = $COOCH_3$) was isolated in 34% yield from an aqueous methanol system at pH 4.5.

$$HC(NO_2)_3 + CH_2{=}CH{-}Y \xrightarrow[\text{AcOH}-\text{AcO}^- \text{ or } \text{AcO}^-]{\text{MeOH} - H_2O}$$

I

$$C(NO_2)_3CH_2CH_2{-}Y + Y{-}(CH_2)_2C(NO_2)_2CH_2\underset{\displaystyle OH}{\underset{|}{CH}}{-}Y + K^+{}^-C(NO_2)_2CH{=}CH{-}Y$$

II III IV

We now wish to report that derivatives analogous to IV can be obtained from the heterogeneous reaction of the potassium salt of nitroform with the appropriate acrylic augend in methanol. Thus stirring a slurry of potassium trinitromethide in absolute methanol with methyl acrylate or acrylonitrile until a constant ultraviolet spectrum was obtained for the insoluble potassium salts, afforded a 48 and 50% yield, respectively, of the potassium salts of methyl 4,4-dinitro-2-butenoate (IV, Y = $COOCH_3$) and 4,4-dinitro-2-butenenitrile (IV, Y = CN). With acrylamide, in addition to the expected potassium salt of 4,4-dinitro-2-butenamide, there also was obtained a yellow potassium salt (V).

(1) Presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, Abstracts of Papers, p. 560.
(2) L. A. Kaplan and M. J. Kamlet, *J. Org. Chem.*, **27**, 780 (1962).

$$K^{+-}C(NO_2)_3 + CH_2{=}CHCONH_2 \xrightarrow{MeOH}$$

IV, Y = $CONH_2$ + V

Derivatives of 4,4-Dinitro-2-butenoic Acid.—The potassium salts (IV, Y = $COOCH_3$, CN, and $CONH_2$) were obtained as orange crystalline materials which were soluble in water, slightly soluble in methanol, and generally insoluble in organic solvents. Elemental analyses agreed well with those values calculated for the respective empirical formulas, and their ultraviolet spectra (Table I) showed them to be structurally similar. A comparison of the ultraviolet spectra of the potassium salts IV with that of the dipotassium salt of 4,4-dinitro-2-butenoic acid[3] (Table I) indicated that the salts IV also had the 3,3-dinitro-1-propene chromophore with the residual functionality: *viz.*, $-COOCH_3$, $-CN$, or $-CONH_2$, attached to C-1.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF $K^{+-}C(NO_2)_2CH{=}CH{-}Y$

Y	$\lambda_{max}^{H_2O}$	log ε
$-COOCH_3$	326	4.24
	396–402	3.98
$-CONH_2$	322	4.23
	401–406	3.96
$-CN$	320	4.29
	396–402	4.00
$-COO^-$	313	4.20
	406–413	3.92

Evidence for the four-carbon chain structure containing the C_2–C_3 double bond came from the results of the hydrolysis of the salts IV with hydrochloric acid. Under these conditions,[4] the dinitromethyl anion is converted to a carboxyl group. The product isolated from the hydrolysis of the salts IV was the expected fumaric acid.[5]

Confirmation of the structural assignments given to the potassium salts IV was based upon their convertibility to the previously prepared[3] dipotassium salt of 4,4-dinitro-2-butenoic acid with alkali. This conversion was found to be essentially quantitative.

The Yellow Salt V.—This salt was formed in roughly equimolar amounts together with the potassium salt of 4,4-dinitro-2-butenamide in the reaction of acrylamide with potassium trinitromethide in absolute methanol. Following a tedious fractional crystallization procedure, an analytical sample of the salt V was obtained which agreed with the empirical formula $C_4H_6N_3O_6K$. This formula is consistent with that of the monohydrate of potassium 4,4-dinitro-2-butenamide.[6] However, extended drying at 70° and 20 μ produced no change in the analytical results and, therefore, the previously mentioned empirical formula was presumed not to be a hydrate.

The infrared spectrum of the salt V afforded considerable information as to the functionality present in the molecule (Table II). The spectrum exhibited three –NH absorption bands, the frequencies of which were essentially identical with those of the potassium salt of 4,4-dinitrobutyramide (VI). In addition the band at 3400 cm.$^{-1}$, absent in the salt VI, was assigned to the hydroxyl group

TABLE II

PRINCIPAL INFRARED ABSORPTION BANDS OF THE POTASSIUM SALTS[a]

Compound	–NH	–OH	C=O	Amide II	$-C(NO_2)_2^-$
Salt V	3160, 3350, 3450	3400[b]	1680	1580	1170, 1270
Amide VI	3180, 3350, 3450	...	1665	1595	1160, 1260
Salt VII	...	3380[c]	1600	...	1168, 1270
Acid VIII	...	...[d]	1570	...	1170, 1270

[a] ν_{max} in cm.$^{-1}$, samples run as Nujol mulls. [b] A strong band at 1080 cm.$^{-1}$ may be assigned to the –OH group. [c] A strong band at 1090 cm.$^{-1}$ may be assigned to the –OH group. [d] Two weak bands present at 3200 and 3500 cm.$^{-1}$ are probably due to water of hydration.

The carbonyl stretching frequencies for both V and VI agreed with the range given for the amide I band[7] and both the salts exhibited the amide II band. The presence of the dinitromethyl anion was evidenced by two strong absorption bands at about 1170 and 1270 cm.$^{-1}$.[8] On the basis of the previous spectral interpretation, it was evident that the salt V was a primary amide containing both the dinitromethyl anion and a hydroxyl group.

On treating V with aqueous alkali, ammonia was evolved and a new salt was produced. Elemental analyses after normal drying procedures agreed fairly well with the empirical formula $C_4H_4N_2O_7K_2{\cdot}H_2O$. After drying at 70° and 20 μ for seven days, the resulting product analyzed well for the anhydrous salt VII. A comparison of the infrared spectrum of the salt VII with that of the dipotassium salt of 4,4-dinitrobutyric acid (VIII)[6] (Table II) indicated that the net effect of alkaline hydrolysis was the conversion of the amide function to the carboxylate anion. Thus the –NH and amide II absorption bands were no longer present in the salt VII and the amide I (>C=O) band had shifted to 1600 cm.$^{-1}$ which is characteristic of the carboxylate anion.[9]

The fact that the salt V or the hydrolysis product VII was not degraded completely to small fragments in alkaline media suggested that the hydroxyl group was not attached to the carbon atom α to the dinitromethyl group. Such a structure (VIIa) would be expected to be degraded by alkali as shown.

$$K^{+-}C(NO_2)_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2{-}COO^- \xrightarrow{Base}$$

VIIa

$$H\bar{C}(NO_2)_2 + O{=}CHCH_2COO^-$$

This path for hydrolytic cleavage of the structural fragment, $^-C(NO_2)_2CH(OH)-$, has been observed previously in the case of α-dinitromethylcarbinols,[10]

(3) D. J. Glover, *Tetrahedron*, in press.

(4) M. J. Kamlet, L. A. Kaplan, and J. C. Dacons, *J. Org. Chem.*, **26**, 4371 (1961).

(5) Extensive decomposition occurred when potassium 4,4-dinitro-2-butenenitrile was hydrolyzed under these conditions. No fumaric acid was isolated.

(6) The dipotassium salt of 4,4-dinitrobutyric acid was found to form a stable hydrate. Private communication, D. J. Glover, these laboratories.

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 203.

(8) J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955).

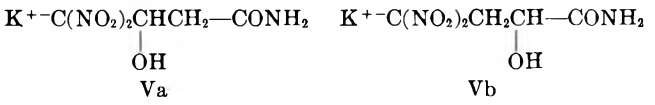
(9) R. N. Jones in "Chemical Applications of Spectroscopy," in "Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1956.

(10) P. Duden and G. Ponndorf, *Ber.*, **38**, 2031 (1905).

a 4,4-dinitro-5-hydroxyvalerate,[11] and 2,2-dinitro-1,3-propanediol.[12]

Confirmation of the four-carbon chain was obtained by refluxing the salt V with concentrated hydrochloric acid. Under these conditions, the dinitromethyl anion is converted to the carboxyl group.[13] However, instead of the expected product, malic acid, fumaric acid was isolated in about 25% yield.[14]

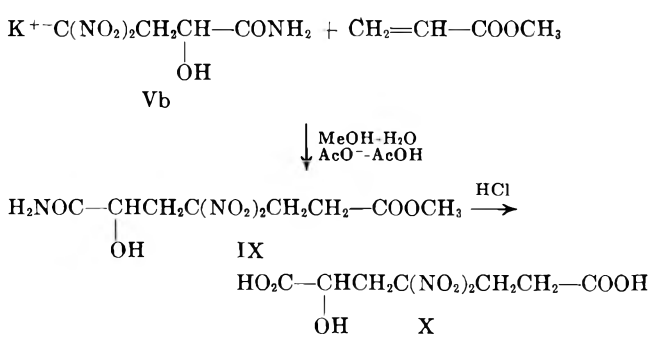
The isolation of fumaric acid taken together with the infrared spectral evidence suggested two possible structures for the salt V: 4,4-dinitro-3(or 2)-hydroxybutyramide, Va or Vb.



Va Vb

Preliminary evidence for the preference of the α-hydroxyamide structure Vb was based upon absorption maximum for the salt V in the ultraviolet; $\lambda_{max}^{H_2O}$ mμ (log ϵ), 380 (4.21). Not only was this spectrum quite different from those of the unsaturated potassium salts IV, but the presence of a single maximum at 380 mμ (log ϵ >4.0) was shown to be characteristic of the chromophore $^-C(NO_2)_2CH_2$-Y, where Y is hydrogen, alkyl, or substituted alkyl.[15] By contrast, when Y is hydroxyl, λ_{max} is shifted to shorter wave lengths. Thus for potassium 2,2-dinitroethanol, $\lambda_{max}^{dil\ KOH}$ mμ (log ϵ), is 365 (4.29).[15]

Final proof of the structural assignment given to the salt V was based upon its conversion to the previously characterized[2] 4,4-dinitro-2-hydroxypimelic acid (X). When the salt V was used as an addend in a Michael addition to methyl acrylate, the α-hydroxyamide ester IX was isolated as a crystalline solid. The conversion of IX to the dibasic acid X was readily accomplished by refluxing with constant boiling hydrochloric acid. Since the acid X is the α-hydroxy acid, the salt V must be the α-hydroxy amide, Vb.



Experimental[16,17]

Potassium 4,4-dinitro-2-butenoate (IV, Y = COOCH$_3$) was prepared by adding 0.32 mole (60 g.) of potassium trinitromethide (99% assay) to a solution of 0.48 mole (39.4 g.) of methyl acrylate in 750 ml. of absolute methanol. The resulting slurry was stirred at room temperature for 20 hr. During this time the insoluble potassium salts had changed from a fine yellow to a coarser orange solid, and the solvent phase became cherry-red in color. The insoluble material was filtered off, washed with ether, and dried *in vacuo*. Twenty-four grams of orange crystals (32.9%) were obtained, $\epsilon_{326}/\epsilon_{399}$ 1.81. Concentration of the filtrates to about one-half their original volume caused the precipitation of an additional 12.2 g. of similar material. Combined yield, 48%.

Recrystallization of a portion of the above combined product from methanol gave an analytical sample as thick hexagonal yellow-orange plates, $\epsilon_{326}/\epsilon_{399}$ 1.82.

Anal. Calcd. for $C_5H_5N_2O_6K$: C, 26.3; H, 2.2; N, 12.3; K, 17.1. Found: C, 26.4, 26.2; H, 2.5, 2.7; N, 12.8, 12.5; K, 17.1.

Further concentration of the mother liquors afforded a light yellow solid which proved to be mainly potassium nitrite. Three crops of this material totaling 6.5 g. were collected. This amounted to 50% of the theoretical amount based on the yield of IV (Y = $COOCH_3$) obtained. The remainder of the nitrite was probably lost as nitrous acid or methyl nitrite.

The red oil remaining after the removal of potassium nitrite was extracted with low boiling petroleum ether. Evaporation of the solvent from the combined extracts left a solid product (17.7 g.), m.p. 24–29°, which proved to be methyl 4,4,4-trinitrobutyrate (II). Authentic II had m.p. 27–28°.

The residue from the petroleum ether extraction was then taken up in ether, treated with charcoal, and concentrated. A white solid precipitated (4.1 g.), melting at 72.4–74.5°. This material did not depress the melting point of an authentic sample of dimethyl 4,4-dinitro-2-hydroxypimelate, m.p. 75.6–76.4°.[2]

Potassium 4,4-dinitro-2-butenenitrile (IV, Y = CN), was prepared by adding 1.0 mole (189 g.) of potassium trinitromethide to a solution of 1.5 moles (80 g.) of freshly distilled acrylonitrile in 1500 ml. of absolute methanol. The mixture was stirred continuously at room temperature. After 48 hr., the spectrum of the suspended solids exhibited two maxima: 322 and 380 mμ. The maximum at 380 mμ decreased in intensity and shifted to longer wave lengths with time, until after 235 hr. the insoluble material exhibited a constant ultraviolet spectrum with maxima at 320 and 396 mμ.

At this point the solids were filtered from the mixture, washed with 300 ml. of methanol, then 300 ml. of ether, and air dried. One hundred and four grams of a finely divided yellow solid were obtained. This crude product was recrystallized once from methanol–water to yield 97 g. (50%) of IV (Y = CN) as dichromatic orange crystals.

Anal. Calcd. for $C_4H_2N_3O_4K$: C, 24.6; H, 1.0; N, 21.6. Found: C, 24.2, 24.0; H, 1.2, 1.0; N, 23.0, 22.8.

Potassium 4,4-Dinitro-2-butenamide (IV, Y = CONH$_2$) and Potassium 4,4-Dinitro-2-hydroxybutyramide (Vb).—To a solution of 1.5 moles (107 g.) of acrylamide in 1500 ml. of absolute methanol was added 1.0 mole (189 g.) of potassium trinitromethide. The resulting slurry was stirred at room temperature and from time to time samples of the suspended solids were withdrawn for ultraviolet spectrophotometric analysis. After 14 days the intensity of the trinitromethide ion maximum (350 mμ) had decreased, while absorption on both sides of this peak had increased. At the end of 19 days, the trinitromethide ion maximum had been replaced by two new maxima at 328 and 380 mμ. After 26 days the ultraviolet spectrum of the suspended solids was essentially constant and it was presumed that the reaction had gone to completion. The suspended solids were separated from the mixture by filtration, washed with methanol, and dried. The yield of crude yellow salts was 125 g.

The crude salts were dissolved in a minimum amount of warm water, the solution heated to boiling, and an equal volume of methanol added. On slow cooling, the following crops of crystals were obtained: (a) 75.2 g. of mixed orange and yellow crystals; (b) 22.5 g. of mixed orange and yellow crystals containing about

(11) L. Herzog, M. H. Gold, and R. D. Geckler, *J. Am. Chem. Soc.*, **73**, 749 (1951).

(12) H. Feuer, G. B. Bachman, and W. May, *ibid.*, **76**, 5124 (1954).

(13) The acid hydrolysis of potassium 4,4-dinitrobutyramide yields succinic acid,[4] while potassium 4,4-dinitro-2-butenamide yields fumaric acid under these conditions (*vide supra*).

(14) An equilibrium between fumaric and malic acids undoubtedly exists under the conditions of acid hydrolysis [J. M. Weiss and C. R. Downs, *J. Am. Chem. Soc.*, **44**, 1118 (1922)]. Because of the difference in solubility between the two acids in water, the malic acid present probably was lost during the work-up procedure.

(15) M. J. Kamlet and D. J. Glover, *J. Org. Chem.*, **27**, 537 (1962).

(16) Microanalyses were performed by Mary Aldridge, Department of Chemistry, American University, Washington, D. C. Ultraviolet spectra were determined in 1-cm. quartz cells with either a Cary Model 14 or Beckman Model DU spectrophotometer. Infrared spectra were determined with a Beckman Model IR-4 spectrophotometer with the samples prepared as Nujol mulls. All melting points are uncorrected.

(17) Many of the compounds described are explosive in nature and quite sensitive to impact or grinding. Appropriate precautions should be taken in their handling.

50% of colorless needles[13]; (c) 4.7 g. of almost colorless needles[18]; and (d) 18.6 g. of a dark red-brown pasty mass with some colorless needles.[18]

Subjecting crop a to a similar fractional crystallization procedure yielded following additional crops: (a1) 54.6 g. of mixed orange and yellow crystals; (a2) 9.7 g. of mixed orange and yellow crystals together with some colorless needles[18]; (a3) 5.5 g. of material which was visually identical with (a2); and (a4) 4.8 g. of a somewhat dark red residue which was obtained by evaporating the mother liquors.

A final fractional crystallization of crop a1 afforded 26.0 g. of lemon yellow crystals of the salt Vb and 18.6 g. of the salt IV (Y = $CONH_2$) as dichromatic orange crystals. The residues from this crystallization were combined with crops a2 and a3 and reworked to obtain an additional quantity of the two salts of somewhat lower purity.

Analytical samples of the salts Vb and IV (Y = $CONH_2$) were obtained by recrystallizing the previously obtained fractions from methanol–water.

Anal. of **potassium 4,4-dinitro-2-hydroxybutyramide (Vb)**. Calcd. for $C_4H_6N_3O_6K$: C, 20.8; H, 2.6; N, 18.2; K, 16.9. Found: C, 20.7, 20.7; H, 2.6, 2.7; N, 18.2, 18.1; K, 16.9, 16.9. Drying the analytical sample 70° and 20 μ for 5 days did not change these analytical results.

Anal. of **potassium 4,4-dinitro-2-butenamide (IV, Y = $CONH_2$)**. Calcd. for $C_4H_4N_3O_5K$: C, 22.5; H, 1.9; N, 19.7. Found: C, 22.4, 22.6; H, 2.1, 2.0; N, 20.3, 20.1.

Acid Hydrolysis of the Salts IV and Vb.—To 0.01 mole of IV (Y = $COOCH_3$) was added 20 ml. of 12 *N* hydrochloric acid, and the resulting mixture was refluxed for 18 hr. The resulting brown solution was concentrated to about 10 ml.[19] and extracted thoroughly with ether. The combined ether extracts were concentrated to about 5 ml. and 30 ml. of *n*-pentane was added. This caused the separation of a light tan solid which, after filtering and drying, had a melting point of 286–287° (sealed tube) (lit.[20] m.p. 293–295°). The yield was 0.1 g.

The crude fumaric acid was converted to its dimethyl ester by refluxing it with a solution of hydrogen chloride in methanol. Following the removal of the methanol and recrystallization from ether–pentane, the ester, obtained as glistening plates, melted at 100.8–102° and did not depress the melting point of an authentic sample of dimethyl fumarate prepared from fumaryl chloride.

In a similar manner, **potassium 4,4-dinitro-2-butenamide** and **potassium 4,4-dinitro-2-hydroxybutyramide** were converted to fumaric acid. Yields of the crude acid in these cases were about 0.5–0.7 g. In each case the acid was converted to the dimethyl ester for characterization.

Attempts were made to effect the acid hydrolysis of **potassium 4,4-dinitro-2-butenenitrile**. In each instance there was excessive carbonization of the organic material and it was not possible to extract fumaric acid from the resulting reaction mixture.

Alkaline Hydrolysis of the Potassium Salts IV.—Exactly 0.3598 g. of **potassium 4,4-dinitro-2-butenamide** was weighed into a 200-ml. volumetric flask and made up to volume with water. A 25-ml. aliquot of this solution was transferred to a 100-ml. volumetric flask, 10 ml. of 50% potassium hydroxide solution was added and, after mixing, the resulting solution was allowed to stand overnight. After diluting to volume, the following dilutions were made: 10 ml. to 100 ml., and 15 ml. of the resulting solution to 100 ml. with water. The optical density of the resulting solution was determined at 313 and 411 mμ.

O.D.$_{313}$ = 0.543, log ϵ_{313} 4.19; O.D.$_{411}$ = 0.288, log ϵ_{411} 3.92.

For the **dipotassium salt of 4,4-dinitro-2-butenoic acid**, log ϵ_{313} 4.20, log ϵ_{411} 3.92.

Carrying out the previous procedure with **potassium 4,4-dinitro-2-butenenitrile** gave the following optical density and log ϵ values for a final concentration of 2.92×10^{-5} *M*.

O.D.$_{313}$ = 0.458, log ϵ 4.19; O.D.$_{411}$ = 0.244, log ϵ_{411} 3.92.

On a synthetic scale, 0.0044 mole (1.0 g.) of **potassium methyl 4,4-dinitro-2-butenoate** in 15 ml. of water was added to 2.0 g. of potassium hydroxide in 10 ml. of water. To the resulting solution was added 75 ml. of methanol and the solution cooled in ice. Since no precipitate formed, an additional 5.0 g. of potassium hydroxide was added. As soon as this had dissolved, a yellow precipitate began to form. This solid was filtered from the solution, washed with cold methanol and ether, and air dried. There was obtained 0.71 g. (71%) of the **dipotassium salt of 4,4-dinitro-2-butenoic acid**; $\epsilon_{360}/\epsilon_{410}$ 0.438. Glover[3] reports $\epsilon_{360}/\epsilon_{410}$ 0.440. An analytical sample prepared by recrystallization from a large volume of methanol gave the following results.

Anal. Calcd. for $C_4H_2N_2O_6K$: N, 11.1. Found: N, 11.2, 11.6.

Hydrolysis of Potassium 4,4-Dinitro-2-hydroxybutyramide (Vb) to Dipotassium 4,4-Dinitro-2-hydroxybutyrate (VIIb).—To a solution of 0.0217 mole (5.01 g.) of the salt Vb in 30 ml. of warm water was added a solution of 0.0434 mole (2.44 g.) of potassium hydroxide in 20 ml. of methanol. The resulting solution was heated on the steam bath for 48 hr., at which time the evolution of ammonia had ceased. The resulting yellow solution was concentrated *in vacuo* until the mixture became pasty due to the separation of the dipotassium salt VIIb. The yellow salt was collected on a Büchner funnel and washed with 10 ml. of ice–water.[21] The material remaining on the funnel was then washed with 200 ml. of methanol, 50 ml. of ether, and sucked dry. After drying in the vacuum oven at 40° the following analytical results were obtained.

Anal. Calcd. for $C_4H_4N_2O_7K_2 \cdot H_2O$: C, 16.7; H, 2.1; N, 9.7; K, 27.1. Found: C, 16.6, 15.8; H, 2.0, 2.2; N, 10.2, 9.9; K, 28.9.

Since these results agreed fairly well with those calculated for a monohydrate of VIIb, it was decided to subject the material to vigorous drying at 70° and 20 μ in an Abderhalden pistol with phosphorus pentoxide. After 7 days under these conditions, the following analytical results were obtained.

Anal. Calcd. for $C_4H_4N_2O_7K_2$: C, 17.8; H, 1.5; N, 10.4; K, 28.9. Found: C, 17.4, 17.0; H, 1.8, 1.7; N, 10.3, 10.7; K, 27.3, 28.3.

6-Carbomethoxy-4,4-Dinitro-2-hydroxyhexanamide (IX).—A solution of 0.028 mole (6.65 g.) of the salt Vb was prepared in 100 ml. of water containing 0.03 mole (1.80 g.) of glacial acetic acid and 0.03 mole (2.46 g.) of sodium acetate. To this solution was added 0.06 mole (5.16 g.) of methyl acrylate and sufficient methanol to render the mixture homogeneous. The resulting solution was stirred for 7 days at room temperature. At the end of this time, a small amount of oil had separated. The mixture was thoroughly extracted with ether and the combined extracts were dried over magnesium sulfate, treated with Norit, and evaporated to dryness *in vacuo* to leave 6.5 g. of a pale yellow solid.

A portion of the crude material (4 g.) was purified for analysis by dissolving it in 1 l. of ether and treating the solution with Norit. The resulting colorless solution was concentrated to about 150 ml., whereupon the amide ester slowly crystallized in the form of fine white needles melting at 92.2–93°.

Anal. Calcd. for $C_7H_{13}N_3O_8$: C, 34.4; H, 4.7; N, 15.1. Found: C, 34.4, 34.4; H, 4.6, 4.4; N, 15.5, 15.0.

Infrared Spectrum.—–NH, 3180, 3280, 3450 cm.$^{-1}$; –OH, 1100, 3380 cm.$^{-1}$; –C=O, 1730 ($COOCH_3$), 1665, 1675 cm.$^{-1}$ $CONH_2$, possibly bonded and unbonded to OH; amide II, 1578 cm.$^{-1}$; $>C(NO_2)_2$, 1320, 1558 cm.$^{-1}$.

Hydrolysis of the Amide Ester IX.—Sixteen-thousandths of a mole (4.4 g.) of IX was refluxed with 60 ml. of concentrated hydrochloric acid and 20 ml. of water for 5.5 hr. The resulting solution was evaporated to near dryness *in vacuo* and the residual paste was extracted with 500 ml. of ether. The combined ether extracts were dried over magnesium sulfate, treated with Norit, and the solvent was removed *in vacuo*. The residual oil slowly crystallized on standing to yield 3.8 g. of a white solid melting at 137–139°. This product did not depress the melting point of an authentic sample of **4,4-dinitro-2-hydroxypimelic acid** and its infrared spectrum could be superimposed upon that of the authentic sample.

Acknowledgment.—We are grateful to Messrs. F. Taylor, Jr., and B. Wilkerson for supplying some of the intermediates used in this work and to Dr. D. V. Sickman who contributed helpful suggestions.

(18) The colorless needles were shown to be potassium nitrate by comparison of the refractive index (1.506) and predominant crystal angle (78°) with that of an authentic sample.

(19) Some solid (potassium chloride) may separate at this point.

(20) E. H. Huntress and S. P. Mulliken, "Identification of Organic Compounds, Order I," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 176.

(21) Although washing with water purified the salt VIIb, it also effected a considerable reduction in yield due to the extreme solubility of the salt in water at 0°.

Synthetic Nucleosides. LVI.[1,2] Facile Displacement Reactions in the D-Mannitol Series. III. Transformation of Tetrahydropyranyl Derivatives

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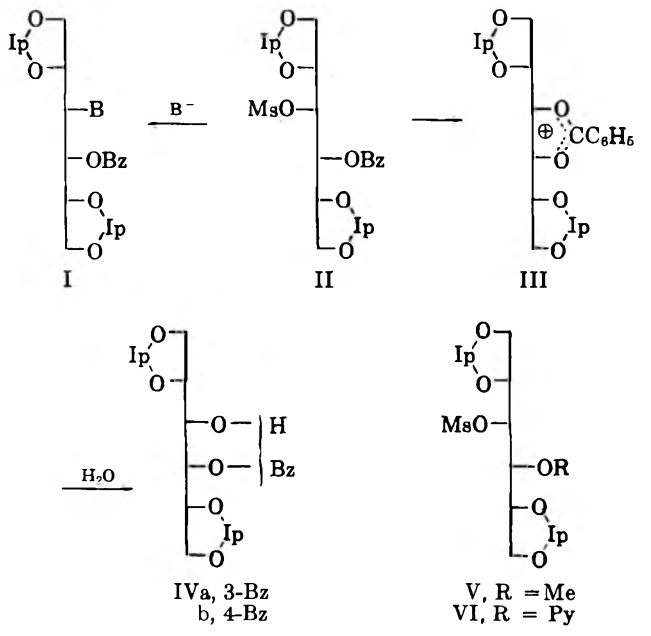
Acid-catalyzed reaction of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VII) with dihydropyran gave a 73% yield of the crystalline 4-O-(2-tetrahydropyranyl) derivative (VIII). Base-catalyzed methanolysis of VIII afforded a 73% yield of crystalline 1,2:5,6-di-O-isopropylidene-3-O-(2′-tetrahydropyranyl)-D-mannitol (XI). The latter could be oxidized with chromium trioxide–pyridine to the corresponding 3-*arabo*-hexulose (XI) in 40% yield or mesylated to the key intermediate, 1,2:5,6-di-O-isopropylidene-3-O-mesyl-4-O-(2-tetrahydropyranyl)-D-mannitol (VI), in 80% yield. The mesyloxy group of VI could be bimolecularly displaced with either acetate or azide ions which, by further transformations, gave 1,2:5,6-di-O-isopropylidene-D-talitol (XXII) and 3-benzamido-4-O-benzoyl-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (XVII), respectively. A key reaction to these transformations was the selective removal of the tetrahydropyranyl group by acid-catalyzed methanolysis with retention of the isopropylidene blocking groups.

Previous papers in this area[1,3] on displacement reactions of 3-O-benzoyl-1,2,5,6-di-O-isopropylidene-4-O-mesyl-D-mannitol have shown that the reaction can proceed *via* anchimeric formation of the ortho ester ion (III) or by direct SN2 reaction (II→I) depending upon the relative strengths of the attacking nucleophile (B^-) and the anchimeric group. With a strong nucleophile such as azide ion, the SN2 reaction was



favorably competitive with formation of I (B = N_3^-). However, with weaker nucleophiles the anchimeric reaction predominated with resultant formation of talitol derivatives (IV) sans introduction of the nucleophile. A neighboring methyl ether group of V is such a poor anchimeric group that only SN2 reaction took place with acetate ion.

The success with the ether group suggested that an ether group more easily removable than the methyl might make the mannitol displacement reactions more attractive as a source for synthesis of unusual carbohydrates. The acid-labile tetrahydropyranyl blocking group meets these requirements and its use in the mannitol series is the subject of this paper.

Reaction of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VII)[4] with dihydropyran in the presence of a trace of *p*-toluenesulfonic acid gave the tetrahydropyranyl ether (VIII). A short reaction time was essential; after fifteen minutes the product was crystallized in 73% by addition of petroleum ether, but with a longer reaction time the product could not be crystallized.

In order to carry out certain transformations to be discussed later, it was necessary to remove the tetrahydropyranyl group with minimal effect on the isopropylidene blocking groups. Since the tetrahydropyranyl group can be removed only under acid conditions, unless proper conditions could be found, the hexitol would lose more or less of its isopropylidene blocking groups. The usual conditions of aqueous mineral acid[5] or dilute acetic acid[6] also could be expected to cause partial or total loss of the isopropylidene groups. In contrast, it can be anticipated that acid-catalyzed interchange of the tetrahydropyranyl group with a monohydric alcohol should show great selectivity since the dioxalane ring formed from a glycol such as in VIII should not exchange readily with a monohydric alcohol.

Treatment of VIII with reagent methanol containing a catalytic amount of *p*-toluenesulfonic acid at room temperature did indeed remove the tetrahydropyranyl group with formation of VII in about 30% yield; investigation of the mother liquor showed that the material had still lost some isopropylidene blocking groups. In order to minimize the dioxalane exchange reaction, 2,2-dimethoxypropane and acetone were used in addition to methanol and an 82% yield of VII was obtained; the dimethoxypropane served either to keep the equilibrium of isopropylidene removal in favor of the dioxalane (VII) or acted as a scavenger for traces of water or both, whereas acetone could contribute to the former.

Debenzoylation of VIII with methanol containing a trace of sodium methoxide gave a mixture of IX and methyl benzoate. After removal of the methyl

(1) For the previous paper of this series (LV), see B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963).

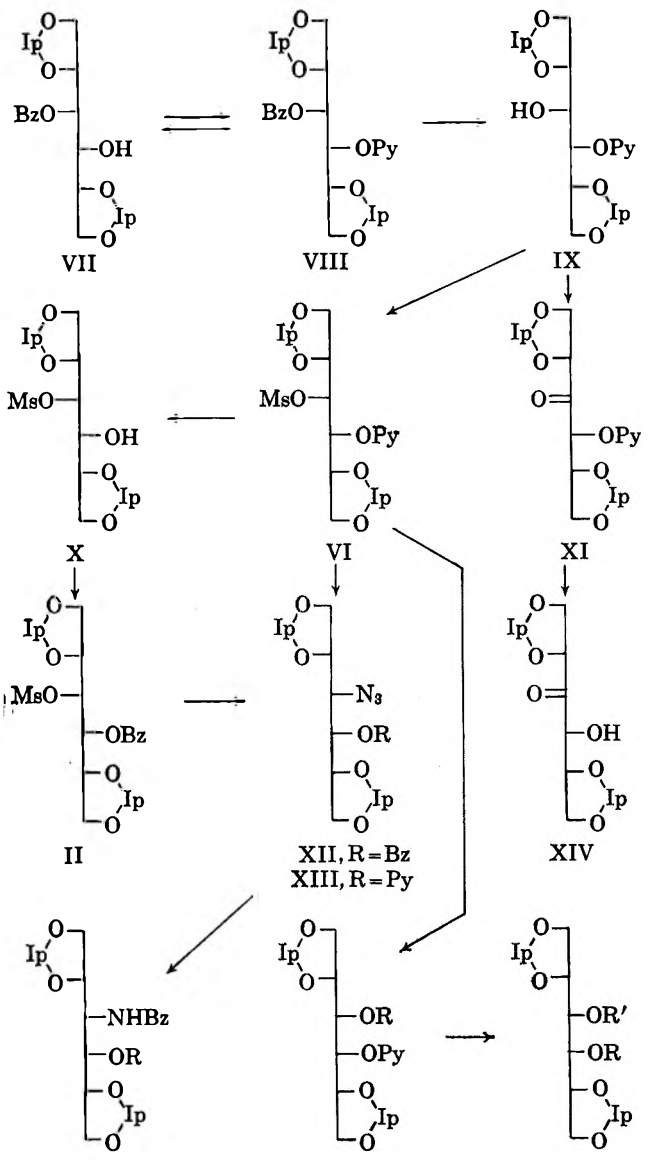
(2) This work was generously supported by grant no. CY-5845 from the National Cancer Institute, U. S. Public Health Service.

(3) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963), paper LIV of this series.

(4) J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.*, **79**, 5780 (1957).

(5) G. F. Woods and D. N. Kramer, *ibid.*, **69**, 2246 (1947); E. Dyer C. P. J. Glavdemans, M. J. Koch, and R. H. Marchessault, *J. Chem. Soc.*, 3361 (1962).

(6) D. H. Rammler and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 3112 (1962).



Bz = Benzoyl; Py = 2-tetrahydropyranyl; Ms = methanesulfonyl; Ac = acetate; Ip = isopropylidene

benzoate by steam distillation *in vacuo*, IX could be crystallized from petroleum ether as a low-melting solid in 73% yield.

The hydroxyl group of IX smoothly reacted with mesyl chloride in pyridine at 0° to give the crystalline mesylate (VI) in 80% yield, showing the stability of the tetrahydropyranyl group to cold pyridine–pyridine hydrochloride. That the tetrahydropyranyl group also was stable to pyridine–chromium trioxide was shown by oxidation of IX to the crystalline pyranyl ketone (XI)[7] in 43% yield under conditions previously used for oxidation of VII to the corresponding ketone,[4] where a similar yield was obtained.

Depyranylation of the mesyl derivative (VI) by the methanolysis procedure gave an 88% yield of the hydroxy mesylate (X) which could not be crystallized, but which was converted to the known crystalline benzoyl derivative (II)[3] in 61% yield. The hydroxy mesylate (X) should serve as a useful intermediate for introducing neighboring groups that could be used for anchimeric introduction of functions into the hexitol chain.

The displacement reactions of the pyranyl mesylate (VI) were studied with both acetate and azide ions; although the mesylate group of VI was somewhat less active than the mesylate of II, the pyranyl group was, fortunately, sufficiently stable to the displacement conditions that the reactions proceeded smoothly.

Treatment of VI with sodium acetate in boiling dimethylformamide for twenty-four hours caused complete displacement of the mesyloxy group; the product was an oil, primarily the talitol acetate (XVIII) contaminated slightly with the alcohol (XIX) formed by partial hydrolytic loss of the acetyl group. The mixture of XVIII and XIX was deacetylated with methanolic sodium methoxide giving XIX as an oil in 67% yield.

Depyranylation of crude XIX by acid-catalyzed methanolysis to give 1,2:5,6-di-O-isopropylidene-D-talitol (XXII) afforded an oil with an infrared spectrum almost identical to authentic XXII; purification at this stage by crystallization appeared unpromising, due in part to the relatively low melting point of XXII.[3,4] Hence the sequence XIX → XX → IVa → XXII was used in a search for an easily isolable crystalline derivative; unfortunately, none of the intermediates could be crystallized. However, benzoylation of XIX and purification on an alumina column gave a 55% yield of analytically pure pyranyl benzoate (XX) as an oil.[8]

Depyranylation of XX gave a sirupy benzoate from which the previously described[3] 1,2:5,6-di-O-isopropylidene-D-talitol (XXII) monobenzoate crystallized slowly in 12% yield. Since this monobenzoate is an easily crystallizable substance and since the oily benzoate in the mother liquor from this crystalline benzoate could be debenzoylated to crystalline XXII in 45% yield, or benzoylated to XXI, probable structural assignments for the crystalline and noncrystalline benzoates can be made.

The product from depyranylation of XX should be the talitol 4-benzoate (IVa); since a mixture of the two isomeric benzoates are obtained, any structural assignment can only be tentative. It previously has been shown that the oily benzoate could slowly rearrange to the crystalline benzoate.[3] Therefore, the predominant isomer obtained in the depyranylation should be the talitol 4-benzoate (IVa), which slowly rearranges to the crystalline talitol 3-benzoate (IVb). The current experiments give further credence to the suggestion[3] that the ortho ester ion (III) reacts with water to give a

(7) Attempts to depyranylate XI to XIV with methanol–acetone–dimethoxypropane containing a trace of *p*-toluenesulfonic acid gave an oil which on benzoylation afforded a small yield of O-benzoyl derivative, m.p. 122°, that was isomeric to the O-benzoyl derivative of XIV[4]; the oily residue from the mother liquor contained what appeared to be a mixture of isomeric ketone benzoates. Either the depyranylation conditions, the benzoylation conditions, or both cause an equilibration of isomers at the 3- and 4-positions probably through an enediol[4]; it also is possible that the supposed intermediate, XIV, is actually an enediol, since it shows no ketone absorption, but does show strong hydroxyl absorption. The n.m.r. spectrum of XIV showed no O–CH_3 hydrogens which could have arisen by formation of a stable hemiketal between XIV and methanol, or formation of a dimethyl ketal.

(8) *A posteriori*, it would be simpler to prepare the pyranyl benzoate (XX) by reaction of the pyranyl mesylate (VI) with sodium benzoate, rather than sodium acetate and subsequent transformation; *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1689 (1959), and references therein.

mixture of both isomeric benzoates (IV), thus showing no unusual selectivity during ring opening.

The pyranyl mesylate (VI) reacted with sodium azide in boiling dimethylformamide to give the azide (XIII). This oily azide (XIII), which showed a typical azido band at 2125 cm.$^{-1}$, was reduced with lithium aluminum hydride as described for XII[1]; the resultant amine was not obtained crystalline, but readily gave a crystalline N-benzoyl derivative (XV) in 40% over-all yield for the three steps from VI. Since the average yield per step was 74%, this was somewhat higher than an average yield of 72% for the three steps for the conversion of II → XII → XVII. Acid-catalyzed depyranylation of XV to XVI with methanol–acetone–dimethoxypropane, followed by benzoylation afforded the previously known[1] and easily crystallizable dibenzoylaminoaltritol (XVII) in 62% yield.

The synthesis of the aminoaltritol (XVII) and the talitol (XXI) from the pyranyl mesylate (VI) shows the utility of the tetrahydropyranyl blocking group for conversion of 1,2:5,6-di-O-isopropylidene-D-mannitol to other hexitol derivatives; further work on displacement reactions of VI with other nucleophiles, therefore, is warranted. In addition, the pyranyl ketone (XI) and the monomesyl pyranyl mannitol (X) may prove useful for introduction of groups into the hexitol chain.

Experimental[9]

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(2-tetrahydropyranyl)-D-mannitol (VIII).—To a stirred suspension of 10 g. (0.033 mole) of VII[4] in 20 ml. of dihydropyran was added 50 mg. of *p*-toluenesulfonic acid over a period of 5 min., during which time a clear solution formed. After being stirred another 10 min., the solution was diluted with 100 ml. of petroleum ether, then kept overnight at −6°. The product was collected on a filter and washed with petroleum ether; yield, 6.7 g., m.p. 118–119°. The combined mother liquor and washings deposited an additional 2.3 g. (total 73%) of product after 3 more days at −6°. A similar preparation was recrystallized from petroleum ether giving white crystals, m.p. 119–120°; $[\alpha]^{25}D$ +22.4 ± 0.7° (0.7%); ν_{max}^{Nujol} 1710 (C=O); 1260, 1200, 1070 (C—O—C); 715 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{24}H_{34}O_8$: C, 64.0; H, 7.55. Found: C, 63.9; H, 7.44.

Selective Removal of the Tetrahydropyranyl Group from 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(2-tetrahydropyranyl)-D-mannitol (VIII).—To a solution of 450 mg. (1 mmole) of VIII in 2 ml. of reagent methanol, 10 ml. of reagent acetone and 2 ml. of 2,2-dimethoxypropane was added 3 mg. of *p*-toluenesulfonic acid. After standing about 18 hr. at room temperature protected from moisture, the mixture was treated with 0.2 ml. of 5% aqueous sodium bicarbonate, then spin evaporated to dryness *in vacuo*. The residue was partitioned between 5 ml. of water and 20 ml. of chloroform, then the aqueous phase was extracted again with 20 ml. of chloroform. Washed with water, the combined organic extracts were evaporated to dryness *in vacuo*. Crystallization from ethyl acetate–petroleum ether gave 300 mg. (82%) of VII, m.p. 103–104°; a mixture with authentic VII gave no depression in melting point and the infrared spectra of the two samples were identical.

If the acetone and 2,2-dimethoxypropane were not present, the product suffered some deacetonation, and only about 30% of pure VII could be isolated.

1,2:5,6-Di-O-isopropylidene-3-O-(2-tetrahydropyranyl)-D-mannitol (IX).—A suspension of 5.3 g. (11.8 mmoles) of VIII in 90 ml. of reagent methanol containing 50 mg. of sodium methoxide was stirred for 48 hr. protected from moisture; solution occurred in about 24 hr. The solution was spin evaporated to dryness *in vacuo;* methyl benzoate was removed by spin evaporation with water *in vacuo*. Crystallization of the residue from petroleum ether at −6° gave 2.95 g. (73%) of product, m.p. 68°. Recrystallization from the same solvent gave the analytical sample, m.p. 69°[10]; $[\alpha]^{25}D$ −14.2 ± 0.6° (1.1%); ν_{max}^{Nujol} 3450 (OH); 1205, 1240, 1070 (C—O—C), and no benzoate absorption at 1710 and 715 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{30}O_7$: C, 59.0; H, 8.67. Found: C, 59.0; H, 8.47.

1,2:5,6-Di-O-isopropylidene-3-O-mesyl-4-O-(2-tetrahydropyranyl)-D-mannitol (VI).—To a stirred solution of 2.8 mmoles) of IX in 8 ml. of reagent pyridine cooled in an ice bath and protected from moisture was added 1.1 g. (9.5 mmoles) of methanesulfonyl chloride over a period of 20 min. After being stirred for an additional 3 hr. at 0°, then allowed to stand overnight at room temperature, the mixture was poured into 25 ml. of ice–water and extracted with chloroform (three 20-ml. portions). Combined extracts were washed with 10 ml. of 5% aqueous sodium bicarbonate, then water. Dried with magnesium sulfate, the organic solution was spin evaporated to dryness *in vacuo* at room temperature. Traces of pyridine were removed by addition and spin evaporation of toluene. Crystallization from petroleum ether afforded 2.8 g. (80%) of product, m.p. 59–61°, that was suitable for further transformations. Recrystallization from ethyl acetate–petroleum ether gave white crystals, m.p. 63°; $[\alpha]^{25}D$ +4.8 ± 0.5° (1%); ν_{max}^{Nujol} 1340, 1165 (—SO_3—); 1265, 1200, 1080, 1060 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{18}H_{32}O_9S$: C, 50.9; H, 7.55; S, 7.55. Found: C, 51.0; H, 7.62; S, 7.76.

1,2:5,6-Di-O-isopropylidene-4-O-(2-tetrahydropyranyl)-D-*arabo*-3-hexulose (XI).—To the chromium trioxide–pyridine complex from 4 g. of chromium trioxide and 50 ml. of reagent pyridine, prepared according to Sugihara and Yuen[4] with observation of their precautions to avoid detonation, was added a solution of 3.0 g. (8.7 mmoles) of IX in 10 ml. of reagent pyridine. After being heated with stirring at 60° for 8 hr., the mixture was cooled, poured into 100 ml. of ice–water, then extracted with ether (four 40-ml. portions). Combined extracts were washed with water, dried with magnesium sulfate, then evaporated *in vacuo*. Traces of pyridine were removed by addition and spin evaporation of toluene *in vacuo*. Crystallization from petroleum ether gave 1.2 g. (40%) of white crystals, m.p. 83°; $[\alpha]^{25}D$ −16.1 ± 0.6° (0.6%); ν_{max}^{Nujol} 1720 (C=O); 1255, 1200, 1120, 1120, 1065 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{17}H_{28}O_7$: C, 59.3; H, 8.14. Found: C, 59.2; H, 8.23.

1,2:5,6-Di-O-isopropylidene-3-O-mesyl-D-mannitol (X).—Depyranylation of 424 mg. (1 mmole) of VI as described for the depyranylation of VIII gave 300 mg. (88%) of X as an oil which could not be crystallized; ν_{max}^{film} 3500 (OH); 1360, 1170 (—SO_3—); 1260, 1210, 1070 cm.$^{-1}$ (C—O—C).

For characterization, 300 mg. of X was benzoylated with 154 mg. of benzoyl chloride in 5 ml. of reagent pyridine for 2 hr. at 0° and 24 hr. at room temperature, then worked up as usual.[1,3] Crystallization from ethyl acetate–petroleum ether gave 250 mg. (61%) of II, m.p. 73–74°, that was identical with an authentic sample of II as shown by mixture melting point and comparative infrared spectra.

4-O-Benzoyl-1,2:5,6-di-O-isopropylidene-3-O-(2-tetrahydropyranyl)-D-talitol (XX).—A mixture of 850 mg. (2 mmoles) of VI, 492 mg. (6 mmoles) of anhydrous sodium acetate, and 20 mg. of anhydrous dimethylformamide (Spectro Grade) was refluxed with stirring for 24 hr. Solvent was removed by spin evaporation *in vacuo* on a boiling water bath. The residue was suspended in 10 ml. of water and extracted with chloroform (three 30-ml. portions). Combined extracts were washed with water, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. A solution of the residue in 20:1 petroleum ether–ethyl acetate was clarified with charcoal. Evaporation *in vacuo* gave 690 mg. of an oil that was predominately XVIII since it showed strong carbonyl absorption at 1740 cm.$^{-1}$ and weak hydroxyl absorption at 3500 cm.$^{-1}$ of some contaminating XIX; the product could not be crystallized.

The crude XVIII was deacetylated by solution in 50 ml. of reagent methanol containing 50 mg. of sodium methoxide. After

(9) Melting points were determined in capillary tubes with a Mel-Temp block and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. Optical rotations were measured in a 1-dm. microtube in chloroform solution. Petroleum ether refers to that fraction with b.p. 60–75°.

(10) Earlier preparations gave a low melting dimorph, m.p. 45°; only the high melting dimorph was encountered in later work.

about 18 hr. at room temperature protected from moisture, the solvent was removed *in vacuo*. The residue was suspended in 10 ml. of water and extracted with chloroform (two 30-ml. portions). Combined extracts were washed with water, dried with magnesium sulfate, and evaporated to dryness *in vacuo;* yield, 480 mg. (67% from VI) of oily XIX that could not be crystallized; ν_{max}^{film} 3550 (OH); 1255, 1210, 1065 (C—O—C) and no acetate C=O at 1740 cm.$^{-1}$.

To a stirred solution of 1.04 g. (3 mmoles) of a similar preparation of XIX in 6 ml. of reagent pyridine was added 490 mg. (3.5 mmoles) of benzoyl chloride with ice cooling. After 24 hr., the mixture was processed in the usual way[1,3] to give 0.95 g. of an oil showing benzoate C=O at 1710 cm.$^{-1}$. A solution of this crude XX in 20 ml. of benzene was poured onto a column of about 65 g. of neutral alumina (Brockmann activity III). Elution with 50 ml. of benzene, then 50 ml. of 1:1 chloroform–benzene gave 50 mg. of material with weak benzoyl absorption at 1710 cm.$^{-1}$ and was rejected. Further elution with 200 ml. of chloroform afforded 0.75 g. (56%) of pure XX as an oil that could not be crystallized; $[\alpha]^{25}D$ +18 ± 1° (0.2%); ν_{max}^{film} 1710 (ester C=O); 1260, 1200, 1070 (C—O—C); 715 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{24}H_{34}O_8$: C, 64.0; H, 7.55. Found: C, 64.1; H, 7.73.

4-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-talitol (IVa).—Depyranylation of 200 mg. (0.44 mmole) of XX, as described for depyranylation of VIII, afforded 135 mg. (83%) of a syrup. Crystallization from ethyl acetate–petroleum ether slowly occurred over 2 days at −5° giving 20 mg. (12%) of the 3-benzoate (IVb), m.p. 123–124°, that was identical with the material previously prepared from II.[3] Spin evaporation of the mother liquor *in vacuo* gave the remainder of the product as the sirupy 4-benzoate (IVa) (115 mg., 71%) which had ν_{max}^{film} 3550 (OH); 1710, 710 (benzoate); 1260, 1080 cm.$^{-1}$ (C—O—C) and which was debenzoylated (description follows).

1,2:5,6-Di-O-isopropylidene-D-talitol (XXII).—The preceding sirupy 4-benzoate (IVa) was debenzoylated as described for the preparation of IX. Crystallization from petroleum ether gave 45 mg. (37% based on XX), m.p. 62–63°, that was identical with an authentic sample.

3,4-Di-O-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (XXI).—Benzoylation of 115 mg. of sirupy benzoate (IVa) with 60 mg. of benzoyl chloride in 1.5 ml. of reagent pyridine, then work-up as usual,[1,3] gave 60 mg. of XXI, m.p. 144°, that was identical with an authentic sample.[3]

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-4-O-(2-tetrahydropyranyl)-D-altritol (XV).—A mixture of 0.85 g. (2 mmoles) of VI, 0.39 g. (6 mmoles) of sodium azide, and 10 ml. of dimethylformamide was refluxed for 6 hr. The solvent was removed by spin evaporation *in vacuo* on a boiling water bath. The residue was suspended in 20 ml. of ice–water and extracted with chloroform (three 20-ml. portions). Dried with magnesium sulfate, combined extracts were evaporated to residue *in vacuo;* yield, 0.66 g. (89%) of crude azide (XIII); ν_{max}^{film} 2125 (—N_3); 1255, 1210, 1065 cm.$^{-1}$ (C—O—C).

To a stirred suspension of 230 mg. (6 mmoles) of lithium aluminum hydride in 40 ml. of reagent ether was added a solution of 1.01 g. (2.73 mmoles) of crude azide (XIII) in 10 ml. of reagent ether at such a rate that gentle reflux was maintained. After being refluxed for 1 hr., the excess hydride was decomposed by the careful addition of 1 ml. of ethyl acetate followed by 0.35 ml. of water. The mixture was filtered and the salts washed with ether. The filtrate was decolorized with charcoal, then spin evaporated *in vacuo;* yield, 0.797 g. (90%) of 3-aminodeoxy-1,2:5,6-di-O-isopropylidene-4-O-(2′-tetrahydropyranyl)-D-altritol that could not be crystallized and had ν_{max}^{film} 3400 (NH); 1260, 1080 (C—O—C); and no azide absorption at 2125 cm.$^{-1}$.

To a stirred solution of 0.70 g. (2 mmoles) of the amine in 7 ml. of reagent pyridine cooled in an ice bath and protected from moisture was added 326 mg. (2.3 mmoles) of benzoyl chloride. After being stirred for 3 hr. in the ice bath and 18 hr. at room temperature, the mixture was processed in the usual manner.[1,3] Crystallization from ethyl acetate–petroleum ether gave 504 mg. (56%, or 40% from VI) of XV, m.p. 140°. Recrystallization from chloroform–petroleum ether afforded white needles, m.p. 141°; $[\alpha]^{25}D$ +8.2 ± 0.6° (0.8%); ν_{max}^{Nujol} 3325 (NH); 1640, 1525 (amide); 1250, 1210, 1065 (C—O—C); 705 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.2; H, 7.78; N, 3.11. Found: C, 64.3; H, 7.99; N, 3.34.

3-Benzamido-4-O-benzoyl-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (XVIII).—Depyranylation of 150 mg. of XV as described for the depyranylation of VIII gave 110 mg. (90%) of crude XVI, which was benzoylated with 64 mg. of benzoyl chloride in 2 ml. of reagent pyridine in the usual manner.[3] Recrystallization of the product from ethyl acetate–methanol afforded 90 mg. (67%) of XVII, m.p. 202–203°, which was identical with an authentic sample prepared by a different route.[1]

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by contract no. SA-43-ph-4346.

Synthetic Nucleosides. LVII.[1] Facile Displacement Reactions in the D-Mannitol Series. IV. Investigation of Thiourethane Derivatives[2]

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Reaction of the monosodium salt of 1,2:5,6-di-O-isopropylidene-D-mannitol (V) with phenyl isothiocyanate did not form the expected phenylthiourethane derivative (VI). Instead, a facile cyclization took place to give a cyclic carbonate (XIV), a thionocarbonate (IX), or a phenyliminocarbonate (X) derivative of V, depending upon the work-up conditions. Additional evidence to support a proposed mechanism for these reactions also is presented.

Possible routes to synthesis of sugars containing a *cis*-mercapto alcohol system (I) such as that in the 2-mercapto-2-deoxy-D-ribose or 3-mercapto-3-deoxy-D-ribose of Baker and co-workers[3-5] has been under investigation for several years; nucleosides containing such sugars might afford interesting biological properties.[3] Although thio sugars with a *trans* relationship of OH and SR groups (IV) are readily synthesized by ring opening of sugar epoxides (III) with mercaptides,[6] successful routes to *cis* compounds with a *cis* relation-

(1) For the previous paper in this series, see B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2132 (1963).

(2) This work was generously supported by grant CY-5845 of the National Cancer Institute, U. S. Public Health Service.

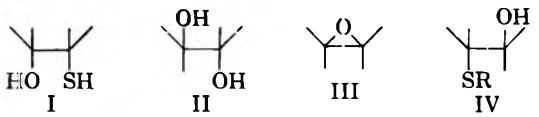
(3) B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Am. Chem. Soc.*, **80**, 6582 (1958).

(4) L. Goodman, A. Benitez, C. D. Anderson, and B. R. Baker, *ibid.*, **80**, 6582 (1958).

(5) E. J. Reist, J. H. Osieeki, A. Benitez, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 3554 (1961).

(6) (a) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959); (b) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 898 (1959); (c) J. Davoll, B. Lythgoe, and S. Tripett, *J. Chem. Soc.*, 2230 (1951); (d) R. Jeanloz, D. A. Prins, and T. Reichstein, *Helv. Chim. Acta*, **29**, 371 (1946); (e) W. Pigman, "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1957.

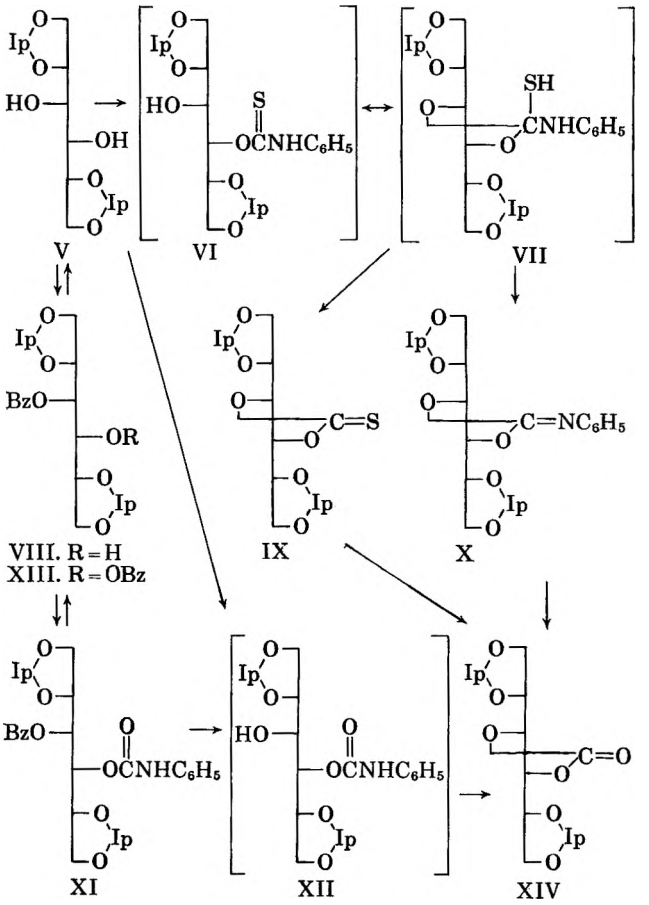
ship (I) have so far been elusive. Terminal thio functions readily can be introduced into the sugar molecule by displacement reactions,[6e] but the displacement of a ring secondary tosylate by mercaptide ion has been uniformly unsuccessful due to the weak electrophilic character of these sugar ring tosylates[7]; therefore, our attention has been directed primarily to the introduction of a *cis*-mercapto group by anchimeric assistance of a neighboring group where the energy barrier is considerably reduced and reactions are accelerated a thousandfold compared to the SN2 type.[8]



That the *cis*-mercapto alcohol system in a ring can be synthesized by utilization of the neighboring phenylthiocarbonyl group has been established in the cyclopentane series. Although the appropriate thiocarbonyl derivative in a pentofuranose[5] and a hexopyranose[3] could be synthesized, their conversion to the *cis*-mercapto alcohol system of type I failed primarily due to the difficulty of removing an isopropylidene blocking group in the furanose case, and the instability of a benzylidene blocking group in the second case. Since we have been undertaking a study of reactions of 1,2:5,6-di-O-isopropylidene-D-mannitol (V) for synthesis of sugars containing a new functional group in place of a hydroxyl,[7,9] this compound (V) appeared to be an attractive one to study the introduction of sulfur by the neighboring phenylthiocarbamyl group; although this approach so far has been unsuccessful in its ultimate goal, the unusual nature of the reactions encountered has prompted this paper.

Similar to methyl 4,6-O-benzylidene-α-D-glucopyranoside,[3] but in contrast to 1,2-*trans*-cyclopentanediol,[4] 1,2:5,6-di-O-isopropylidene-D-mannitol (V) failed to react with phenyl isothiocyanate in boiling toluene; therefore, the more strenuous conditions employed for the glucopyranoside,[3] *i.e.*, formation of the sodium alcoholate with sodium hydride in dimethylformamide, then reaction with phenyl isothiocyanate, was investigated. Surprisingly, none of the desired phenylthiourethane (VI) was obtained, but either the tricyclic product, XIV, or a mixture of IX and X could be obtained depending upon how the reaction mixture was processed.

When the reaction mixture was acidified with glacial acetic acid then diluted with water as previously described for the glucopyranoside,[3] diphenylthiourea was isolated in 33% yield; from the mother liquor was obtained 30% of a crystalline mixture of the cyclic carbonate (XIV) and the cyclic thionocarbonate (IX). These two compounds were difficultly separable by fractional crystallization, but were obtained pure; the two compounds were readily distinguishable by their infrared spectra and the composition of a mixture of the two could be estimated since XIV had a five-membered ring carbonyl group at 1780 cm.$^{-1}$ and carbonate C–O–C at 1260 and 1065 cm.$^{-1}$, whereas IX showed additional carbonate C–O–C bands at 1325 and 1300 cm.$^{-1}$ and no carbonyl absorption. When the organic material was quickly separated from the aqueous solution by extraction, the product was primarily the thionocarbonate (IX) and little hydrolysis to XIV took place. The thionocarbonate (IX) was converted to the carbonate (XIV) in 80% yield by reaction with silver carbonate in methanol. That no change of configuration had taken place during the conversion of V to XIV *via* VI was shown by synthesis of the carbonate, XIV, from V with methyl chlorocarbonate in 55% yield under conditions that could not cause inversion.[10,11]



Bz = benzoyl; Ip = isopropylidene

Some insight into the possible mechanism of formation of the thionocarbonate (IX) from the supposed thiourethane (VI) was gained when the dimethylformamide solution of the sodium salt of VI was processed without addition of glacial acetic acid; in this case neither diphenylthiourea nor the thionocarbonate (IX) were formed; instead a new compound containing nitrogen and no sulfur was obtained in about 30% yield. That this crystalline compound was the phenyliminocarbonate (X) was shown by the presence of five-membered ring exocyclic C=N absorption at 1690 cm.$^{-1}$, monosubstituted benzene absorption at 700 cm.$^{-1}$, lack of NH absorption near 3303 cm.$^{-1}$, and by hydrolysis with dilute acetic acid to the cyclic carbonate (XIV).

(7) See B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963), paper LIV of this series, for a discussion of displacement of ring tosylates by various nucleophiles, including the advantages of anchimeric assistance by a neighboring group.

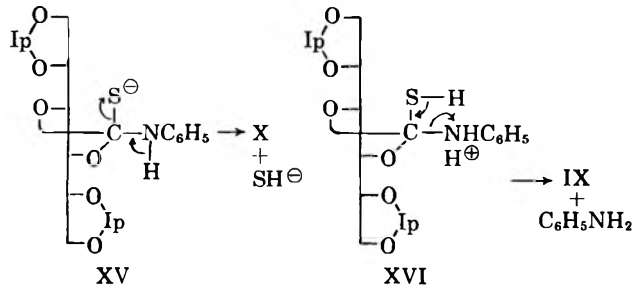
(8) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

(9) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963), paper LV of this series.

(10) E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1958 (1958).

(11) L. Hough, J. E. Priddle, and R. S. Theobald, *J. Chem. Soc.*, 1934 (1962).

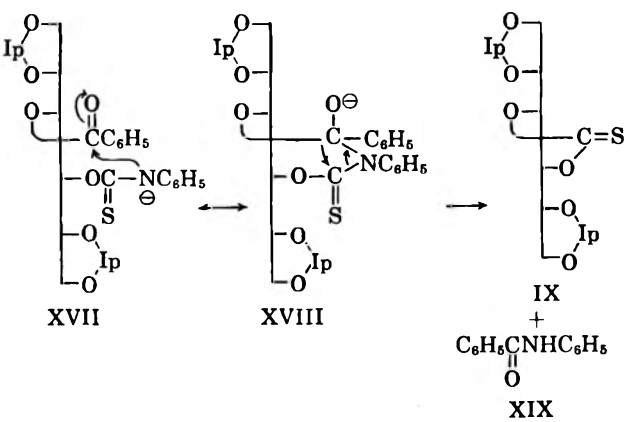
The mere addition or nonaddition of glacial acetic acid at room temperature prior to work-up giving different products suggests that the anion in dimethylformamide is not derived from the thiourethane (VI), but has structure XV derived from the cyclic structure VII; XV would be stabilized by a favorable "zig-zag" conformation.[9] Apparently, addition of water predominantly causes loss of bisulfide ion with formation of X. In contrast, when this anion (XV) is acidified with glacial acetic acid in anhydrous solution, the protonated form (XVI) readily loses aniline with formation of IX;



XV XVI

the resultant aniline then immediately forms diphenylthiourea with some unchanged phenyl isothiocyanate that is present.

Since the formation of the thiourethane (VI) was precluded by the presence of the adjacent hydroxyl group, it was clear that this hydroxyl would have to be blocked. The availability of the monobenzoate (VIII)[12] in this laboratory for other studies[7,9] suggested that an attempt be made to convert it to a phenylthiourethane; even though it was anticipated that sodium alcoholate of VIII might equilibrate to a mixture of VIII and its dibenzoate, there was a possibility that this intermolecular equilibration would be sufficiently slow to allow conversion to the phenylthiourethane derivative (XVII). Reaction of VIII with one equivalent of sodium hydride in dimethylformamide required only fifteen minutes at 50°; however, when this sodium salt was treated with phenyl isothiocyanate, a 40% yield of benzanilide along with 20% yield of a crystalline mixture of the carbonate (XIV) and thionocarbonate (IX) were obtained and none of the protonated XVII could be isolated.



XVII XVIII IX + $C_6H_5CNHC_6H_5$ (O) XIX

Although in an independent experiment, it was shown that the sodium salt of VIII could equilibrate to V, VIII, and a dibenzoate in boiling toluene, such an explanation for the formation of benzanilide and the thionocarbonate (IX) *via* VII is untenable with the isolation of the iminocarbonate (X) from VII. The anion, XV, apparently does not release aniline until acidified, conditions being too mild to allow reaction of aniline with the benzoate group of a molecule such as VIII to form benzanilide. A more tenable explanation is that the anion (XVII) is predominantly in the cyclic form, XVIII (again stabilized by the favorable "zig-zag" conformation[9]). This anion could collapse to the thionocarbonate (IX) and benzanilide (XIX) either during reaction or during work-up; further support for this explanation was obtained.

The monobenzoate, VIII, reacted smoothly with phenyl isocyanate in boiling toluene to give the crystalline urethane (XI) in 78% yield. When XI was partially converted to the anion with 6 mole % of sodium hydride in dimethylformamide, then heated at 90–100°, 71% of the urethane residue was converted to diphenylurea, 12% of XI was recovered unchanged, and 9% yield of the cyclic carbonate (XIV) was isolated; in contrast to the breakdown of the supposed XVII, no benzanilide could be isolated although a trace could be detected by thin layer chromatography. These results are tenable with the retrogression of the anion of XI to phenyl isocyanate and the monobenzoate, VIII; the latter then equilibrates to V and a dibenzoate (XIII). The phenylurethane (XII) is then formed from V and phenyl isocyanate or by *trans*-benzoylation between V and XI; a small yield of cyclic carbonate (XIV) from the monophenylurethane (XII) is then tenable. The fact that practically no benzanilide is formed from XI, but 40% is formed from XVII certainly indicates that different mechanisms for conversion to a cyclic carbonate or thionocarbonate from XI to XVII are involved and that the retrogression mechanism *via* V and XII cannot account for benzanilide. A further argument for the formation of benzanilide *via* XVIII is that the intermediate XVIII would be more likely to form than the corresponding anion of XI since the thiourethane is a far more nucleophilic group than is the urethane.

The ease of interaction of the benzoate carbonyl with the adjacent thiourethane group in XVII is certainly unexpected. Thus to prepare a thiourethane such as VI it would be necessary to use a noncarbonyl blocking group that could be removed later, such as the tetrahydropyranyl blocking group.[1] When the sodium salt of 1,2:5,6-di-O-isopropylidene-3-O-tetrahydropyranyl-D-mannitol[1] was treated with phenyl isothiocyanate in toluene, an oil was isolated that had the proper infrared spectrum; that is, it showed NH, but no carbonyl, none of the usual by-products were obtained such as diphenylthiourea, the thionocarbonate (IX), or the cyclic carbonate (XIV). Whether or not the tetrahydropyranyl group can be removed from the oil to give VI without formation of diphenylthiourea and the tricyclic by-products is worthy of pursuit.

Experimental[13]

Reaction of 1,2:5,6-Di-O-isopropylidene-D-mannitol (V) Sodium Salt with Phenylisothiocyanate.—(A) Acetic Acid Work-Up.—To a solution of 5.20 g. (0.02 mole) of dry V in 30 ml. of di-

(12) J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.*, **79**, 5780 (1957).

(13) Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Infrared spectra were determined with a Perkin-Elmer 137B spectrophotometer. Optical rotations were measured in a 1-dm. microtube in chloroform solution at the % concentration indicated. Petroleum ether used for purification was a fraction boiling at 30–60°.

methylformamide (Spectro Grade) was added 0.873 g. (0.02 mole) of a 55% sodium hydride emulsion in mineral oil. The mixture was heated at 90° for 90 min. protected from moisture when the formation of the sodium salt was complete, and an off-white suspension was obtained. After the addition of 3.38 g. (0.025 mole) of phenyl isothiocyanate, the mixture was stirred for another 90 min. at 90–95° during which time a brown solution was formed. After being cooled to room temperature, the solution was acidified with 1.8 ml. (0.03 mole) of glacial acetic acid, stirred 5 min., then poured into 125 ml. of ice–water. A light brown oil separated which soon solidified. The material was collected on a filter and washed with a little cold water. Recrystallization from 75% ethanol afforded 1.5 g. (33%) of diphenylthiourea, m.p. 150–151°, which gave no depression in melting point when mixed with an authentic sample and which had an infrared spectrum identical with that of an authentic sample.

The mother liquor from the 1.5 g. of diphenylthiourea deposited additional crystals after standing for 2 hr. at −5°. The material was collected on a filter and washed with cold water; yield was 1.0 g. (17%), m.p. 140–141°, of a mixture of the cyclic carbonate (XIV) and the thionocarbonate (IX) as shown by its infrared spectrum. Two recrystallizations from chloroform–petroleum ether gave 0.60 g. (10%) of 2:1 mixture of IX and XIV, m.p. 149–151°.

The mother liquor from the 1.0 g. of XIV and IX was diluted with water, then kept overnight at −5° to give 0.80 g. (13%) of cyclic carbonate XIV, m.p. 135–140°. Recrystallization from ethyl acetate–petroleum ether gave 0.50 g. (8%) of pure XIV, m.p. 145–146°; this compound gave no depression in melting point when mixed with an authentic sample of XIV, prepared as described later, and their infrared spectra were identical.

A similar preparation with 2.6 g. of V, 0.873 g. of 55% sodium hydride, and 3.38 g. of phenyl isothiocyanate was processed by immediate chloroform extraction (three 50-ml. portions) after the acidified dimethylformamide mixture was added to ice–water; thus processed, no appreciable hydrolysis of the thionocarbonate (IX) to the carbonate (XIV) took place. After removal of the solvent *in vacuo*, the residue was recrystallized from ethanol to give, in three crops, 1.05 g. (35%) of thionocarbonate IX, m.p. 160–161°. A second recrystallization of the first crop from ethanol gave pure IX as white crystals, m.p. 160–161°; $[\alpha]^{25}D$ −11 ± 1° (0.3%); ν_{max}^{Nujol} 1325, 1300, 1260, 1065 (C—O—C) and a weak band at 1780 cm.$^{-1}$ from a trace amount of XIV.

Anal. Calcd. for $C_{13}H_{20}O_6S$: C, 51.3; H, 6.50; S, 10.5. Found: C, 51.6; H, 6.08; S, 10.5.

From the mother liquor of the 1.05 g. could be isolated by crystallization from benzene 1.0 g. (44%) of diphenylthiourea, m.p. 149–150°.

(B) **By Alkaline Work-Up.**—After 2.6 g. (0.01 mole) of V had been converted to the sodium salt with 0.436 (0.01 mole) of 55% sodium hydride, then treated with 2.02 g. (0.015 mole) of phenyl isothiocyanate as described in A, the cooled dimethylformamide solution was poured into 200 ml. of ice-cold water and extracted twice with chloroform. Fractional crystallization from ethyl acetate–petroleum ether gave first 0.5 g. (19%) of unchanged V and then 0.60 g. (20%) of pure iminocarbonate X as white needles, m.p. 111–112°; $[\alpha]^{25}D$ −6.6 ± 0.5° (1.1%); ν_{max}^{KBr} 1690 (C=N); 1590, 700 (phenyl); 1250, 1060 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.85; N, 3.87. Found: C, 63.2; H, 6.51; N, 3.77.

By further processing of the mother liquors, 0.25 g. of a crystalline mixture of iminocarbonate X and carbonate XIV was obtained which was not further separated, but which was predominantly the iminocarbonate.

1,2:5,6-Di-O-isopropylidene-D-mannitol 3,4-Carbonate (XIV).

(A) **From V.**—To a solution of 5.2 g. (0.02 mole) of V in 15 ml. of reagent pyridine and 20 ml. of chloroform cooled in an ice bath was added dropwise with stirring 2.07 g. (0.022 mole) of methyl chloroformate over a period of 25 min.[10] After being stirred for an additional 6 hr. at 0° and standing at 5° for 16 hr., protected from moisture, the mixture was poured into 50 ml. of ice–water and the organic layer separated.

The aqueous layer was extracted further with chloroform (three 20-ml. portions); combined extracts were washed successively with 10 ml. of saturated aqueous sodium bicarbonate and 15 ml. of cold water. Dried with magnesium sulfate, the solution was spin evaporated to dryness *in vacuo*. The semisolid residue showed a weak cyclic carbonate band at 1790 cm.$^{-1}$ and a strong linear carbonate band at 1745 cm.$^{-1}$. To a solution of this intermediate in 20 ml. of dimethylformamide was added 100 mg. of sodium methoxide and the mixture was heated at about 100° for 20 min. After removal of the solvent by spin evaporation *in vacuo*, the residue was triturated with 15 ml. of water containing 0.1 ml. of acetic acid. To a solution of the solid in 50 ml. of chloroform was added 75 ml. of petroleum ether; after 3 hr. at 0°, 1.9 g. (37%) of unchanged V was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue recrystallized from aqueous methanol; yield, 2.0 g. (55% based on the amount of V not recovered), m.p. 144–146°. Two recrystallizations from ethyl acetate–petroleum ether gave white needles of pure XIV, m.p. 147°; $[\alpha]^{25}D$ + 8.0 ± 0.6° (0.9%); ν_{max}^{Nujol} 1780 (cyclic carbonate C=O); 1260, 1065 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{13}H_{20}O_7$: C, 54.2; H, 6.90. Found: C, 54.3; H, 7.09.

Hough, *et al.*,[11] reported the preparation of this compound by a different route after the previous experiment was completed. They report m.p. 146.5–147°; $[\alpha]^{20}D$ 14.9° (*c* 1.8, acetone); and C=O absorption at 1790 cm.$^{-1}$

(B) **From the Iminocarbonate (X).**—A solution of 70 mg. of X in 1 ml. of 50% aqueous acetic acid was heated on a steam bath for 20 min., then cooled, and neutralized with 5% aqueous sodium bicarbonate to pH 8. The product was collected on a filter, washed with cold water, and recrystallized from ethyl acetate–petroleum ether; yield, 25 mg. (55%) of XIV, m.p. 146–147°. A mixture with preparation A gave no depression in melting point and the two materials had identical infrared spectra. No attempt was made to obtain a second crop.

(C) **From the Thionocarbonate (IX).**—A solution of 51 mg. (1.66 mmoles) of IX in 10 ml. of methanol was stirred with 46 mg. (1.66 mmoles) of silver carbonate at room temperature for 1 hr. The black precipitate was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Recrystallization from ethyl acetate gave 40 mg. (82%) of XIV, m.p. 146–147°, that was identical with preparation A.

Reaction of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VIII) Sodium Salt with Phenyl Isothiocyanate.—To a solution of 1.82 g. (5 mmoles) of dry VIII in 30 ml. of dimethylformamide (Spectro Grade) was added 218 mg. (5 mmoles) of a 55% dispersion of sodium hydride in mineral oil. Conversion to the insoluble gelatinous sodium salt was complete after the mixture was stirred for 15 min. at 50° protected from moisture. After the addition of 0.65 ml. (5.5 mmoles) of phenyl isothiocyanate, the mixture was stirred at 90–100° for 1 hr. Cooled to room temperature, the mixture was acidified with 0.5 ml. of glacial acetic acid, then diluted with 100 ml. of ice–water, and extracted with chloroform (three 40-ml. portions). Dried with magnesium sulfate, combined extracts were spin evaporated *in vacuo;* last of the dimethylformamide was removed at 1 mm. and 100°. The semisolid residue was triturated with 40 ml. of benzene and the white insoluble solid was collected on a filter; yield, 0.40 g. (40%) of benzanilide, m.p. 158–159°, that was identical with an authentic sample. The benzene filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from 1:1 chloroform–petroleum ether gave 0.30 g. (20%), m.p. 145–149°, of a mixture of the cyclic carbonate (XIV) and the thionocarbonate (IX), as shown by its infrared spectrum.

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(phenylcarbamoyl)-D-mannitol (XI).—A solution of 1.82 g. (5 mmoles) of VIII and 1.34 g. (10 mmoles) of phenyl isocyanate in 80 ml. of reagent toluene was refluxed for 20 hr. protected from moisture. The solvent was removed by spin evaporation *in vacuo* and the gummy residue triturated with 25 ml. of warm petroleum ether to remove the remaining phenyl isocyanate. Recrystallization of the insoluble solid from ethyl acetate–petroleum ether gave 1.8 g. (78%) of product in two crops, m.p. 117–118°. Recrystallization from the same solvents gave white crystals of unchanged melting point; $[\alpha]^{25}D$ +65.2 ± 0.6° (1%); ν_{max}^{Nujol} 3400 (NH); 1740 (urethane C=O); 1715 (ester C=O); 1525 (amide II); 1600, 755, 715 cm.$^{-1}$ (phenyl).

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.3; H, 6.39; N, 2.88. Found: C, 64.5; H, 6.47; N, 3.12.

Treatment of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(phenylcarbamoyl)-D-mannitol (XI) with Sodium Hydride.—To a solution of 0.97 g. (2 mmoles) of dry XI in 12 ml. of dimethylformamide protected from moisture was added 0.11 g. (2.5 mmoles) of 55% sodium hydride dispersion in mineral oil. The mixture was stirred at 90–100° for 90 min., cooled, acidified with 0.5 ml. of acetic acid, then processed as described before for the reaction of the sodium salt of V with phenyl isocyanate. The first material isolated was 150 mg. (71%) of diphenylurea,

m.p. 235°. Then 50 mg. (8.5%) of cyclic carbonate (XIV), m.p. 149–150°, and 120 mg. (12%) of unchanged XI were isolated, all three characterized by mixture melting points and comparative infrared spectra with authentic samples. The final residue (150 mg.) appeared to be mainly a mixture of the monobenzoate (VIII) and V, by its infrared spectrum.

The same results were obtained if a catalytic amount (6 mole %) of sodium hydride was employed.

3,4-Di-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XIII).—Benzoylation of V or VIII with excess benzoyl chloride in pyridine overnight at room temperature gave an 85% yield of the dibenzoate as an oil which was free of hydroxyl absorption in the infrared. For analysis, the compound was absorbed from a benzene solution on a column of neutral alumina (Brockmann activity III), then eluted with 1:1 benzene–chloroform. The colorless oil had ν_{max}^{film} 1715 (C=O); 1260, 1100, 1080 (C—O—C); 715 cm.$^{-1}$ (benzoyl CH); $[\alpha]^{25}D$ +64.9 ± 0.7° (0.6%).

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.4; H, 6.44. Found: C, 66.7; H, 6.24.

Benzoate Equilibration of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VIII) with Sodium Hydride.—To a solution of 1.10 g. (3 mmoles) of dry VIII in 60 ml. of reagent toluene was added 130 mg. (3 mmoles) of 55% soduim hydride dispersion in mineral oil. After being refluxed for 90 min. protected from moisture, the mixture was spin evaporated to dryness *in vacuo*. The residue was suspended in 20 ml. of water containing 0.2 ml. of acetic acid; the mixture was extracted with chloroform (four 20-ml. portions). Dried with magnesium sulfate, combined extracts were evaporated to dryness *in vacuo*. Crystallization from ethyl acetate–petroleum ether gave 0.20 g. (25%) of debenzoylated product, V, identical with an authentic sample.

The filtrate was evaporated to dryness *in vacuo* leaving 0.7 g. of a semisolid. Further traces of V were removed by absorption on neutral alumina (Brockmann activity III) from a hexane solution, then elution with 8:1 benzene–methanol. The resultant 0.55 g. showed two spots on silica thin-layer chromatography with benzene–methanol (7:1) as the solvent system and iodine vapor as the detecting agent. The two spots had R_f values of 0.77 and 0.96 and moved identically with authentic samples of VIII and 3,4-di-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XIII), respectively.

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Notes

Nitration of Phenylcyclopropane. *ortho–para* Ratios for Nitration of Alkylbenzenes with Acetyl Nitrate[1]

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In connection with another study,[2] we had occasion to refer to the ultraviolet spectrum of *p*-nitrophenylcyclopropane obtained by Levina, Shabarov, and Patapov.[3] This spectrum, however, was inconsistent with data that we had accumulated[2] and was not typical of a *p*-nitroalkylbenzene. We, therefore, felt obliged to repeat their work in order to clarify the problem. Nitration at −40 to −20° with fuming nitric acid–acetic anhydride afforded a product whose ultraviolet spectrum was nearly identical with that previously published.[3] The proof of structure for the nitration product was based primarily on its oxidation with chromic acid to *p*-nitrobenzoic acid in 70% yield.[3] When our nitration product was subjected to gas chromatographic analysis, two major components in a ratio of 2:1 were observed. The smaller, slower-moving fraction crystallized on cooling (m.p. 32°) and gave an ultraviolet spectrum typical of a *p*-nitroalkylbenzene.[4] Furthermore, the infrared absorption pattern in the 5–6-μ region was typical of *p*-disubstituted benzenes.[5] The *larger*, faster-moving fraction could not be crystallized and showed a typical ultraviolet absorption spectrum for an *o*-nitroalkylbenzene.[4] In this case the infrared spectrum in the 5–6-μ region was typical of an *o*-disubstituted benzene.[5] Oxidation of the solid nitration product with chromic acid gave *p*-nitrobenzoic acid in 88% yield. The oil afforded 64% of *o*-nitrobenzoic acid under the same conditions. It is thus established that the cyclopropyl group, as expected, is an *ortho–para* director but that the major product is the *ortho* isomer.

Brown and Bonner have reported[6] *ortho–para* ratios for nitration of toluene, ethylbenzene, cumene, and *t*-butylbenzene with concentrated nitric acid–concentrated sulfuric acid at 40°. In order that our result with phenylcyclopropane could be compared directly, we have repeated the nitrations of these four alkylbenzenes with fuming nitric acid–acetic anhydride at −40°. This reagent gives results which are very similar to those from the "mixed acid" except that the yields are higher, the rate of decrease of the *ortho–para* ratio is greater, and smaller amounts of *meta* isomers were observed. When the nitrating mixture was prepared at room temperature and cooled to −40° for nitration, the *ortho–para* ratio for the branched alkylsubstituted benzene was much smaller, whereas with phenylcyclopropane the ratio was considerably higher. The nitration of phenylcyclopropane with this

(1) This work was supported, in part, by Cancer Research Funds of the University of California and by an American Cancer Society Institutional grant 1N 33D.

(2) L. A. Strait, R. Ketcham, and D. Jambotkar, paper presented at 14th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, March, 1963.

(3) R. Ya. Levina, Yu. S. Shabarov, and V. K. Patapov, *Zh. Obschch. Khim.*, **29**, 3233 (1959); *J. Gen. Chem., USSR*, **29**, 3196 (1959).

(4) W. G. Brown and H. Reagan, *J. Am. Chem. Soc.*, **69**, 1032 (1947).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 67–69.

(6) H. C. Brown and W. H. Bonner, *J. Am. Chem. Soc.*, **76**, 605 (1954).

TABLE I

Compound	H_2SO_4–HNO_3 ortho–para	H_2SO_4–HNO_3 % yield	$AcONO_2$[b] ortho–para	$AcONO_2$[b] % yield	$AcONO_2$[c] ortho–para
Toluene	1.57[a]	80[a]	1.78	94	1.76
Ethylbenzene	0.93[a]	80[a]	0.86	93	0.90
Cumene	.48[a]	80[a]	.41	95	.27
t-Butylbenzene	.217[a]	80[a]	.17	91	.066
Phenylcyclopropane	2.10	70	1.99	93	4.0–4.7

[a] Ref. 6, the yields are given as approximately 80%. [b] Nitrating reagent prepared at −40°. [c] Nitrating reagent prepared at room temperature.

latter reagent was not reproducible. The range of *ortho–para* ratios is given in Table I.

The general agreement between the values obtained with acetyl nitrate and nitric acid–sulfuric acid mixtures indicates that the results are not due to the special *ortho* orientation property of acetyl nitrate which has been observed for nitration of anisole or acetanilide[7] with this reagent, but that phenylcyclopropane is inherently nitrated preferentially in the *ortho* position. This contention was confirmed by the fact that nitration of phenylcyclopropane with nitric acid–sulfuric acid afforded a product mixture with an *ortho–para* ratio not greatly different from that obtained with acetyl nitrate. The results of the nitration experiments are in Table I.

Bordwell and Garbisch recently have studied the reactions of acetyl nitrate with a series of styrenes and stilbenes.[8] They have found that, although the major products of these reactions result from addition to the ethylenic double bond, there is, in most cases, some nuclear substitution. These workers did not determine the *ortho–para* ratios, but they did indicate that the amount of *ortho*-substituted product was in excess of the *para* isomer.

The most common cases of high *ortho–para* ratios have been observed in nitrations of deactivated systems such as nitrobenzene, benzaldehyde, and ethyl benzoate.[9] All of these compounds have unsaturated systems, and interactions between the substituents and the attacking nitronium ion have been postulated. In the case of styrene similar interactions can also be thought of as existing between the incoming nitronium ion and the vinyl group, thereby directing substitution preferentially to the *ortho* position.

Stericly the cyclopropyl group should exert an effect similar to that of the isopropyl group. However, the contraction in size introduced by the strained three-membered ring should make the cyclopropyl group somewhat smaller so that its steric effect should be intermediate between those of an ethyl and an isopropyl group. This should have led to an *ortho–para* ratio of about 0.75.

The unsaturated nature of the cyclopropyl system has been observed in a number of situations.[10] These manifestations of unsaturation have been related to the double bond character of the three-membered ring caused by the highly strained carbon–carbon bonds which have approximately sp^4 hybrid orbitals.[11] The *ortho*-directing influence of the cyclopropyl system observed in this work appears to be still another example of the unsaturated character of this three-membered ring system.

Phenylcyclopropane was prepared from styrene according to the method[12] used by Doering and Hoffman to prepare norcarane from cyclohexene. The reaction between styrene and dibromomethylene, generated from bromoform by the action of potassium *t*-butoxide, afforded 1-phenyl-2,2-dibromocyclopropane. Reduction with sodium and wet methanol afforded phenylcyclopropane.

It should be pointed out that the earlier workers reduced their nitrophenylcyclopropane to the corresponding amine[3] and that studies on this reduction product cannot be completely valid since it too must have been a mixture.

Experimental[13]

1-Phenyl-2,2-dibromocyclopropane.—To a stirred solution of 0.33 mole of potassium *t*-butoxide (prepared by adding 13 g. of potassium to the *t*-butyl alcohol at 70°) and 181 g. (200 ml., 1.74 moles) of styrene in 400 ml. of *t*-butyl alcohol at 15–20° was added dropwise 100 g. (0.4 mole) of bromoform. After stirring an additional 30 min., 300 ml. of water was added and the product extracted with pentane. The extract was dried over sodium sulfate and the solvent removed under reduced pressure. Vacuum distillation afforded 48.9 g. (53%) of 1-phenyl-2,2-dibromocyclopropane, b.p. 90–100° at 1 mm.

Anal. Calcd. for $C_9H_8Br_2$: C, 39.16; H, 2.97; Br, 57.92. Found: C, 39.24; H, 2.96; Br, 57.66.

Phenylcyclopropane.—To a stirred solution of 27.6 g. (0.1 mole) of 1-phenyl-2,2-dibromocyclopropane in 100 ml. of ether was added dropwise a solution of 270 ml. of methanol and 50 ml. of water and portionwise 46 g. (2 moles) of sodium over a 3-hr. period. An additional 23 g. (1 mole) of sodium and 180 ml. of methanol and 20 ml. of water was added and the reaction mixture stirred an additional 2 hr. A final 23 g. (1 mole) of sodium and 100 ml. of methanol was added and the reaction mixture stirred for 7 hr. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with dilute hydrochloric acid and dried over sodium sulfate. Removal of the ether *in vacuo* and vacuum distillation of the crude product afforded 9.90 g. (84%) of phenylcyclopropane, b.p. 93–97° at 45 mm.

***o*- and *p*-Nitrophenylcyclopropane.**—To a solution of 13.0 ml. of acetic anhydride and 4 ml. of fuming nitric acid at −40° was added dropwise 3.25 g. (0.027 mole) of phenylcyclopropane at a rate such that the temperature did not rise above −20°. The reaction mixture was poured into hot water and the product was extracted with ether. The ether extract was dried and the ether removed under vacuum. Crude distillation gave about 5 ml. of product, b.p. 77–120° at 1–3 mm. Gas chromatography (Aerograph Model A-90-C) on a 10-ft. silicone rubber, analytical column at 135° showed two main bands in addition to smaller amounts of other substances.

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(7) For a discussion of the nature of this nitrating reagent see F. G. Bordwell and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **82**, 3588 (1960).

(8) F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 2322 (1962).

(9) G. S. Hammond, F. J. Modic, and R. M. Hedges, *J. Am. Chem. Soc.*, **75**, 1388 (1953); see, however, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 261–264.

(10) (a) R. A. Raphael in "Chemistry of Carbon Compounds," Vol. IIA, E. H. Rodd, Ed., Elsevier Publishing Company, New York, N. Y., 1953, Chap. 1, pp. 25–28; (b) S. Sarel and E. Brewer, *J. Am. Chem. Soc.*, **81**, 6522 (1959); (c) E. N. Tractenberg and G. Odian, *ibid.*, **80**, 8018 (1958); (d) G. W. Cannon, A. A. Santilli, and P. Shenian, *ibid.*, **81**, 4264 (1959); (e) N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang, *ibid.*, **83**, 974 (1961).

(11) L. L. Ingraham in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 11, p. 518.

(12) W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(13) Melting points and boiling points are uncorrected. Microanalyses are by the Microanalytical Laboratory, Department of Chemistry, Berkeley, Calif.

Preparative scale gas chromatography on a 6-ft. Apiezon preparative column afforded sufficient quantities of the two main fractions for characterization.

The largest of the two main fractions had the smallest retention volume. Its infrared spectrum showed a typical *ortho*-disubstitution pattern between 5 and 6 μ and was, therefore, identified as *o*-nitrophenylcyclopropane. This substance is an oil (n^{20}D 1.5606) which could not be made to crystallize; $\lambda_{max.}^{C_2H_5OH}$ 211, 249 mμ; ϵ 1150; 4550. The smaller of the two main fractions, having the larger retention volume, showed an absorption pattern in the 5–6-μ region typical of *p*-disubstituted benzenes and was identified as *p*-nitrophenylcyclopropane. This isomer is a low melting solid, m.p. 32–33°; $\lambda_{max}^{C_2H_5OH}$ 218, 280 mμ (ϵ 8080, 11,000).

Anal. Calcd. for $C_9H_{10}NO_2$: C, 66.24; H, 5.56; N, 8.58. Found for *o*-nitrophenylcyclopropane: C, 65.98; H, 5.40; N, 8.54. Found for *p*-nitrophenylcyclopropane: C, 66.25; H, 5.54; N, 8.67.

Oxidation of *o*-Nitrophenylcyclopropane.—A sample of 0.50 g. (3.1 mmoles) of *o*-nitrophenylcyclopropane was heated under reflux for 2 hr. with a solution of 4.3 g. (43 mmoles) of chromic acid, 5.7 ml. of concentrated sulfuric acid, and 8.5 ml. of water. The reaction mixture was diluted with water and extracted with ether. The extract was dried and concentrated to give the crude product which on crystallization gave 0.33 g. (64%), m.p. 140–144° (lit.[14] m.p. 147–147.5°), of *o*-nitrobenzoic acid, identical with an authentic sample (mixture melting point and infrared spectrum).

Oxidation of *p*-Nitrophenylcyclopropane.—A sample of 100 mg. (0.61 mmole) of *p*-nitrophenylcyclopropane was heated under reflux for 2 hr. with a solution of 0.85 g. (8.5 mmoles) of chromic acid and 1.1 ml. of concentrated sulfuric acid in 2 ml. of water. The reaction mixture was diluted with water and the solid was collected to afford 90 mg. (88%) of *p*-nitrobenzoic acid, m.p. 240–242° (lit.[14] m.p. 239–240°), identical with an authentic sample (infrared spectra and mixture melting point).

Nitrations of Alkylbenzenes and Analysis of the Product Mixtures.—To a solution of 26.1 g. (24 ml., 0.26 mole) of acetic anhydride and 10.9 g. (7.3 ml., 0.16 mole) of fuming nitric acid (density 1.49–1.50) at −50° was added dropwise with stirring 0.05 mole of the alkylbenzene. The reaction mixture was allowed to come to room temperature (30 min.) and was poured into hot water. The product mixture was extracted with ether, the extract was dried, and concentrated to give the crude residue (always above 95% of the theoretical amount). This was dissolved in acetone in a 25-ml. volumetric flask and analyzed on a 10-ft. silicone rubber, analytical column (Aerograph A-90-C equipped with a disk integrator). The ratio of the areas under the two peaks was taken as the *ortho–para* ratio. Each analysis was carried out at least three times; the analyses were reproducible within ±1%. The total yields based on the gas chromatograms were always above 90%. These values are subject to errors of ±3%, owing to variations in the sample size. The gas chromatograms gave evidence for only very small amounts of unchanged starting materials, *meta* isomers, and polynitro compounds.

A second series of nitrations with acetic anhydride–fuming nitric acid prepared at room temperature was carried out in the same manner. Here also the yields were above 90%. In this case, nitration of phenylcyclopropane produced a rather wide range of *ortho–para* ratios.

Nitration of Phenylcyclopropane with Nitric Acid–Sulfuric Acid.—A sample of 2.3 g. of phenylcyclopropane was nitrated in 3.83 g. sulfuric acid and 1.42 g. of nitric acid according to the method of Brown and Bonner.[4] The crude yield was 2.30 g. (78%). The chromatographic analysis is given in Table I.

Infrared and Ultraviolet Spectra.—Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were recorded in 95% ethanol on a Carey Model 11 ultraviolet spectrophotometer.

Acknowledgment.—The authors wish to thank Dr. L. A. Strait for many helpful discussions and Mr. Michael Hrenoff for determining some of the infrared and ultraviolet spectra.

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Competition Reactions of Cycloalkanes with Trichloromethanesulfonyl Chloride and Bromotrichloromethane

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The suggestion was made in an earlier publication that the hydrogen abstracting radical in the peroxide- and light-induced chlorinations of hydrocarbons with trichloromethanesulfonyl chloride (I) was not the trichloromethyl radical.[2] This conclusion was based on the difference in the relative reactivities of toluene and cyclohexane toward chlorination by I and toward bromination by bromotrichloromethane. Two different free radical chain sequences were suggested to account for the products obtained from the reaction of trichloromethanesulfonyl chloride with hydrocarbons (equation 1).

$$\underset{\text{I}}{Cl_3CSO_2Cl} + RH \longrightarrow RCl + SO_2 + HCCl_3 \quad (1)$$

CHAIN SEQUENCE A

$$R\cdot + Cl_3CSO_2Cl \longrightarrow RCl + Cl_3C\cdot + SO_2 \quad (2)$$

$$Cl_3C\cdot + RH \longrightarrow HCCl_3 + SO_2 \quad (3)$$

CHAIN SEQUENCE B

$$R\cdot + Cl_3CSO_2Cl \longrightarrow RCl + Cl_3CSO_2\cdot \quad (4)$$

$$Cl_3CSO_2\cdot + RH \longrightarrow Cl_3CSO_2H + R\cdot \quad (5)$$

$$Cl_3CSO_2H \longrightarrow HCCl_3 + SO_2 \quad (6)$$

In Chain Sequence A, the hydrogen abstraction from the hydrocarbon is performed by the trichloromethyl radical (equation 2) whereas in Chain Sequence B, the trichloro methanesulfinyl radical ($Cl_3CSO_2\cdot$) is postulated to be the hydrogen abstracting radical (equation 5). The trichloromethanesulfinic acid formed in this reaction is reported to be unstable, decomposing into chloroform and sulfur dioxide.[3] The peroxide- and light-induced brominations of hydrocarbons by bromotrichloromethane (equation 7) very likely involve the

$$BrCCl_3 + RH \longrightarrow RBr + HCCl_3 \quad (7)$$

free radical chain sequence (8 and 9), a sequence which almost certainly involves hydrogen abstraction

$$R\cdot + BrCCl_3 \longrightarrow RBr + Cl_3C\cdot \quad (8)$$

$$Cl_3C\cdot + RH \longrightarrow HCCl_3 + R\cdot \quad (9)$$

by a trichloromethyl radical.[4] A comparison of the relative reactivities of the medium-size cycloalkanes toward halogenation by trichloromethanesulfonyl chloride

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(2) E. S. Huyser and B. Giddings, *J. Org. Chem.*, **27**, 3391 (1962); E. S. Huyser, *J. Am. Chem. Soc.*, **82**, 5246 (1960).

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and by bromotrichloromethane support the suggestion made previously that Chain Sequence B is operative in the chlorinations of hydrocarbons with trichloromethanesulfonyl chloride.

The relative reactivities of cyclopentane, cyclohexane, cycloheptane, and cyclooctane toward reaction with trichloromethanesulfonyl chloride and bromotrichloromethane are shown in Table 1. These values were determined by competition reactions (see Experimental) of the cycloalkanes toward halogenation by the indicated reagent. That the same radical is not involved in the hydrogen abstraction in the two cases is evident from the different relative reactivities of these cycloalkanes toward halogenation by trichloromethanesulfonyl chloride and bromotrichloromethane. Cyclopentane and cyclohexane have essentially the same reactivity toward reaction with trichloromethanesulfonyl chloride, whereas cyclopentane is more reactive than cyclohexane in reaction with bromotrichloromethane. Although the relative reactivity of cycloheptane with respect to cyclohexane is very nearly the same toward both trichloromethanesulfonyl chloride and bromotrichloromethane, cyclooctane is at least two times more reactive than cycloheptane toward the latter reagent.

TABLE I

RELATIVE REACTIVITIES OF CYCLOALKANES TOWARD REACTION WITH TRICHLOROMETHANESULFONYL CHLORIDE AND BROMOTRICHLOROMETHANE AT 80°

Cycloalkane	Relative reactivity[a]	No. of runs
	Cl_3CSO_2Cl	
Cyclopentane	1.00[b] ± 0.07	14
Cyclohexane	1.00	..
Cycloheptane	2.67 ± 0.16	4
Cyclooctane	4.20[c] ± 0.04	3
	$BrCCl_3$	
Cyclopentane	1.57 ± 0.17	18
Cyclohexane	1.00	..
Cycloheptane	3.30 ± 0.50	10
Cyclooctane	9.20[d] ± 0.54	7

[a] Relative to a unit reactivity of cyclohexane. [b] Average deviation from average value obtained from number of runs indicated. [c] Determined from relative reactivity of cyclooctane with respect to cycloheptane which was 1.57 ± 0.02. [d] Determined from relative reactivity of cyclooctane with respect to cycloheptane which was 2.79 ± 0.18.

Two factors are probably responsible for the difference in the reactivities of the cycloalkanes toward hydrogen abstraction. These are (1) the relative stabilities of the cycloalkyl radicals that are produced, and (2) the relative stabilities of the cycloalkyl carbonium ions, a factor arising from polar contributions encountered in the transition state of the hydrogen abstraction reactions. Both of these factors may be important if there is a considerable amount of bond breaking in the transition state of the reaction as shown for hydrogen abstraction by the trichloromethyl radical. The inferred order of stability of the cycloalkyl radicals and carbonium ions based on kinetic measurements involving other systems[5] and, consequently, the predicted order of reactivity of the cycloalkanes toward hydrogen abstraction is cyclooctyl > cycloheptyl > cyclopentyl > cyclohexyl. The observed orders of reactivity of the cycloalkanes toward reaction with both trichloromethanesulfonyl chloride and bromotrichloromethane are consistent with this prediction.

$$\overset{\delta+}{[R}\ldots H\ldots\overset{\delta-}{C}Cl_3]$$

The lower degree of specificity found for the reactions with trichloromethanesulfonyl chloride suggests that the extent of bond breaking in the hydrogen abstraction step in the reactions of this reagent is less than that in hydrogen abstractions by the trichloromethyl radical. A lower degree of bond breaking compared to that encountered in the hydrogen abstractions by the trichloromethyl radical might well be expected if the $Cl_3CSO_2\cdot$ were the hydrogen abstractor (Chain Sequence B). The dissociation energy (D_{C-H}) for the carbon–hydrogen bond in the cycloalkanes is ~94 kcal./mole.[6] Hydrogen abstraction by a trichloromethyl radical is a process which is endothermic to the extent of ~5 kcal./mole (D_{Cl_3C-H} 90 kcal./mole[6]). The bond dissociation energy of an oxygen–hydrogen bond in $(CH_3)_3CO-H$ is ~104 kcal./mole,[7] and, although resonance stabilization of the trichloromethanesulfinyl radical might be expected to lower the oxygen–hydrogen bond dissociation

$$Cl_3CS(O)\cdot \longleftrightarrow Cl_3CS(O)\cdot \longleftrightarrow Cl_3CS(O)\cdot$$

energy in trichloromethanesulfinic acid to some extent, it does not seem unlikely that $D_{Cl_3CS(O)O-H}$ may be above 94 kcal./mole. This would make hydrogen abstraction from a cycloalkane by $Cl_3CSO_2\cdot$ an exothermic reaction. Such a reaction, in terms of the Hammond postulate,[8] might be expected to involve a transition state with less bond breaking than encountered in the endothermic hydrogen abstraction by $Cl_3C\cdot$. Contribution to the transition state involving stabilities of the cycloalkyl radical and carbonium ions would not be so great and, hence, the differences in reactivity less pronounced.

Although apparently less selective as a halogenating agent that bromotrichloromethane, trichloromethanesulfonyl chloride is a far more selective chlorinating agent than chlorine itself. The ratio of reactivities of $C_8H_{16}:C_7H_{14}:C_5H_{10}:C_6H_{12}$ toward chlorination with chlorine was found by Russell[9] to be 1.5:1.0:1.0:1.0 at 40°. In 12 *M* carbon disulfide, a solvent which markedly enhances the selectivity of chlorine atoms as hydrogen abstractors, the ratio of reactivities was found to be 3.8:2.0:1.2:1.0 at 40° for $C_8H_{16}:C_7H_{14}:C_5H_{10}:C_6H_{12}$,[9] a degree of selectivity somewhat less than we observed in reactions with trichloromethanesulfonyl chloride at 80°.

Experimental

The nature of the products and the stoichiometry of the reactions of trichloromethanesulfonyl chloride and bromotrichloromethane with hydrocarbons are discussed in earlier reports (see ref. 2 and 3).

(5) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951); C. G. Overberger, H. Biletch, A. B. Finestone, J. Lilker, and J. Herbert, *ibid.*, **75**, 2078 (1953).

(6) *Cf.* C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chap. 2, for tables of bond dissociation energies and discussion of their use in free radical reactions.

(7) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

(8) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(9) G. A. Russell, *ibid.*, **80**, 4997 (1958).

The relative reactivities shown in Table I were determined by competition reactions performed in the following manner. A mixture consisting of known amounts of two of the cycloalkanes was allowed to react with about a half of an equivalent amount of the halogenating agent. Benzene or chlorobenzene also was added in an amount equivalent to the cycloalkanes to serve as an internal standard for the gas chromatographic analysis. The reactions were performed in sealed tubes, induced with benzoyl peroxide, and allowed to proceed at the indicated temperature until about 30–70% of the halogenating reagent had been consumed. Relative reactivity ratios, that is the ratio of the reaction rate constants of the particular cycloalkanes toward attack by the hydrogen abstracting radical, were calculated in the usual manner using the equation, $\frac{k_A}{k_B} = \log (A_{init}/A_{fin})/\log (B_{init}/B_{fin})$, where the subscript, init and fin refer to the amounts of the cycloalkanes A and B before and after the reaction, respectively. The value for the amounts of the two cycloalkanes remaining after reaction were obtained by gas chromatographic analysis of the reaction mixtures.

Solubilities of Organic Salts in Hydrocarbons[1]

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It is known generally that salts of large organic ions are more soluble in organic solvents than salts of small inorganic ions. It might be imagined that this is a result of some specific attractive forces between organic molecules. However, solubilities of a wide variety of hydrocarbons in water[2,3] have been correlated by an equation whose derivation specifically assumed that energies arising from van der Waals or London forces were the same for hydrocarbon–hydrocarbon interactions as for hydrocarbon–water attractive forces.

This cancelling out of energies arising from London dispersion forces can be rationalized this way. Let us consider a molecule such as benzene immersed first in water and then in hexane. The energy arising from London forces between two small spherical molecules in the gas phase is given by this well known equation.

$$E = (-3/2)(\alpha_1\alpha_2/r^6)I_1I_2/(I_1 + I_2) \qquad (1)[4]$$

The polarizability, α, and ionization potential, I, for benzene are common factors for equation 1 applied to either benzene–water or benzene–hexane. The ionization potentials for water and hexane are 12.5 and 10.5 e.v.[5] Although the absolute difference between these two numbers may seem large, the per cent difference is small when used in equation 1 so that only small energy differences arise from differences in ionization potential. The relative invariance of ionization potential is characteristic of compounds of C, H, O, and N, and these are of primary interest in organic chemistry. When elements such as sulfur, iodine, etc., are introduced, their effect is overshadowed by the mass of hydrocarbon so that, on the average, the effective ionization potential for intermolecular attractions is that of a typical hydrocarbon.

The electronic polarizabilities of water and hexane are 3.70 and 29.8 cm.^{3}/mole.[6] These values initially seem much different, but what governs interaction energies in solution is the polarizability per unit volume of the solvents. These values are 0.21 and 0.23 for water and hexane, respectively. The London dispersion forces will nearly cancel, and this result can be generalized to most systems of interest in organic chemistry.

Table I presents data on the solubilities of a series of R_4NClO_4 salts. It is evident that the solubility in benzene (or ethanol) relative to water increases as the size of R increases. Such results cannot be rationalized by a consideration of ion–solvent electrostatic forces. Such forces must always be greater in water than benzene leading to the erroneous expectation that the salts will always be more soluble in water. Neither can such results be rationalized by a consideration of London forces since the energies arising from such forces cancel, as explained in the preceding paragraph. It is evident that any explanation based only on solute–solvent interaction energies fails.

TABLE I

RELATIVE SOLUBILITIES OF R_4N^+ SALTS (25°)[a]

	—Solubility in moles/l.—			—Relative solubility—	
Salt	Water	Ethanol	Benzene	EtOH-H_2O	C_6H_6-H_2O
$KClO_4$[b]	0.149	0.00065		0.0044	
$RbClO_4$[b]	.071	.00039		.0055	
$CsClO_4$[b]	.085	.00037		.0044	
$(CH_3)_4NClO_4$	.075	.00089	0.000165	0119	0.0022
$(C_2H_5)_4NClO_4$	.217	.0114	.000113	.0525	.00052
$(C_3H_7)_4NClO_4$	.0204	.0149	.000075	.75	.0037
$(C_6H_5)_4NClO_4$	.000187	.00102	.000176	5 45	.94
$(C_6H_{11})_4NClO_4$	.00067	.037	.00111	56	1.67
$(C_6H_{13})_4NClO_4$	.00044	.292	.871	660	2000
$(CH_3)_4NI$[b]	0.26	0.0045		0.017	
$(C_2H_5)_4NI$[b]	1 4	.38		.27	
$(C_3H_7)_4NI$[b]	0 60	.64		1 .1	

[a] The solid phase in equilibrium with the saturated ethanol solution was analyzed in each case and shown to be the simple R_4NClO_4 salt (Table II). Data on $(C_4H_9)_4NClO_4$ is omitted because Ralph Seward of Pennsylvania State University found that the phase in equilibrium with the saturated solution in benzene contained benzene in the crystal lattice. The alkyl groups are the straight chain *n*-alkyl groups except for C_6H_5, which is phenyl. [b] Data from A. Seidell, 'Solubilities," D. Van Nostrand Co., New York, N. Y., 1960.

The answer lies in solvent–solvent forces and the principle of volume energies.[2,3,7,8] Briefly, it costs energy to make a hole in the solvent to place a solute molecule or ion. This energy is the product of the volume of the hole times the internal pressure of solvent. This energy will be greater for a solvent such as water with its high internal pressure arising from intermolecular hydrogen bonding. In contrast, this energy will be much smaller for most organic liquids in which the intermolecular forces are predominantly London forces.[4] In the series listed in Table I, as the size of R increases,

(1) This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(2) J. C. McGowan, *J. Appl. Chem.*, **1**, 5120 (1951); **2**, 323, 651 (1952); **4**, 41 (1954).

(3) N. Deno and H. E. Berkheimer, *J. Chem. Eng. Data*, **4**, 1 (1960).

(4) F. London, *Trans. Faraday Soc.*, **33**, 8 (1937).

(5) F. H. Field and J. L. Franklin, "Electron Impact Phenomena," Academic Press, Inc., New York, N. Y., 1957, pp. 116 and 122.

(6) Calculated by the familiar relation, $(n^2 - 1)(n^2 - 2)/(M/e)$.

(7) F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

(8) H. Reiss, H. L. Frisch, E. Helfand, and J. L. Lebowitz, *J. Chem. Phys.*, **32**, 119 (1960); F. H. Stillinger, Jr., "Equilibrium Theory of Pure Fused Salts," a chapter in "Selected Topics in the Physical Chemistry of Molten Salts," Milton Blander, Ed., Interscience Publishers, Inc., New York, N. Y., 1962.

the volume energy increasingly favors greater solubility in benzene relative to water. At $(C_4H_9)_4NClO_4$, the volume energy effect equals the effect of the ion–solvent electrostatic energy and the salt is equally soluble in water and benzene. As the size of R increases beyond butyl, the ratio of solubility in benzene to solubility in water appears to increase without limit. The overshadowing of the electrostatic effect by the volume energy is, of course, aided by a decrease in the electrostatic effect with increasing size of R as well as the clustering of ions in the benzene phase.

TABLE II

NITROGEN ANALYSES AND MELTING POINTS FOR TETRAALKYL AMMONIUM PERCHLORATES

$R_4N^+ClO^-$	Nitrogen, %			
		Found		
R	Calcd.	*a*	*b*	M.p., °C.
Methyl	8.07	8.15	8.14	
Ethyl	6.10	6.17	6.20	
Propyl	4.90	4.87	5.12	237–239
Butyl	4.10	4.49	4.67	207–209
Pentyl	3.52	3.90	3.89	110–116
Hexyl	3.09	3.15	3.04	105–106

[a] Prepared as described in the Experimental. [b] Precipitated from ethanol.

Two practical results are suggested. If it is desired to conduct a reaction in a hydrocarbon solvent using a small inorganic ion, solubility can be achieved by using a salt of a large counter ion of the size of C_{20} or larger, preferably spherical to minimize micelle formation. Fortunately, such large salts generally have low lattice energies so that the absolute solubility will not be reduced to insignificance by high lattice energies.

The second practical result is that large salts will be extracted from water by organic solvents and may be recrystallized from the organic solvent. These possibilities must be recognized in purification. Lest a misunderstanding arise, proteins, although large salts, will still be more soluble in water than benzene because each hydrogen bond between the protein and water changes the distribution coefficient by about 10^2.[3]

Experimental

The $R_4N^+ClO_4^-$ salts, (R = methyl, ethyl, propyl, and phenyl) were prepared by treating a water solution of $R_4N^+Br^-$ or $R_4N^+I^-$ (commercially available) with perchloric acid and washing with cold water with or without added alcohol to decrease solubility.

For R = butyl, pentyl, and hexyl, the $R_4N^+I^-$ salts were prepared by treating R_3N with RI using procedures patterned after those of Smith and Frank.[9] To prepare the perchlorate, a warm solution of silver perchlorate in ethanol was added to a warm solution of the $R_4N^+I^-$ salt in 95% ethanol. The silver iodide was removed by filtration. Cold water was added to the filtrate and much of the ethanol allowed to evaporate. The precipitated $R_4N^+ClO_4^-$ was filtered, washed with water, recrystallized from ethyl acetate, and washed with ether in that order.

The method used for R = methyl was not applicable for R = C_4–C_6 because the $R_4N^+I^-$ salts were too insoluble in water. The tetraphenylammonium perchlorate is a well known insoluble salt.[10]

(9) P. A. S. Smith and S. Frank, *J. Am. Chem. Soc.*, **74**, 509 (1952).
(10) H. Willard and L. Perkins, *Anal. Chem.*, **25**, 1634 (1953).

Kinetics of Reaction of Lithium Aluminum Hydride with Terminal Acetylenes in the Presence of Lithium Aluminum Amides[1]

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It has been reported[3] that lithium aluminum amides produced by the reaction of excess lithium aluminum hydride in ethyl ether with primary and secondary amines and amine N-oxides are catalysts for the reaction for lithium aluminum hydride with 1-hexyne in ethyl ether.

$$LiAlH_4 + 4HC{\equiv}C{-}C_4H_9 \longrightarrow LiAl(C{\equiv}C{-}C_4H_9)_4 + 4H_2 \quad (1)$$

With carefully purified 1-hexyne and the initial concentrations of 1-hexyne and lithium aluminum hydride 1 *M* and 0.25 *M*, respectively, and at 36°, the half-life of reaction 1 is about twelve hours when a catalyst is not present. The presence of a catalyst can so increase the rate that it has been described as "instantaneous."[3] The reaction of phenylacetylene is similar to that of 1-hexyne except that the phenylacetylene reacts faster than hexyne in the absence of catalyst (half-life about one hour).

The purpose of this note is to report the results of some kinetic studies of the catalyzed reaction with 1-hexyne. Experiments were carried out to determine the dependence of the reaction rate upon the catalyst concentration, the 1-hexyne and lithium aluminum hydride concentrations, and the temperature. The kinetics was found to be complex, but susceptible to an approximate description that permits a comparison of the different catalysts. It was found that, except for the case of the lithium aluminum dicyclohexylamide, the kinetics might be described approximately as first order in 1-hexyne in the following sense: the logarithm of the hexyne concentration is a linear function of the time for at least 70% of the reaction, even when the hexyne was in excess. Analogous plots of the logarithm of the lithium aluminum hydride concentration are not linear for cases in which the hydride was in excess. First-order rate constants were calculated from the slopes of the linear plots. The dependence of the rate constant on the catalyst concentration was found to be approximately linear, *i.e.*

$$k \simeq \alpha M + 2 \times 10^{-5}\ (\text{sec.}^{-1})$$

where α is a constant, and M is the molar concentration of the catalyst (in terms of amine added). Values of the constants α for all the catalysts studied are given in Table I. A value is given for dicyclohexylamine for comparison purposes, although the reaction in the presence of that catalyst is better described as second order (first order in hexyne and first order in hydride). However, even in this case, when the hydride was in excess plots of the logarithm of the hexyne concentration as a function of the time were sufficiently close to

(1) This work was sponsored by the U. S. Army Research Office (Durham).
(2) To whom inquiries should be sent.
(3) G. B. Smith, D. H. McDaniel, E. Biehl, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **82**, 3560 (1960).

linearity to permit one to calculate approximate first-order constants, from which a value of α was calculated.

Activation energies were determined by obtaining rate constants at three different temperatures between 15° and 40°. Since the reaction with no catalyst is very slow at 15° (and also follows no simple rate law, even approximately) it was necessary to use initial rates to determine the activation energy in that case. The activation energies decrease with increasing catalyst concentration and then level off to a constant value. These limiting constant values of E_a are given in Table I for four different catalysts. It is probable that the lower effectiveness (smaller α) of the catalysts from diphenylamine and the dicyclohexylamine is not the result of higher activation energies, but rather of lower frequency factors.

TABLE I

CATALYTIC EFFECTS OF DIFFERENT CATALYSTS

Source of catalyst	α ($\times 10^2$)[a]	E_a (kcal.)
Diethylamine	70 (±10%)	13 (±1)
Di-*n*-propylamine	60	..
Di-*n*-butylamine	55	12
Diisobutylamine	6.5	..
Di-*sec*-butylamine	4.0	..
Diphenylamine	1.0	10
Diisopropylamine	0.8	..
Dicyclohexylamine	0.6	12
No catalyst	..	17

[a] These values are for 36.5° and the units are l. $\times$ mole^{-1} sec.$^{-1}$ The initial concentrations of lithium aluminum hydride and 1-hexyne ranged from 0.33 to 0.41 *M* and from 1.00 to 1.33 *M*, respectively.

Experimental

Materials.—1-Hexyne (Farchan) was found to contain traces of catalytic impurities after distillation. In order to remove these, most of the hexyne was treated with 2% hydrochloric acid solution, 2% sodium carbonate solution, washed with distilled water, dried with anhydrous calcium chloride, passed through an alumina column, and then distilled, b.p. 68° (745 mm.). Further treatment had no observable effect. In one case the hexyne was passed over alumina and distilled without the pretreatment with acid, and the results were not noticeably different from those obtained with the hexyne which had been washed with acid.

Phenylacetylene was passed over alumina and distilled, b.p. 140° (730 mm.).

The liquid amines were freshly distilled; diphenylamine was Fisher Certified. Dilute ether solutions were made and then stored under refrigeration.

The preparation of the lithium aluminum hydride solution has been described elsewhere.[3]

Apparatus.—The apparatus and method used to determine the reaction rates by following the hydrogen evolution previously has been described.[3] The reacting mixture was maintained under reflux and the temperature was varied by adding the appropriate amount of butane or hexane, or a mixture of these, to the ether solution. The total volume of hydrocarbon added never exceeded 21% of the total volume and no significant solvent effect other than the temperature effect was observed.

Error Estimates.—The estimated error of ±1 kcal. for the activation energies is based on the maximum scatter that was observed. Most points were within ±0.5 kcal. of the values given in Table I.

It was impossible to obtain a good estimate of the error in the values of α. The most rapid reactions were less reproducible than the slower ones. With some of the catalysts there was a definite decrease in the value of the rate constant with increasing initial lithium aluminum hydride concentration. This effect was not studied in detail and causes an increase in the uncertainty in the values of α. However, it is not likely that the error is great enough to cause the true relative order of the catalysts to be different from that shown in Table I.

A Convenient Preparation of Allyllithium[1]

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The recently reported preparation of allyllithium by the metal–metal exchange reaction between allyltin derivatives and organolithium compounds[3] has made accessible pure samples of this reactive organolithium compound. The chemical versatility of allyllithium has been exploited for the preparation of allyl derivatives of both metal and organic substrates in high yields.[3,4] However, the necessity of employing allyltin and organolithium starting materials detracts from the convenience of the method. On the other hand, alternate approaches to allyllithium, such as the interaction of allylsodium with lithium chloride,[5] the treatment of allyl Grignard reagents with metallic lithium,[6] and the cleavage of allyl halides by lithium,[3,7] are less advantageous and often low-yielding processes. Wurtz coupling, leading to biallyl, is a prominent side reaction when allyl halides are exposed to lithium metal.[3,7]

As a sequel to the observation that anisole could be cleaved by lithium–biphenyl adducts in refluxing tetrahydrofuran (THF) solution,[1c,8] the analogous cleavage reaction of allyl phenyl ether was investigated. Indeed, the cleavage of the allyl ether by the 2:1 lithium–biphenyl adduct proceeded rapidly even below 0°. Subsequently, it was found that lithium metal alone in tetrahydrofuran readily cleaved allyl phenyl ether at −15° to form allyllithium and lithium phenoxide[9] (equation 1).

$$CH_2{=}CH{-}CH_2{-}O{-}C_6H_5 + 2Li \xrightarrow[-15°]{THF} CH_2{=}CH{-}CH_2Li + C_6H_5{-}O{-}Li \quad (1)$$

The yields of allyllithium, as determined by the double titration method of Gilman and Haubein,[10] ranged from 45%, in runs using stoichiometric quantities of lithium metal, up to 65%, when a sixfold excess of lithium was employed. Yet in instances where the yields of allyllithium also were determined by formation of chemical derivatives and subsequent isolation of the pure product (*cf. infra*), the resultant figures were ap-

(1) Paper IV in the series, Chemistry of Alkali Metal–Unsaturated Hydrocarbon Adducts. Previous papers are (a) J. J. Eisch and W. C. Kaska, *J. Org. Chem.*, **27**, 3745 (1962); (b) J. J. Eisch and R. M. Thompson, *ibid.*, **27**, 4171 (1962); and (c) J. J. Eisch, *ibid.*, **28**, 707 (1963).

(2) Undergraduate Research Participant, National Science Foundation, 1962.

(3) D. Seyferth and M. A. Weiner, *J. Org. Chem.*, **24**, 1395 (1959); **26**, 4797 (1961).

(4) D. Seyferth and M. A. Weiner, *Org. Syn.*, **41**, 30 (1961).

(5) E. J. Lanpher, *J. Am. Chem. Soc.*, **79**, 5578 (1957).

(6) T. E. Londergan, U. S. Patent 2,734,091 (February 7, 1956).

(7) W. Kawai and S. Tsutsumi, *J. Chem. Soc. Japan, Pure Chem. Sect.* **81**, 109 (1960), report the preparation of allyllithium from allyl halides and lithium metal in ethyl ether solution. However, subsequent workers (ref. 3) were unable to achieve satisfactory results with this approach.

(8) J. J. Eisch and W. C. Kaska, *Chem. Ind.* (London), 470 (1961).

(9) Although the presence of biphenyl had little discernible effect upon the yields of allyllithium obtained from allyl phenyl ether and lithium metal, small amounts of biphenyl served as an excellent initiator for the cleavage. (*Cf.* Paper III of this series, *J. Org. Chem.*, **28**, 707 (1963), for the role of lithium–biphenyl adducts in such cleavage reactions).

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

proximately 5% higher. This suggests that the yields based upon the titration data are to be viewed as minimum values.

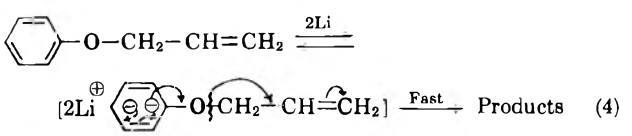
The methods employed for the formation of chemical derivatives of allyllithium illustrate the high reactivity of this organometallic reagent in two types of reactions. The first involved the facile addition of allyllithium to the azomethine linkage of benzophenone anil[11] (equation 2), while the second was the substitutional allylation of chlorotriphenylsilane[12] (equation 3).

$$CH_2{=}CH{-}CH_2Li \xrightarrow[2.\ H_2O]{1.\ (C_6H_5)_2C{=}N{-}C_6H_5} (C_6H_5)_2C(NHC_6H_5){-}CH_2{-}CH{=}CH_2\ (68\%) \quad (2)$$

$$CH_2{=}CH{-}CH_2Li \xrightarrow[2.\ H_2O]{1.\ (C_6H_5)_3SiCl} (C_6H_5)_3Si{-}CH_2{-}CH{=}CH_2\ (66\%) \quad (3)$$

If it is assumed that the preceding reactions (equations 2 and 3) occur quantitatively, the yield of allyllithium (equation 1) must be at least about 70%. The cleavage of allyl phenyl ether by lithium metal, therefore, constitutes a convenient method for the preparation of allyllithium from readily accessible and stable starting materials. Moreover, its preparation in tetrahydrofuran furnishes directly an excellent solvent medium for subsequent chemical reactions.[13] It should be noted that the by-product, phenol, can be separated easily from the hydrolyzed reaction products simply by extraction of the lithium phenoxide with water.

The striking ease with which allyl phenyl ether undergoes lithium metal cleavage contrasts sharply with the inertness of anisole toward lithium metal alone in refluxing tetrahydrofuran.[1c,8] Rather it is with other allylic ether types, such as alkyl cumyl ethers[14] and alkyl benzyl ethers,[15] that a similar facility toward metal cleavage must be sought. In a previous study[1c] the ease with which related unsaturated substrates were cleaved by lithium metal was correlated with the tendency of such substrates to form transitory lithium adducts. In this view the marked facility with which allyl phenyl ether is cleaved, compared with methyl phenyl ether, can be related to the resonance stabilization of *both* the incipient anionic fragments in the transition state of the cleavage reaction (equation 4).



$$[2Li^{\oplus}\ \ominus O{-}CH_2{-}CH{=}CH_2] \xrightarrow{\text{Fast}} \text{Products} \quad (4)$$

$$[2Li^{\oplus}\ \ominus O{-}CH_3] \xrightarrow{\text{Slow}} \text{Products} \quad (5)$$

Amplification of these principles for the preparation of other useful organometallic compounds is being actively investigated.

(11) *Cf.* H. Gilman and J. J. Eisch, *J. Am. Chem. Soc.*, **79**, 2150 (1957), for the reaction of benzophenone anil with allyl and alkyl Grignard reagents.

(12) R. H. Meen and H. Gilman, *J. Org. Chem.*, **22**, 684 (1957).

(13) For the enhanced rates of organolithium reactions in tetrahydrofuran, *cf.* H. Gilman and B. J. Gaj, *ibid.*, **22**, 447, 1165 (1957), and H. Gilman and S. Gray, *ibid.*, **23**, 1476 (1958).

(14) K. Ziegler, F. Crössman, K. Kleiner, and O. Schäfer, *Ann.*, **473**, 1 (1929); K. Ziegler and H. Dislich, *Chem. Ber.*, **90**, 1107 (1957).

(15) *Cf.* H. Gilman and G. L. Schwebke, *J. Org. Chem.*, **27**, 4259 (1962), for the preparation of benzyllithium from such ether cleavages.

Experimental[16]

Cleavage of Allyl Phenyl Ether.—To a 500-ml., three-necked, round-bottomed flask, equipped with a sealed paddle stirrer, a Friedrichs condenser surmounted by a nitrogen inlet tube and a pressure-equalized addition funnel, were added 50 ml. of anhydrous tetrahydrofuran and 4.2 g. (0.60 g.-atom) of freshly cut lithium pieces (2 × 12 mm.). The system was cooled to −15 ± 5° (external temperature) by an ice–salt bath while a solution of 6.7 g. (0.050 mole) of allyl phenyl ether[17] in 25 ml. of anhydrous ethyl ether was added dropwise to the rapidly stirred lithium suspension. (If a pale green or blue color signaling the start of the cleavage was not noticed after a portion of the allyl phenyl ether was added, a pinch of biphenyl was introduced.[1c]) At the close of the 45-min. addition period the cooling bath was removed and the reaction mixture was stirred for an additional 15 min. The dark red solution was decanted through glass wool from the lithium metal and aliquots were analyzed by the usual double titration technique.[10] Yields obtained in this manner ranged from 62 to 66%.

The titrated yields of allyllithium ranged from 40 to 50% in runs in which 0.10 mole of the allyl phenyl ether in 25 ml. of ethyl ether were added to 0.22 g.-atom of lithium pieces in 50 ml. of tetrahydrofuran over a 60-min. period at 0°.

Derivatives of Allyllithium. (a) **With Benzophenone Anil.**—A solution of 12.85 g. (0.050 mole) of benzophenone anil in 50 ml. of dry benzene was added to the allyllithium solution obtained from the treatment of 0.050 mole of allyl phenyl ether with 0.60 g.-atom of lithium, according to the first procedure described in the preceding section. The system was allowed to stir for 12 hr. and then was treated with water. The organic components were extracted with ether and the ether layer then dried with anhydrous calcium sulfate. The organic solvents were evaporated and the residue was taken up in a minimum of petroleum ether (b.p. 30–60°). This solution was chromatographed on an alumina column and the 1-allyl-1,1-diphenylmethylaniline was eluted from the column selectively by additional portions of petroleum ether. The total yield of 1-allyl-1,1-diphenylmethylaniline thereby obtained was 10.2 g. (68%), m.p. 75–77° (lit.[11] m.p. 78.5–80°). Recrystallization of this product from 95% ethanol raised the melting point to 77.5–79.5°. Admixture with an authentic sample caused no melting point depression.

(b) **With Chlorotriphenylsilane.**—A solution of 13.28 g. (0.045 mole) of chlorotriphenylsilane in 50 ml. of anhydrous ethyl ether was added to a solution of allyllithium which was prepared in the aforementioned manner and was estimated to contain 0.031 mole by the double titration method.[10] The resulting solution was stirred at the reflux temperature for 12 hr. and thereupon hydrolyzed. The separated ether layer was dried with anhydrous calcium sulfate and then evaporated. The residual colorless solid was recrystallized from 95% ethanol to yield 9.90 g. (66%) of allyltriphenylsilane, m.p. 88–89° (lit.[12] m.p. 91°).

(16) All organometallic reactions were conducted under an atmosphere of dry, oxygen-free nitrogen. The tetrahydrofuran was purified by successive treatments with sodium hydroxide pellets, sodium slices, and lithium aluminum hydride. The tetrahydrofuran was distilled from the lithium aluminum hydride directly into the reaction vessel. All glassware was dried at 120° for at least 4 hr. All melting points are uncorrected.

(17) L. Claisen, *Ann.*, **418**, 78 (1919).

Cleavage of Silicon–Silicon Bonds on an Alumina Column

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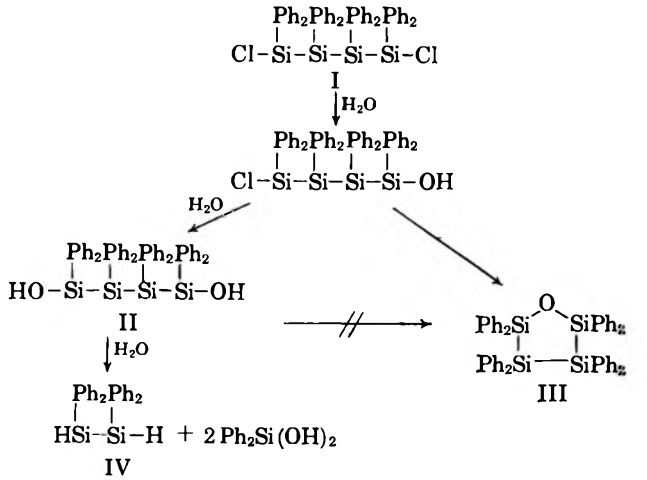
In a recent publication from these laboratories,[1] it was proposed that dilute hydrochloric acid promoted the hydrolytic cleavage of the silicon–silicon bonds in 1,4-dihydroxyoctaphenyltetrasilane (II) which were

(1) A. W. P. Jarvie and H. Gilman, *Chem. Ind.* (London), 1271 (1960).

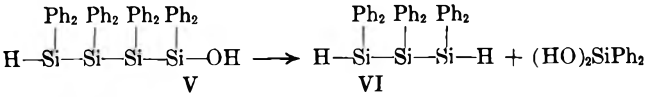
adjacent to the hydroxy groups. Isolation of *sym*-tetraphenyldisilane (IV) by chromatography on alumina of the crude hydrolysate obtained from 1,4-dichlorooctaphenyltetrasilane (I)[2] was taken as indication of the validity of this proposal. In this previous investigation, the 1,4-dihydroxy compound was not isolated in pure form; large amounts of its condensation product, octaphenyloxacyclopentasilane (III), were isolated.



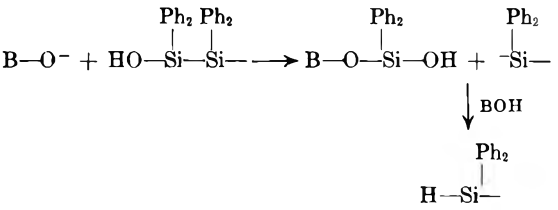
Subsequent work in this area has shown that basic alumina is an effective reagent in causing scission of silicon–silicon bonds adjacent to hydroxy groups. Therefore, in the present work and probably in the previous investigation, it appears that silicon–silicon bond cleavage occurs during chromatography.

When 1,4-dichlorooctaphenyltetrasilane was hydrolyzed in tetrahydrofuran by dilute hydrochloric acid, 1,4-dihydroxyoctaphenyltetrasilane (II) was the main product isolated. The high yield of this compound may be due to the rapid hydrolysis of both Si–Cl groups to Si–OH. Similarly, the product obtained from the reaction between Kipping's Compound B[2] and phosphorus pentachloride[3] was hydrolyzed in a mixture of tetrahydrofuran and dilute hydrochloric acid to give the corresponding dihydroxy compound.[4]

When 1,4-dihydroxyoctaphenyltetrasilane was chromatographed on an alumina column, there was obtained a 46% yield of *sym*-tetraphenyldisilane (IV) and a 4% yield of octaphenylcyclotetrasiloxane[5] $(Ph_2SiO)_4$ which may have been formed by the action of base on diphenylsilanediol. 1,5-Dihydroxydecaphenylpentasilane afforded a 62% yield of 1,1,2,2,3,3-hexaphenyltrisilane (VI). This latter reaction supports the view that the dihydroxy derivative of Kipping's compound B is 1,5-dihydroxydecaphenylpentasilane and not (as previously designated) 1,6-dihydroxydodecaphenylhexasilane.[4] Similarly, 1,5-dichlorodecaphenylpentasilane gave 1,1,-2,2,3,3-hexaphenyltrisilane (VI) in 50% yield and 1,1,2,2,3,3,4,4-octaphenyltetrasilan-1-ol (V)[6] gave the same product in 51% yield. Instead of the previous silanol, its chloro derivative (1-chloro-1,1,2,2,3,3,4,4-octaphenyltetrasilane) also could be used directly and gave a 52% yield of 1,1,2,2,3,3-hexaphenyltrisilane. 1,1,2,2,3,3-Hexaphenyltrisilan-1-ol was not isolated from the alumina column treatment of 1,4-dihydroxyoctaphenyltetrasilane. However, 1,1,2,2,3,3,4,4-octaphenyltetrasilan-1-ol (V) was obtained from 1,5-dihydroxydecaphenylpentasilane.



In order to ascertain whether the silicon–silicon bond cleavage is enhanced by the presence of acids, 1,4-dihydroxyoctaphenyltetrasilane was treated with 6 *N* hydrochloric acid for two hours. No change in the infrared spectrum was observed and it seems that, under these conditions, no cleavage of silicon–silicon bonds or cyclization to octaphenyloxacyclopentasilane occurred. The alumina[7] used in these experiments was basic and this basicity is considered to be responsible for the observed reaction. Whether the base effecting the cleavage is alumina itself or some other adsorbed inorganic base is not known. In any case, the diphenylsilanediol postulated as forming in the previous reaction scheme is probably bound chemically to the alumina through oxygen bonds. This would account for the absence of the product in the eluates. The course of the reaction might be as depicted. The same scheme might apply equally well to the chloropolysilanes, with possible conversion of the silicon–chlorine linkage to silicon–oxygen. Silicon–silicon bond cleavage can conceivably occur at other points in the reactants and products, which could account for the only moderate yields of silicon–hydrogen compounds.



From these results, it may be expected that when polysilanes have strongly electron-withdrawing groups on the terminal silicon atoms they may be cleaved fairly specifically on alumina.

Experimental

Preparation of 1,4-Dihydroxyoctaphenyltetrasilane.—To 5 g. (0.0062 mole) of 1,4-dichlorooctaphenyltetrasilane in 100 ml. of tetrahydrofuran was added 150 ml. of dilute hydrochloric acid. The mixture was stirred for 15 min. The hydrolyzate was then extracted with ether and 0.35 g. (7%) of solid, m.p. 183–185° (mixture melting point with starting material undepressed), was isolated as an insoluble solid. The ether extracts, after drying over anhydrous sodium sulfate, were evaporated. All residues were fractionally crystallized from benzene–petroleum ether (b.p. 50–60°) to give 2.65 g. (70%) of a solid, m.p. 208–210°. Recrystallization from benzene–petroleum ether raised the m.p. to 212–213°. This solid, which showed no Si–H or Si–O–Si bands in the infrared spectrum, but had a band due to Si–OH, is 1,4-dihydroxyoctaphenyltetrasilane.

(2) F. S. Kipping and J. E. Sands, *J. Chem. Soc.*, **119** 830 (1921).
(3) D. R. Chapman, unpublished studies.
(4) A. W. P. Jarvie, H. J. S. Winkler, and H. Gilman, *J. Org. Chem.*, **27** 614 (1962).
(5) C. Eaborn, "Organosilicon Compounds," Butterworths Scientific Publications, London, 1960, pp. 228–264.
(6) G. L. Schwebke, unpublished studies.
(7) The activated alumina for chromatography was obtained from the Chicago Apparatus Co., Chicago 22, Ill.

Anal. Calcd. for $C_{48}H_{42}O_2Si_4$: Si, 14.71. Found: Si, 14.50, 14.51.

Similarly, hydrolysis of 1,5-dichlorodecaphenylpentasilane (19.2 g.) in tetrahydrofuran (150 ml.) using 80 ml. of 0.1 *N* hydrochloric acid gave 1,5-dihydroxydecaphenylpentasilane, 17.05 g. (92.2%); m.p. after recrystallization from cyclohexane and benzene, 172–174°; m.m.p. with an authentic specimen, 171–174°. Additional identification of the product was obtained from the superimposability of the infrared spectra.

1,4-Dihydroxyoctaphenyltetrasilane on an Alumina Column.—1,4-Dihydroxyoctaphenyltetrasilane (1.45 g.) was placed on an alumina column. Elution with successive portions of petroleum ether (b.p. 50–60°), carbon tetrachloride, benzene, and ethyl acetate gave 0.32 g. (46%) of *sym*-tetraphenyldisilane, m.p. 76–78°, and 0.02 g. (4%) of octaphenylcyclotetrasiloxane, m.p. 184–185°, identified by mixture melting point and infrared spectra.

Treatment of 1,4-Dihydroxyoctaphenyltetrasilane with Hydrochloric Acid.—1,4-Dihydroxyoctaphenyltetrasilane (3.0 g.) in 10 ml. of ether was treated with 10 ml. of 6 *N* hydrochloric acid solution for 2 hr. The ether layer was separated and evaporated to yield a solid, m.p. 198–200°, which had an infrared spectrum identical with that of the starting material and contained no bands due to Si–H and Si–O–Si.

1,5-Dihydroxydecaphenylpentasilane on an Alumina Column.—1,5-Dihydroxydecaphenylpentasilane (23.7 g.) was dissolved in benzene and placed on an alumina column 16 in. high and 2 in. in diameter. Fractions were eluted with benzene and, subsequent to recrystallization from acetone and methanol, gave 1,1,2,2,3,3-hexaphenyltrisilane, 8.54 g. (62.1%), m.p. 95–97°; m.m.p. with an authentic specimen, 95–97°.

In a second run, 1,5-dihydroxydecaphenylpentasilane (5.7 g.) was placed on an alumina column and eluted with benzene, to give 0.4 g. of a solid, m.p. 97–98°. This had the same infrared spectrum as the 1,1,2,2,3,3-hexaphenyltrisilane isolated from the chromatography of 1,1,2,2,3,3,4,4-octaphenyltetrasilane-1-ol. There was no depression of the melting point of a mixture of the two products. Ethyl acetate elutions afforded 1.9 g. of a mixture of 1,1,2,2,3,3,4,4-octaphenyltetrasilan-1-ol, m.p. 180–181° (identified by mixture melting point and infrared spectrum); and also some of the starting material (infrared).

1,5-Dichlorodecaphenylpentasilane on an Alumina Column.—1,5-Dichlorodecaphenyl pentasilane (29.5 g.) was dissolved in benzene and placed on an alumina column 18 in. high and 2 in. in diameter. Elution of all the fractions with benzene and recrystallization from methanol and acetone gave 8.25 g. (50.0%) of 1,1,2,2,3,3-hexaphenyltrisilane, m.p. 95–97° (mixture melting point with authentic specimen undepressed). The other products were glues which could not be crystallized. The 1,1,2,2,3,3-hexaphenyltrisilane was identified additionally from the superimposability of its infrared spectrum with that of an authentic specimen.

1,1,2,2,3,3,4,4-Octaphenyltetrasilan-1-ol on an Alumina Column.—A solution of 2.7 g. of 1,1,2,2,3,3,4,4-octaphenyltetrasilan-1-ol in 25 ml. of carbon tetrachloride was placed on an alumina column. Carbon tetrachloride and benzene elutions afforded 0.99 g. (51%) of a solid, m.p. 96–98°, which was 1,1,2,2,3,3-hexaphenyltrisilane.

Anal. Calcd. for $C_{36}H_{32}Si_3$: Si, 15.3. Found: Si, 15.40, 15.45.

The infrared spectrum is similar to those of *sym*-tetraphenyl disilane and 1,1,2,2,3,3,4,4-octaphenyltetrasilane, but possesses an Si–H band of intermediate intensity. This trisilane was separated from the starting material, which was also partially eluted, by its solubility in hot petroleum ether (b.p. 50–60°). In the preparatory method for the trisilane, better results were obtained with a long alumina column.

Similarly, 50 g. of 1-chloro-1,1,2,2,3,3,4,4-octaphenyltetrasilane afforded 18.5 g. (52%) of 1,1,2,2,3,3-hexaphenyltrisilane. This latter reaction appeared to take a longer time than that starting with the corresponding silanol.

Acknowledgment.—This research was supported by the U. S. Air Force under contract AF 33(616)-6463 and monitored by the Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright Patterson Air Force Base, Ohio.

The Structures of Substituted *o*-Quinone Methide Trimers

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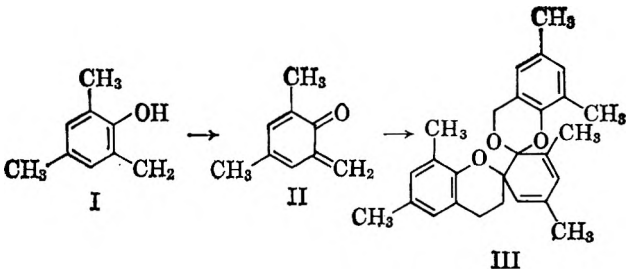
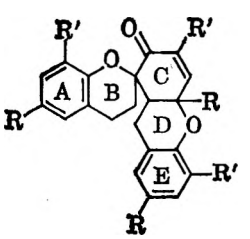
The facility with which substituted *o*-quinone methides dimerize and trimerize was recognized as early as 1907.[1] While a great deal of literature bearing on the structures of trimers has been written, most of it is concerned specifically with the trimer of 3,5-dimethylquinone-(2)-methide (II).[2] No less than three structures have been proposed for this substance. The most recent of these, the "benzodioxan" structure (III), was suggested[3] in 1941 and given additional support more recently.[4,5]



I II III

Recent studies on the structure of the trimer of *o*-quinone methide itself led to the assignment shown in IV[2] and prompted a re-examination of the properties of earlier reported substituted trimers. The trimer of 3,5-dimethylquinone-(2)-methide and of 3-chloromethyl-5-methylquinone-(2)-methide were studied as representative cases. Evidence is now presented establishing that these two are related and have a ring system identical with that of the parent (IV). They are, therefore, formulated as V and VI, respectively.

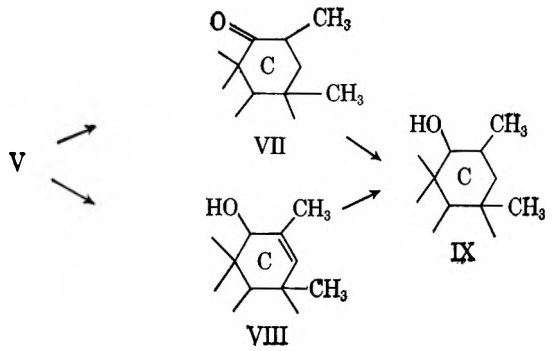


IV, R = R′ = H
V, R = R′ = CH_3
VI, R = CH_3, R′ = CH_2Cl

Although V does not form carbonyl derivatives, the presence of an α,β-unsaturated ketone functionality was suggested by infrared data (ν_{max} 5.91 μ) and confirmed by quantitative microhydrogenation. It absorbed 0.97 mole equivalent of hydrogen to afford a dihydroketone (VII), m.p. 180–181°, ν_{max} 5.81 μ. Further reduction with lithium aluminum hydride

(1) K. Fries and K. Kann, *Ann.*, **353**, 339 (1907).
(2) S. B. Cavitt, H. Sarrafizadeh R., and P. D. Gardner, *J. Org. Chem.*, **27**, 1211 (1962), and references cited therein.
(3) G. Schiemann and K. Hultzsch, *Naturwissenschaften*, **35**, 124 (1948).
(4) G. Schiemann, *Rev. fac. sci. univ. Istanbul*, **17A**, 290 (1952); *Chem. Abstr.*, **48**, 3293 (1954).
(5) H. Civelekoglu, *Rev. fac. sci. univ. Istanbul.*, **18A**, 14 (1953); *Chem. Abstr.*, **48**, 5139 (1954).

gave a carbinol (IX), m.p. 133–135°. Alternatively, reduction of V afforded an unsaturated carbinol (VIII), m.p. 145–146°, which in turn gave IX upon hydrogenation. The presence of two benzenoid rings in this product is indicated by its ultraviolet absorption, λ_{max} 280 and 287 mμ; ε 3890 and 3840, respectively.



These assignments were corroborated by n.m.r. data. The lone olefinic proton of V was observed at 3.63 τ and identified by comparison with the spectrum of IV. This proton is not strongly coupled indicating the absence of protons on adjacent carbon atoms. The small splitting (J = 1.3 c.p.s.) is due to coupling with the methyl group adjacent to the carbonyl (8.21 τ). The methyl is observed as a doublet and the olefinic proton as a quartet. The methyl group at the bridgehead of rings C and D is at 8.37 τ while three of the aromatic methyls are at 7.83 τ and the fourth at 7.87 τ. The higher field resonance of one aromatic methyl group is thought to be the result of steric repulsion by the bridgehead methyl group, an effect which has been observed with other substances in this laboratory. Additional examples must be examined, however, before it is possible to draw from these data the suggested stereochemical conclusions. The spectrum suggested the absence of protons on carbon atoms adjacent to ethereal oxygen.

The relationship between V and VI was shown by hydrogenation of the latter; the product (VII) was identical with a sample obtained from V.

Experimental

2-Methoxymethyl-4,6-dimethylphenol (I).—The methiodide of 2-dimethylaminomethyl-4,6-dimethylphenol[6] (32.5 g.) was heated under reflux in 200 ml. of 10% methanolic potassium hydroxide for 3 hr. The cooled solution was diluted with a large volume of water and extracted with two portions of ether. The aqueous layer was cooled and acidified whereupon an oily layer separated. It was isolated by several extractions with ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and with water and were then dried with anhydrous sodium sulfate. Freeing of solvent at an aspirator and distillation of the residue through a short column gave 7.35 g. (44%) of 2-methoxymethyl-4,6-dimethylphenol (I), b.p. 46° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.34; H, 8.57.

3,5-Dimethylquinone-(2)-methide Trimer (V).—The pyrolysis system employed was that described for the preparation of the parent trimer (IV).[2] Conditions used were those described. The passage of 13.1 g. of 2-methoxymethyl-4,6-dimethylphenol through the 0.9-cm. tube at 800–850° with nitrogen as a diluent gave crystalline material in the cold receiver as well as in the lower portion of the tube. This combined pyrolysate was recrystallized from ethyl acetate–petroleum ether to give 6.4 g. (60%) of colorless solid, m.p. 199–201°. This material was shown to be identical with that obtained from 2-chloromethyl-4,6-dimethylphenol[1] by means of the usual comparisons. This substance exhibits ultraviolet absorption at 206, 221, and 281 mμ with extinction coefficients 63,000, 21,700, and 2910, respectively. Carbonyl absorption in the infrared is at 5.91 μ.

Anal. Calcd. for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.66; H, 7.60.

Hydrogenation of 3,5-Dimethylquinone-(2)-methide Trimer (V).—A solution of 0.109 g. of the trimer in 15 ml. of ethanol was stirred with 0.075 g. of 10% palladium–carbon (pre-saturated) under 1 atm. of hydrogen. Hydrogen uptake ceased at 5.8 ml. (97% for one double bond). The product, isolated in the usual manner, melted at 179–180° without purification. Several recrystallizations from ethyl acetate–petroleum ether gave a pure sample, m.p. 180.0–180.5°. This dihydro trimer (VII) exhibits carbonyl absorption in the infrared at 5.81 μ. Ultraviolet maxima at 280 and 287 mμ have ε values 3890 and 3840, respectively. This substance, like its precursor, does not form carbonyl derivatives.

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 79.84; H, 7.79.

Lithium Aluminum Hydride Reduction of 3,5-Dimethylquinone-(2)-methide Trimer (V).—A mixture of 1.0 g. of trimer V, 0.095 g. of lithium aluminum hydride and 20 ml. of purified tetrahydrofuran was stirred at room temperature for 24 hr. Excess reductant was destroyed by the cautious addition of water and then dilute hydrochloric acid. The mixture was extracted with ether and the extract washed thoroughly with water. Drying (sodium sulfate) and evaporation of solvent followed by recrystallization of the residue from ethyl acetate–petroleum ether gave 0.70 g. (70%) of colorless carbinol (VIII), m.p. 145–146°. This substance exhibits no carbonyl absorption in the infrared. It absorbs in the ultraviolet at 280 mμ (ε 3620).

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.00; H, 7.71.

Tetrahydro-3,5-dimethylquinone-(2)-methide Trimer (IX). (A) **From VII.**—A solution of 0.30 g. of dihydro trimer (VII) and 0.10 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran was stirred at 30° for 12 hr. Moist ether was slowly added followed by dilute hydrochloric acid. The usual isolation by ether extraction and processing of the extract gave a viscous gum. Chromatography (alumina) of a benzene solution of the product afforded crystalline material. Two recrystallizations from petroleum ether gave 0.080 g. (27%) of IX, m.p. 133.5–135.0°. The infrared spectrum of this substance exhibits no absorption in the carbonyl region.

Anal. Calcd. for $C_{27}H_{34}O_3$: C, 79.76; H, 8.43. Found: C, 79.33; H, 8.27.

(B) **From VIII.**—A solution of 0.35 g. of trimer carbinol (VIII) in 40 ml. of ethanol was shaken with 0.20 g. of 10% palladium–carbon under 1 atm. of hydrogen. When hydrogen was no longer absorbed, the catalyst was removed by filtration and the product isolated by evaporation of solvent. Three recrystallizations from petroleum ether afforded 0.115 g. (33%) of IX, m.p. and m.m.p. 133.5–134.0°. The infrared spectrum is identical with that of material prepared from VII.

Reduction of 3-Chloromethyl-5-methylquinone-(2)-methide Trimer (VI).—The chloro trimer (VI, 6.0 g.)[7] in 100 ml. of ethyl acetate was shaken with 5.05 g. of triethylamine and 1.0 g. of 10% palladium–carbon under 3 atm. of hydrogen. When hydrogen uptake ceased, the mixture was processed as described before to give a solid product. Recrystallization from ethanol–petroleum ether afforded 3.0 g. (64%) of VII, m.p. 177–178°. A mixture melting point determination and a comparison of spectra established the identity of this product.

Acknowledgment.—The authors are indebted to The Robert A. Welch Foundation for the financial support of this study.

(6) P. D. Gardner, H. S. Rafsanjani, and L. Rand, *J. Am. Chem. Soc.*, **81**, 3364 (1959).

(7) K. Hultzsch, *J. prakt. Chem.*, **159**, 180 (1941).

A New Method for Preparing 5-Aryl-2,3-dihydro-1*H*-1,4-benzodiazepines

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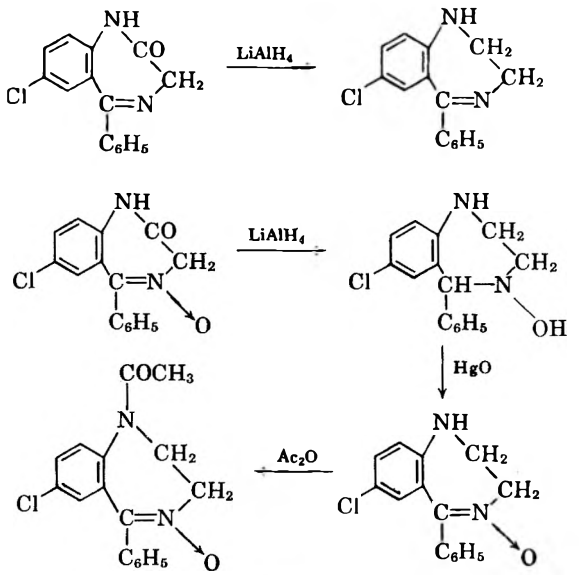
A recent publication[1] has described the preparation of 7-nitro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine from 2-chloro-5-nitrobenzophenone and ethylenediamine. We have had occasion to prepare benzodiazepines of this type, but have found this method to be of limited use. Nitro activation of the aryl chloride appears to be necessary since treatment of 2-bromo-5-chlorobenzophenone with ethylenediamine afforded no benzodiazepine. A more versatile method is the lithium aluminum hydride reduction of 5-aryl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.



Reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one with lithium aluminum hydride in ether has afforded 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine in good yield. 7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine was prepared similarly.

Lithium aluminum hydride reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide gave 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine which could be oxidized by mercuric oxide to afford 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide. The 5-*o*-chlorophenyl analog was made by the same route.

Since a large variety of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with differing substituents in positions 3,5,6,7,8, and 9 has been disclosed,[2,3] this method can afford a varied group of 2,3-dihydro-1*H*-1,4-benzodiazepines.

The 5-aryl-2,3-dihydro-1*H*-1,4-benzodiazepines were potent central nervous system depressants in animal tests.

(1) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).

Experimental[4]

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7 g.) was added in portions to a stirred suspension of lithium aluminum hydride (1.6 g.) in anhydrous ether (200 ml.). The mixture was heated under reflux for an hour and the excess hydride was decomposed by careful addition of water. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. Recrystallization of the residue from ethanol afforded 3.5 g. of product, m.p. 174–176°.

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.17; H, 5.11; Cl, 13.81; N, 10.91. Found: C, 70.32; H, 5.07; Cl, 13.6; N, 10.98.

7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine, m.p. 180–181° (from ethanol), was similarly prepared in 42% yield.

Anal. Calcd. for $C_{19}H_{19}ClN_2$: C, 73.46; H, 6.16; Cl, 11.41; N, 9.01. Found: C, 73.16; H, 5.92; Cl, 11.20; N, 8.71.

7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (10 g.) was treated with lithium aluminum hydride (2.8 g.) in anhydrous ether (250 ml.) as in the preceding example. There was obtained 7 g. of product, m.p. 170–172°.

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; Cl, 12.90; N, 10.20. Found: C, 65.87; H, 5.26; Cl, 13.0; N, 10.32.

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A suspension of the previous solid (12 g.), mercuric oxide (20 g.), acetone (250 ml.), and water (25 ml.) was stirred for 3 hr. at room temperature. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from 95% ethanol afforded 8 g. of product, m.p. 247–248°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.81; Cl, 13.00; N, 10.27. Found: C, 66.20; H, 4.92; Cl, 13.3; N, 9.92.

7-Chloro-5-*o*-chlorophenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide, m.p. 215–217° (from ethanol), was prepared similarly (45%) from 7-chloro-5-*o*-chlorophenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,[5] but without the isolation of the intermediate 7-chloro-5-*o*-chlorophenyl-4-hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O$: C, 58.65; H, 3.94; Cl, 23.09; N, 9.12. Found: C, 58.94; H, 4.04; Cl, 23.50; N, 8.87.

1-Acetyl-7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A solution of 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide (4 g.) in acetic anhydride (20 ml.) was warmed on a steam bath for 0.5 hr. The solution was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to afford 1.5 g. of product, m.p. 222–224°. The carbonyl absorption band was at 6.02 μ.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.27; N, 8.90. Found: C, 64.90; H, 4.76; Cl, 11.2; N, 9.13.

(4) Melting points are uncorrected.
(5) This compound, m.p. 249–250° dec., was prepared by C. Gochman following method A of ref. 3.

The Decomposition of Methylethylphenylbenzylphosphonium Acetate

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Received February 21, 1963

A few examples of thermal decomposition of phosphonium carboxylate salts have been studied.[2] These

(1) Petroleum Research Fund Scholar, 1961–1962.
(2) (a) E. A. Letts and N. Collie, *Phil. Mag.*, **22**, 183 (1886); (b) N. Collie, *J. Chem. Soc.*, **53**, 636 (1888); (c) D. B. Denney and L. C. Smith, *Chem. Ind.* (London), 290 (1961); (d) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

include the acetate, benzoate, and oxalate salts of the tetraethylphosphonium ion,[2a] tetramethylphosphonium benzoate,[2b] and the phosphobetaines, $(C_6H_5)_3\overset{+}{P}(CH_2)_n$-$CO_2^-$ where n = 1,2,3.[2c]

It was the purpose of this research to investigate the thermal decomposition of the unsymmetrical phosphonium salt, methylethylphenylbenzylphosphonium acetate. This compound was chosen because of the possible information it might provide concerning the comparative ease of elimination of the groups bonded to the phosphorus atom in a nucleophilic attack by the acetate ion.[3] More importantly, the system seemed well suited for subsequent stereochemical studies of the type conducted by McEwen, VanderWerf, and coworkers[4] who have investigated other nucleophilic reactions involving the enantiomers[5] of this phosphonium ion.

The outcome of the reaction differed substantially from that of decomposition reactions reported for the symmetrical phosphonium ions.[2a,b,d] The analytical data are summarized in Table I.

TABLE I

ANALYSIS OF REACTION PRODUCTS

Product	Method of analysis	Yield,[a] %
Toluene	V.p.c.[b]	22
Acetic acid	Titration	40
Methyl acetate	V.p.c.	16
Ethyl acetate	V.p.c.	Trace
Phenylacetone	V.p.c.	5
Methylethylphenylphosphine oxide	Infrared	69
cis-2-Methyl-1,3-diphenyl-1-propene	V.p.c.	12
trans-2-Methyl-1,3-diphenyl-1-propene	V.p.c.	16
Ethylphenylbenzylphosphine (as the oxide)	Product isolation	16

[a] 100 × moles product/moles reactant. [b] Vapor phase chromatography.

A mechanistic accounting for the reaction products is somewhat speculative at this point; however, it seems reasonable that the acetate ion may be involved in a nucleophilic attack on a pentacovalent intermediate.

$$(CH_3)(C_2H_5)(C_6H_5)(C_6H_5CH_2)\overset{+}{P} + \bar{O}\text{—}\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons (CH_3)(C_2H_5)(C_6H_5)(C_6H_5CH_2)P\text{—}O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{OAc^-} (CH_3)(C_2H_5)(C_6H_5)P{=}O + (CH_3CO)_2O + C_6H_5CH_2{:}^-$$

This proposal has some support in work of others[4b,6] where it has been noted that ethers are produced from the decomposition of certain phosphonium alkoxides at lower temperatures.

$$R_4\overset{+}{P}\bar{O}R' \xrightarrow{OR'^-} R_3P{=}O + R_2'O + R{:}^-$$

It is likely that phenylacetone is formed by reaction of the benzyl anion with acetic anhydride, and that the isomeric olefins are produced either by a Wittig reaction of the ylid of the methylethylphenylbenzylphosphonium ion with phenylacetone, or by an alternate or competing reaction involving addition of the benzyl anion to phenylacetone with subsequent dehydration of the tertiary alcohol thus formed. That the yields of the olefins from the pyrolysis reaction are nearly equal does not rule out the Wittig pathway to the olefins, since at the elevated temperature of the pyrolysis low stereospecificity would be expected. The appearance of methyl acetate and ethylphenylbenzylphosphine among the reaction products is probably the result of a nucleophilic displacement by acetate ion on the phosphonium ion, and has its analogy in the work of Denney.[2c,d]

Stereochemical assignments for the olefins were made on the basis of the positions of the higher wave-length bands in the near ultraviolet which are usually shifted to higher frequencies for olefins with sterically interacting *cis* substituents[7] (benzyl–phenyl interaction in this case), and comparison of these olefins with those isolated from the isomer mixture obtained from sulfuric acid dehydration of methyldibenzylcarbinol[8] in which *trans*-2-methyl-1,3-diphenyl-1-propene (phenyl and benzyl groups *trans* to each other) should predominate.[9]

Experimental[10]

Methylethylphenylbenzylphosphonium Iodide (I).—This compound was prepared by the method of Bailey[11] and melted at 162–164°.

Methylethylphenylbenzylphosphonium Acetate Hydrate (II).—To a solution of 24.5 g. (0.066 mole) of I in 350 dry methanol was added with stirring at room temperature 12.12 g. (0.0726 mole) of dry, powdered silver acetate. The reaction mixture was protected from atmospheric moisture and heated at 40° with stirring for 6.5 hr. The brown precipitate (16.22 g.) was removed by filtration in a drybox and the methanol distilled under reduced pressure. The viscous liquid was placed in a vacuum desiccator over phosphorus pentoxide and after 5 days it crystallized into a mass of light gray crystals. Two recrystallizations from anhydrous ethyl acetate yielded extremely hygroscopic, fluffy white crystals which were dried *in vacuo* over phosphorus pentoxide at 56° for several days. This treatment produced a substance of m.p. 104.2–105.3° (with softening).

Anal.[12] Calcd. for $C_{18}H_{23}O_2P \cdot {}^2/_3H_2O$: C, 68.77; H, 7.80; P, 9.86. Found: C, 68.52; H, 7.83; P, 10.23.

Pyrolysis of II.—II (14.36 g., 0.0457 mole) was placed in a 25-ml. round-bottomed flask attached to a 44-cm. vacuum jacketed Vigreux column equipped for vacuum distillation. Air was swept out of the system with dry nitrogen. The flask and contents were immersed in an oil bath at 85° and the temperature of the oil bath raised steadily 280° over a period of 22 min. where it was maintained for an hour. First evidence of reaction occurred at a bath temperature of 200° and the reaction became vigorous at 230°. The first fraction (1), 2.93 g., was collected to approximately 120° at atmospheric pressure. The pot was then cooled to 80°, the system placed under vacuum, heating resumed, and a second fraction (2) consisting of 7.95 g. was collected to 165° (9 mm.). A third fraction (3) of 1.68 g. was ob-

(3) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).

(4) (a) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **81**, 3805 (1959); (b) C. B. Parisek, W. E. McEwen, and C. A. VanderWerf, *ibid.*, **82**, 5503 (1960); A. Bladé-Font, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **82**, 2396 (1960); W. E. McEwen, A. Bladé-Font, and C. A. VanderWerf, *ibid.*, **84**, 677 (1962).

(5) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *ibid.*, **81**, 248 (1959).

(6) M. Grayson and P. T. Keough, *ibid.*, **82**, 3919 (1960).

(7) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," 2nd Ed., Edward Arnold Ltd., London, 1957, pp. 267–275.

(8) R. M. Caves, R. L. McLaughlin, and R. H. Wise, *J. Am. Chem. Soc.*, **76**, 522 (1954).

(9) H. C. Brown and M. Nakagawa, *ibid.*, **77**, 3614 (1955).

(10) All melting points and boiling points are uncorrected.

(11) W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, **25**, 1996 (1960).

(12) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

tained at 172–230° (9 mm.) and solidified to a yellow solid on cooling.

Analysis of Fraction 1.—Vapor phase chromatographic separation and examination of infrared spectra indicated the presence of acetic acid, toluene, methyl acetate, and ethyl acetate (trace). Toluene and methyl acetate were determined quantitatively on a 10-ft. Ucon column, and acetic acid by titration with standard base. The fraction contained 31% toluene, 19% methyl acetate, and 38% acetic acid by weight. Water was not determined in this fraction but would theoretically amount to 13.6%.

Analysis of Fraction 2.—A small portion of fraction 2 was extracted with water, the water evaporated, and the infrared spectrum of the residue in chloroform shown to be identical in every respect with that of the authentic material prepared from methylethylphenylbenzylphosphonium iodide by treatment with sodium hydroxide.[4a] The methylethylphenylphosphine oxide was analyzed spectrophotometrically in chloroform solution with a Baird Atomic double beam infrared spectrophotometer using the absorption peak at 8.95 mμ and was shown to represent 67% by weight of fraction 2. Another portion of fraction 2 when treated with 2,4-dinitrophenylhydrazine reagent[13] yielded the 2,4-dinitrophenylhydrazone of phenylacetone, m.p. 152–154°; reported[14] m.p. 152.5–153.5°, m.m.p. 152–154°. Vapor phase chromatographic analysis of fraction 2 on a 10-ft. Ucon column gave the following results: 4% phenylacetone, 19% *trans*-2-methyl-1,3-diphenyl-1-propene, and 14% *cis*-2-methyl-1,3-diphenyl-1-propene by weight. The latter two compounds displayed retention times and ultraviolet spectra identical with the authentic materials prepared by dehydration of methyldibenzylcarbinol.[8] The isomers were separated on a 10-ft. Ucon column from the fraction boiling at 162–164° (9 mm.).[15] The *cis* and *trans* isomers absorbed at 218, 245 and 218, and 249 mμ, respectively.

Fraction 3.—Fraction 3 was recrystallized twice from ethyl acetate–ligroin to yield a compound of m.p. 112–113°; reported[16] m.p. for ethylphenylbenzylphosphine oxide, 110–111°. This compound melted undepressed with purified ethylphenylbenzylphosphine oxide prepared by air oxidation of ethylphenylbenzylphosphine.[16]

Acknowledgment.—This research was supported by a type B grant from the Petroleum Research Fund. Appreciation also is expressed to Mary E. Pate, Richard McAtee, and Larry Becker for their help in the initial phase of this work.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 111.

(14) R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1837 (1952).

(15) Although the mixture of isomers has been reported (ref. 8) this is apparently the first account of their separation. This fraction was shown to consist of 61% *trans* and 39% *cis* isomer.

(16) J. Meisenheimer, J. Casper, M. Horing, W. Lauter, L. Lichtenstadt, and W. Samuel, *Ann.*, **449**, 213 (1926).

Mechanism Study of a Benzilic Acid-Type Rearrangement[1]

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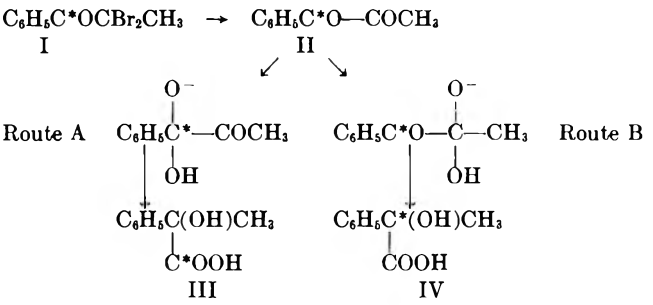
α,α-Dibromopropiophenone (I) rearranges to atrolactic acid (III or IV) during treatment with concentrated sodium hydroxide solution. It has been suggested[4] that the reaction proceeds by way of the intermediate, methyl phenyl diketone (II), which then undergoes a benzilic acid rearrangement.



When these authors subjected dibromo compound I to dilute alkali, no atrolactic acid was recovered; the sole product was 2,5-diphenyl-1,4-benzoquinone, formed in 13% yield by an aldol condensation of two molecules of the diketone. The action of concentrated sodium hydroxide on II produced atrolactic acid in low yield, whereas dilute alkali produced only tar.[4]

The use of carbon-14 as a tracer has been applied here in following the mechanism in the rearrangements starting with both the dibromo compound and the diketone. These two compounds (I and II) were prepared, labeled in the α-position. The atrolactic acid produced by rearrangement of these compounds was degraded by oxidation to acetophenone and carbon dioxide. In both cases essentially all of the original carbon-14 was found in the carbon dioxide. Since this labeled carbon atom was originally adjacent to the phenyl group, 100% phenyl migration must have occurred in both alkaline-catalyzed rearrangements, thereby eliminating route B as a possible mechanism. It is possible that the carbonyl group of II, α to the phenyl group, may be the preferred one for hydroxyl ion attack. However, if hydroxyl ion attack were rapid and reversible, the observed preference of route A also could be explained as due to a tendency of the phenyl group to migrate in preference to the methyl group.

If methyl phenyl diketone is the intermediate in the rearrangement of α,α-dibromopropiophenone, it is obvious that the rearrangement of the diketone must be much faster than the rate of formation. Any appreciable concentration of the diketone would lead to the aldol condensation mentioned previously.

Experimental

(α,α-Dibromopropio-1-C^{14})-phenone (I).—To 9.7 g. (0.4 mole) of magnesium turnings contained in a 250-ml., round-bottomed, three-necked flask was added slowly a solution of 53.6 g. (0.5 mole) of ethyl bromide in 95 ml. of ether. While the flask was cooled in ice, 12.1 g. (0.1 mole) of carbonyl-labeled benzamide was slowly added under dry nitrogen. After a reflux period of 24 hr. the reaction mixture was hydrolyzed with ice and sulfuric acid and extracted with ether. From the extract was obtained 7.5 g. (56% yield) of propiophenone.

One gram of the unpurified propiophenone was treated with a solution of 2.50 g. of bromine in 7.5 ml. of chloroform and allowed to stand at 25.5° for 0.5 hr. before it was refluxed for 4 hr. The solvent was carefully removed to give 2.13 g. (97% theoretical yield) of crude α,α-dibromopropiophenone (I).

Hydrolysis and Rearrangement of α,α-Dibromopropiophenone.—The crude dibromide (I) was stirred vigorously with 42.6 g. of 20% aqueous sodium hydroxide for 3.5 hr. The aqueous phase was extracted with ether and acidified with concentrated hydro-

(1) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corp.

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(4) R. Levine and J. R. Stephens, *J. Am. Chem. Soc.*, **72**, 1642 (1950).

chloric acid. The precipitated crystalline atrolactic acid was removed by filtration and sublimed at 70 to 75°; m.p. 91 to 92°.

Methyl Phenyl Diketone-3-C^{14} (II).—This compound was prepared by the treatment of carbonyl-labeled propiophenone with butyl nitrite, followed by acid hydrolysis of the resultant monoxime.

Rearrangement of Methyl Phenyl Diketone.—The diketone (II), dissolved in a large volume of ether, was stirred vigorously for 1 hr. with an equal volume of 20% sodium hydroxide solution maintained at 0°. Under these conditions, a yield of about 25% of the desired atrolactic acid (III) could be isolated after neutralization of the aqueous layer.

Oxidation of Atrolactic Acid (III).—In a typical degradation, 83 mg. of III was decarboxylated at room temperature by treating with a mixture of 44 mg. of chromium trioxide and 2 ml. of glacial acetic acid in a small flask connected to a barium hydroxide absorption train. The apparatus was swept with nitrogen gas and the evolved carbon dioxide was converted to barium carbonate. The precipitated barium carbonate was washed with water and centrifuged several times before air drying. The residue in the reaction flask was extracted with ether and the ether extract was washed with sodium bicarbonate and then evaporated. The residual acetophenone was converted to the semicarbazone which after two crystallizations from 25% alcohol melted at 198°.

Radioactivity Assay of Oxidation Products.—The determination of carbon-14 was conducted by the wet combustion of small samples of the barium carbonate and acetophenone semicarbazide according to the technique of Raaen and Ropp.[5] The results are given in Table I.

TABLE I

RADIOACTIVITY OF CARBON^{14} IN μC./MMOLE

	Rearrangement experiment with—	
	Dibromo compound I	Diketone II
Original material	1.028	0.935
Acetophenone semicarbazide	0.00579	0.005
Barium carbonate	.909[a]	.857[a]

[a] The approximately 90% material balances of the radiocarbon are attributed to exchange with dissolved carbon dioxide in the wash water (Melvin Calvin and co-authors, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 124) as well as exchange with atmospheric carbon dioxide (M. D. Kamen, "Isotopic Traces In Biology," 3rd Ed., Academic Press, New York, N. Y., 1957, p. 308) during drying of the wet, centrifuged barium carbonate.

(5) V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

The Structure of Hexachlorinated 2,4-Dicarbethoxy-3,5-dimethylpyrrole

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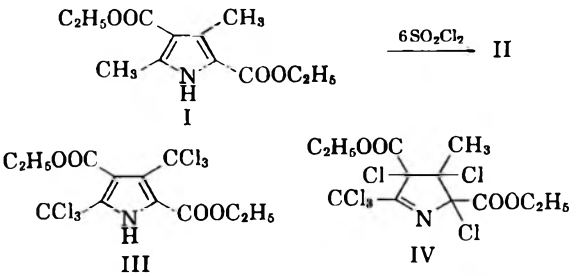
Chlorination with sulfuryl chloride followed by hydrolysis has been a commonly used technique for the oxidation of α-methyl substituents on pyrroles.[1-3] In general, one, two, and three moles of sulfuryl chloride yield, respectively, the mono-, di-, and trichloromethylpyrroles which can be hydrolyzed to the hydroxymethyl-, formyl-, and carboxypyrroles. In this reaction, β methyl groups are not attacked and unsubstituted positions are chlorinated.

(1) H. Fischer, E. Sturm, and H. Friedrich, *Ann.*, **461**, 244 (1928).

(2) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I, Akad. Verlag., Leipzig, 1934, p. 76.

(3) A. H. Corwin, W. A. Bailey, and P. Viohl, *J. Am. Chem. Soc.*, **64**, 1267 (1942); A. H. Corwin and J. L. Straughn, *ibid.*, **70**, 1418 (1948).

The product from the action of three moles of sulfuryl chloride and subsequent hydrolysis on Knorr's pyrrole, 2,4-dicarbethoxy-3,5-dimethylpyrrole (I), is a mixture of the 5-formyl- and 5-carboxypyrroles.[3] Fischer, *et al.*,[1] reported the isolation in high yield of a hexachloro derivative (II) from the action of six moles of sulfuryl chloride on I. Structure III was assigned to II apparently on the basis of the analyses for C, N, Cl, and OC_2H_5. However, hydrolysis with potassium hydroxide did not yield the tetracarboxypyrrole diester, but rather fragmented the compound. The hexachloro derivative could be reduced to 2,4-dicarbethoxy-3-methyl-5-hydroxymethylpyrrole and oxidized to a compound containing one additional oxygen and one less chlorine.[1]



The n.m.r. spectrum of II shows three bands: a triplet at δ 1.37 (p.p.m., tetramethylsilane, 0), a singlet at 2.24, and two almost coincident quartets centered at 2.62 and 2.64. The ratios of triplet/singlet/quartet areas are 6:3:4. This shows that II retains a methyl group (the singlet) which was corroborated by a C-methyl determination. The infrared spectrum of II shows no absorption in the pyrrole NH stretching region (3400–3500 cm.$^{-1}$) or the pyrrole ring vibration region (1470–1600 cm.$^{-1}$).[4] Two bands are observed in the carbonyl region at 1740 and 1760 cm.$^{-1}$, above the normal pyrrole ester positions.[4] There is a band at 1612 cm.$^{-1}$, the position reported for the imine stretching band of Δ^1-pyrrolines.[5] The ultraviolet spectrum of II shows only end absorption with a slight shoulder at 215 mμ (ε 4850). This supports a structure for II in which the imine is not in conjugation with the α ester carbonyl. For example, glyoxylic acid semicarbazone absorbs at 252–253 mμ (ε 12,400), whereas acetone semicarbazone absorbs at 224 mμ (ε 11,000).[6] The iodide test for N–Cl was negative.[7]

The evidence points clearly to structure IV for the hexachloro derivative II.

Experimental

2,4-Dicarbethoxy-3-methyl-5-trichloromethyl-2,3,4-trichloro-$\Delta^{1(5)}$-pyrroline (II and IV).—Knorr's pyrrole (I) in ether was chlorinated with freshly distilled sulfuryl chloride as described by Fischer, Sturm, and Freidrich[1]; m. p. 72° (lit.[1] m.p. 72°).

Anal. Calcd. for $C_{12}H_{13}Cl_6NO_4$: C, 32.12; H, 2.9; Cl, 47.5; C–CH_3, 3/446; mol. wt., 446. Found: C, 32.2; H, 3.0; Cl, 47.0; C–CH_3, 3.1/446; mol. wt., 426 (osmometer).

A sample of II in ether acidified with acetic acid was shaken with aqueous potassium iodide. An iodine color developed only after 4 days.

The n.m.r. spectrum was taken in carbon tetrachloride with tetramethylsilane as internal standard with a Varian Model A-60

(4) U. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

(5) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1278 (1958).

(6) J. A. Olson, *Arch. Biochem. Biophys.*, **85**, 225 (1959).

(7) M. Z. Barakat and M. F. Abd El-Wahab, *Anal. Chem.*, **26**, 1973 (1954).

spectrometer. The infrared spectrum was taken in potassium bromide with a Perkin-Elmer Model 221 spectrophotometer. The ultraviolet spectrum was taken in ethanol with a Cary Model 14 spectrophotometer.

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Configuration Assignments in Symmetrical Alkyl–Aryl Pinacols[1]

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In a study of the mechanism of the pinacol–pinacolone rearrangement it became necessary to synthesize and characterize pure diastereoisomeric forms of PhRC(OH)C(OH)RPh where R = methyl, ethyl, and *n*-propyl. These diols previously have been reported as dimeric reduction products of their respective ketones—acetophenone,[3] propiophenone,[4] and *n*-butyrophenone[5]—or by appropriate Grignard additions to benzil.[3,6] In only one case has a configurational assignment of the *dl* and *meso* isomers been established and that by a synthesis of optically active and inactive 2,3-diphenyl-2,3-butanediol from (−)-methylbenzoin.[7]

Chiurdoglu and others have reported that hydrogen bonding studies could distinguish *threo* and *erythro* isomers in a series of aliphatic 1,2-diols and we have found such studies can provide information upon which to base reliable configurational assignments in aryl–alkyl diols.

By examination of the hydrogen bonding patterns of the three isomeric pairs (see Table I), it is possible to divide the diols into two sets. One member of each pair (II, IV, and VI) shows only a free hydroxyl peak in the 3605–3611-cm.$^{-1}$ region with an attendant shoulder while the other member shows a sharp, distinct pair of free and bonded peaks (in addition to the concentration dependent intermolecular bands).

Steric considerations dictate that in order to exhibit intramolecular hydrogen bonding between hydroxyls the *meso* isomers would have to exist in an unfavored conformation in which the bulky phenyl groups on adjacent carbons would be in close proximity.[9] The *dl*-diastereoisomers can intramolecularly bond their hydroxyls when the phenyls are in a favored *trans* orientation. Hence I, III, and V might be assigned the *dl*-configuration, and II, IV, and VI the *meso*.

TABLE I

HYDROGEN BONDING IN PhRC(OH)RPh

R	M.p., °C.	Free –OH (cm.$^{-1}$)	Bonded –OH (cm.$^{-1}$)	$\Delta\nu$	Position of C–O (cm.$^{-1}$)		Assignment
Methyl							
I	122–123[a]	3615	3580 (s)	35	1143	1191	*dl*
II	117–118[a]	3605	3570 (sh)[e]	35	1126	1167	*meso*
Ethyl							
III	113[b]	3616	3572 (s)	46	1143	1182	*dl*
IV	138–139[b]	3609	3570 (w)[e]	39	1125	1164	*meso*
n-Propyl							
V	95–96[c]	3615	3569 (s)	46	1144	1180	*dl*
VI	128–129[d]	3611	3561 (m)[e]	50	1124	1159	*meso*

[a] Prepared as in ref. 3. [b] Prepared as in ref. 4. [c] Prepared as in ref. 5. [d] Prepared as in ref. 6. [e] The characterization of the position of the bonded peak is approximate since it appears as a shoulder or broad weak band.

The same conclusion might be reached by considering that in *dl* isomers the intramolecularly bonding hydroxyls can attain a perfect *cis* orientation without the severe phenyl–phenyl eclipsing that would be necessary in the *meso* form.

This conclusion is strengthened by examination of the bands associated with C–OH stretching modes for the tertiary hydroxyl which appear at 1140 to 1190 cm.$^{-1}$. Each of the diols II, IV, and VI shows double absorption peaks in this region which shift to higher frequencies in those diols which show strong intramolecular hydrogen bonding, I, III, and V.[10] The shift is exactly in the direction predicted for increased rigidity imparted to the C–O bond by intramolecular associations.[11]

It is also possible that the C–O bond shifts in going from *meso* to *dl* isomers are due to differences in dipole–dipole interactions in the two configurational species. Support for this possibility arises from the fact that the peak displacements show a remarkable constancy, between 16 and 20 cm.$^{-1}$, in the various isomers (see Table I).

If the C–O bond shifts were solely due to increased rigidity imparted to the bond by increased intramolecular association in the *dl* forms then one might expect a proportional increase in the C–O shift differences (between *dl* and *meso* forms of the same compound) as the hydrogen bond becomes tighter. Such a correlation is not observed.

The constancy of the C–O peak displacements suggests that they might possibly serve as qualitative and quantitative tools for identifying such compounds in mixtures.[12]

It also has been observed that the small amount of intramolecular hydrogen bonding which occurs in the *meso* forms increases as one proceeds from methyl to ethyl to *n*-propyl. This is explained by the conformational consideration that the unfavored rotomer for intramolecular bonding in *meso* becomes less and less

(1) Presented at the Fourth Delaware Valley Regional Meeting, American Chemical Society, January, 1962.

(2) A portion of this work is taken from the M.S. thesis of Ned D. Heindel, National Science Foundation Predoctoral fellow, 1959–63.

(3) Ramart-Lucas and M. Salmon-Legagneur, *Bull. soc. chim. France*, (4) **45**, 718 (1929).

(4) G. Ciamician and P. Silber, *Atti Accad. Nazl. Lincei, Mem. Classe Sci. Fis. Mat. Nat. Sez.*, (5) **23-I**, 860 (1914).

(5) I. Nazarov, *Ann. Leningrad State U. Chem. Ser.*, **1**, 123 (1935); *Chem. Abstr.*, **31**, 6617 (1937).

(6) E. Chu and J. Chu, *J. Chinese Chem. Soc.*, **10**, 11 (1943).

(7) D. Cram and K. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).

(8) G. Chiurdoglu, R. de Groote, W. Masschelein, and M. H. van Risseghem, *Bull. soc. chim. Belges*, **70**, 342 (1961); *Chem. Abstr.*, **56**, 8185 (1962).

(9) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 132–133.

(10) Similar shifts of this kind have been previously reported and correlated with hydrogen bonding. H. E Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **75**, 2368 (1953).

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 108–110.

(12) Cram and Kopecky, ref. 7, have observed but not explained these differences in the 8.8-μ region for the diastereoisomeric acetophenone pinacols and have employed them for quantitative analysis purposes.

unfavored as the increasing bulk of the R groups approaches that of the phenyl.

The increase in the strength of the hydrogen bond, as reflected in $\Delta\nu$,[13] from 35 in the *meso*-methyl to 50 cm.$^{-1}$ in *meso*-*n*-propyl is expected in light of previous observations that replacement by increasingly bulky alkyl groups on the carbons bearing the hydroxyl and phenyl reduces the O–C–C angle and brings the hydroxyls into closer proximity. This is in accord with the Thorpe–Ingold deformation hypothesis that says when steric repulsions increase one of the angles at a carbon atom, the opposite angle is decreased.[13,14]

While these observations support the conclusion that in this series simple intramolecular bonding between hydroxyls is occurring, it is impossible to eliminate completely the possibility of –OH to π bonding involving the electrons of the phenyl ring. The $\Delta\nu$'s obtained in this work are of the approximate order of magnitude as those observed for the –OH to π bonding in β-phenyl ethanols,[15] and the diols measured herein might be considered structural analogs of the β-phenyl ethanols with suitable changes in substitution on the α and β carbons.

The possibility of –OH to π bonding in the PhRC(OH)C(OH)RPh series has been tested by employing the known sensitivity of such bonding to the basicity of the acceptor.[15,16] A tighter hydrogen bond is obtained when electron release into the aromatic system is facilitated.

Synthesis and spectral examination of the *dl* forms of *p*-methyl and *p*-methoxyacetophenone pinacols gave $\Delta\nu$ values of 36 and 35 cm.$^{-1}$, respectively, and a strong intramolecular bonding peak. Since these values are in perfect agreement with the unsubstituted *dl*-acetophenone pinacol (see Table I), it appears that bonding between hydroxyls is favored.

The diols I, III, and V can be assigned the *dl*-configuration, and II, IV, and VI, the *meso*. In the case of I and II this is in agreement with the results obtained by Cram and Kopecky.[7]

Experimental

The bonding measurements were performed in these laboratories on a Perkin-Elmer 421 grating spectrophotometer and by P. von R. Schleyer of Princeton University on a Perkin-Elmer Model 21 spectrophotometer with lithium fluoride optics. All diols were examined as dilute solutions in spectral grade carbon tetrachloride according to standard procedures.

The diols were prepared according to the procedure in the references noted (see Table I) and recrystallized to constant melting point. With the exception of the high melting isomer of 4,5-diphenyl-4,5-octanediol (VI), all had melting points in agreement with those reported. Diol VI was obtained after several recrystallizations from 1:1 hexane–benzene as white microneedles of m.p. 128–129°, as reported.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.47; H, 8.88.

The *dl* isomer of 2,3-di-*p*-tolyl-2,3-butanediol was prepared as described by Backer, Stevens, and Van der Bij.[17] The configurational assignments provided by the authors, on the basis of relative oxidation rates with lead tetraacetate, are confirmed by the bonding study.

The *dl* isomer of 2,3-di-*p*-anisyl-2,3-butanediol was prepared by a method employing Cram's rule of asymmetric induction.[7] To an ice-cooled solution containing 0.40 mole of *p*-anisylmagnesium bromide in 700 cc. of anhydrous ether was added 0.10 mole of 2,3-butanedione in 20 cc. of ether. After addition was complete, the mixture was stirred 12 hr. and hydrolyzed with ice–ammonium chloride solution. The ethereal extracts were concentrated to an oil and steam distilled to remove unchanged diketone and other volatiles. The organic portion of the nonvolatiles was dried and chromatographed on alumina with hexane–benzene elutants. A total of 7.1 g. (23%) of the *dl*-diol was obtained, m.p. 122–123°, (lit.[18] m.p. 122–123°).

Acknowledgment.—Appreciation is expressed to Dr. P. von R. Schleyer, Princeton University, for confirming a portion of the bonding measurements and suggesting the possibility of –OH to π bonding and to Dr. Harold C. Beachell, this institution, for helpful discussions and interpretation.

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Preparation of 2-Bromopyrimidines

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Conversion of 2-amino- to 2-chloropyrimidines is usually effected by diazotization in concentrated hydrochloric acid. The yields by this procedure rarely exceed 30%.[2] Alternatively, the amine may be diazotized in the presence of sulfuric acid, giving the 2-hydroxy compound which subsequently is chlorinated with phosphorus oxychloride; the over-all yield in this process is likewise about 30%. In our own experience, application of the first method to 2-amino-4,5-diethoxypyrimidine gave the 2-chloro derivative in 38% yield.

We have observed that significantly better results can be obtained in the analogous preparation of 2-bromopyrimidines, by diazotization in hydrobromic acid after formation of a perbromide. This method, introduced by Craig[3] for application to 2-aminopyridines, seems not to have been used hitherto in the pyrimidine series. Thus, 2-amino-4,5-diethoxypyrimidine gave 2-bromo-4,5-diethoxypyrimidine in 79% yield, and 2-amino-4-chloro-5-ethoxypyrimidine gave 2-bromo-4-chloro-5-ethoxypyrimidine in 67% yield.

However, the utility of this reaction is circumscribed by the possibility of side reactions; in particular, it appears that the ease of electrophilic 5-bromination of the pyrimidine ring[4a] will limit the use of the Craig reaction to 5-substituted pyrimidines. From 2-amino-4-methoxypyrimidine the major product was 2-

(1) American Cyanamid Company, Bound Brook, N. J.

(2) (a) N. Sperber, D. Papa, E. Schwenk, M. Sherlock, and R. Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951), reported a 52% yield of 2-chloropyrimidine from 2-aminopyrimidine; however, (b) I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955), obtained yields of only 26–27% in this same preparation; (c) K. L. Howard, U. S. Patent 2,477,409 (July 26, 1949), quotes only one yield, 26.8% in the conversion of 2-amino-5-chloropyrimidine to 2,5-dichloropyrimidine.

(3) L. C. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(4) (a) G. W. Kenner and Sir A. Todd in R. C. Elderfield, "Heterocyclic Compounds," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 290–295; (b) p. 301.

amino-4-methoxy-5-bromopyrimidine (25%), together with 2,5-dibromo-4-methoxypyrimidine (19%). Under the same conditions, the only product isolable from 2-aminopyrimidine itself was 2% of 2-amino-5-bromopyrimidine.[5]

The low yield of recognizable products in the latter case indicated that some side reaction other than ring bromination also was taking place. In a few other instances, such as 2-amino-4,5-di-*n*-propylpyrimidine and 2-amino-4-chloro-5-*n*-propylpyrimidine, the desired product was obtained in only about 10% yield. The principal products from these reactions, which could not be purified, were bromine-containing solids insoluble both in nonpolar solvents and in water. Since they showed no absorption maxima in the ultraviolet, it may be conjectured that degradation of the pyrimidine ring had occurred.

In all the bromopyrimidines described, the position of the bromine atoms was verified by attempted displacement with sodium methoxide. As is well known, halogen substituents in the 2-, 4-, and 6-positions undergo ready nucleophilic displacement, whereas those in position 5 are resistant to such attacks.[4b] In conformity with expectations, 2-amino-5-bromopyrimidine and 2-amino-4-methoxy-5-bromopyrimidine were recovered unchanged, and 2,5-dibromo-4-methoxypyrimidine underwent selective displacement of the 2-bromine atom to give 2,4-dimethoxy-5-bromopyrimidine. It may be worth noting that, in 2-bromo-4-chloro-5-ethoxypyrimidine, the 4-chloro substituent proved to be more susceptible to nucleophilic attack than the bromine in position 2. With one equivalent of sodium ethoxide, it was converted in 95% yield to 2-bromo-4,5-diethoxypyrimidine. (With excess sodium ethoxide, both halogen atoms were replaced, giving 95% of 2,4,5-triethoxypyrimidine.)

Experimental

2-Bromo-4,5-diethoxypyrimidine.—To a suspension of 20.2 g. (0.11 mole) of 2-amino-4,5-diethoxypyrimidine[6] in 55 ml. of 48% hydrobromic acid, 16.9 ml. (0.32 mole) of bromine was added at 0°, with stirring, over a period of 45 min. During this addition, the mixture became very thick, but subsequently thinned out again. A solution of 19.4 g. (0.28 mole) of sodium nitrite in 28 ml. of water was added, still at 0°, over a 30-min. period and the stirring was continued for an additional 30 min. The resulting dark solution was cooled to −10°, and 200 ml. of a 20% solution of sodium hydroxide was added until a permanent basic reaction was produced. Filtration yielded 21.5 g. (79.0%) of 2-bromo-4,5-diethoxypyrimidine as a pale yellow solid, m.p. 49°, which crystallized from pentane without change in melting point.

Anal. Calcd. for $C_8H_{11}BrN_2O_2$: C, 38.88; H, 4.49. Found: C, 38.61; H, 4.48.

The **hydrochloride**, prepared with ethereal hydrogen chloride, melted at 135°; after softening, 95°.

Anal. Calcd. for $C_8H_{12}BrClN_2O_2$: C, 33.88; H, 4.27. Found: C, 34.29; H, 4.45%.

2-Bromo-4-chloro-5-ethoxypyrimidine.—Under the same conditions, except that the product was isolated by extraction with methylene dichloride, 2-amino-4-chloro-5-ethoxypyrimidine[6] gave a 67% yield of 2-bromo-4-chloro-5-ethoxypyrimidine, m.p. 43–46°, after recrystallization from hexane.

Anal. Calcd. for $C_6H_6BrClN_2O_2$: C, 30.35; H, 2.55; N, 11.80. Found: C, 30.65; H, 2.57; N, 11.80.

2-Bromo-4-chloro-5-*n*-propylpyrimidine.—Diazotization of 2.8 g. (0.0163 mole) of 2-amino-4-chloro-5-*n*-propylpyrimidine (prepared *via* 5-*n*-propylisocytosine, m.p. 236°, by the method reported for 2-amino-4-chloro-5-methylpyrimidine[7]; m.p. 168°) and work-up in the same manner described gave, after concentration of the methylene dichloride extract, a residue which was extracted with pentane. Distillation of the pentane extract yielded 0.35 g. (9.3%) of 2-bromo-4-chloro-5-*n*-propylpyrimidine, b.p. 130° (18 mm.), $n^{22}D$ 1.5475.

Anal. Calcd. for $C_7H_8BrClN_2$: C, 35.69; H, 3.42. Found: C, 35.66; H, 3.74.

The pentane-insoluble residue was recrystallized several times from isopropyl alcohol, yielding 0.98 g. of a solid, m.p. 226–227°, which failed to give a good analysis.

2-Amino-4-methoxy-5-bromopyrimidine.—Twenty-five grams (0.2 mole) of 2-amino-4-methoxypyrimidine was subjected to the Craig bromination procedure, the reaction mixture was extracted with ether, and the extracts evaporated to dryness.

The residue was extracted with hot hexane, and the solution concentrated to a volume of 150 ml. A 10.0-g. sample (24.5%) of 2-amino-5-bromo-4-methoxypyrimidine, separated as pale yellow prisms, m.p. 118°; lit.[3] m.p. 125–126°.

Anal. Calcd. for $C_5H_6BrN_3O$: C, 29.43; H, 2.96; Br, 39.17; N, 20.59. Found: C, 29.58; H, 2.93; Br, 38.88; N, 20.12.

2,5-Dibromo-4-methoxypyrimidine.—The hexane mother liquor was washed with 10% aqueous hydrochloric acid (to remove remaining traces of starting material), then dried, and concentrated. A 10.4-g. sample (19.4%) of 2,5-dibromo-4-methoxypyrimidine crystallized as colorless needles, m.p. 85°.

Anal. Calcd. for $C_5H_4Br_2N_2O$: C, 22.41; H, 1.50; Br, 59.66. Found: C, 22.83; H, 1.50; Br, 59.72.

2-Amino-5-bromopyrimidine.—Treatment of 23.5 g. of 2-aminopyrimidine with bromine and nitrite in the same manner described gave, after ether extraction of the reaction mixture, a residue of 0.7 g. (1.7%) of 2-amino-5-bromopyrimidine as light yellow plates, m.p. 235° (after softening), which crystallized from methanol in long needles; lit. m.p. 242–244°[9] and 235–237°.[10]

Anal. Calcd. for $C_4H_4BrN_3$: C, 27.61; H, 2.32; Br, 45.93. Found: C, 27.33; H, 2.35; Br, 46.20.

Reaction of 2-Bromo-4-chloro-5-ethoxypyrimidine with Sodium Ethoxide. (A) 2-Bromo-4,5-diethoxypyrimidine.—A solution of 16.5 g. (0.0695 mole) of the pyrimidine in 50 ml. of ethanol was added at 0° to a solution of 1.6 g. (0.0695 g.-atom) of sodium in 50 ml. of ethanol. The mixture was heated under reflux for 2 hr., filtered, and concentrated *in vacuo*. To the residue a small amount of water was added and the mixture extracted with pentane. From the extract 16.3 g. (95% yield) of 2-bromo-4,5-diethoxypyrimidine, m.p. 48°, was obtained.

(B) 2,4,5-Triethoxypyrimidine.—In the same way, 22.9 g. (0.0965 mole) of the pyrimidine and 6.7 g. (0.29 g.-atom) of sodium in 150 ml. of ethanol gave 17.9 g. (95%) of 2,4,5-triethoxypyrimidine, as a pale yellow solid, m.p. 33–34°, b.p. 147° (15 mm.), solidifying to a colorless solid, m.p. 35.5°.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.58; H, 7.60. Found: C, 56.81; H, 7.72.

The **hydrochloride**, prepared in ethereal hydrogen chloride solution, crystallized in clusters of needles, m.p. 104°.

Anal. Calcd. for $C_{10}H_{17}ClN_2O_3$: C, 48.28; H, 6.89; N, 11.27. Found: C, 48.32; H, 6.60; N, 11.13.

The same triethoxypyrimidine was obtained in 84% yield from 2-bromo-4,5-diethoxypyrimidine and sodium ethoxide.

5-Bromo-2,4-dimethoxypyrimidine.—A solution of 2.0 g. (0.00747 mole) of 2,5-dibromo-4-methoxypyrimidine and 0.44 g. of sodium methoxide in 50 ml. of methanol was heated under reflux for 16 hr., then evaporated to dryness. The residue was treated with water and extracted with methylene dichloride. The dried extract gave, on vacuum distillation, 0.8 g. (50%) of oil, b.p. 125° (17 mm.), which crystallized as colorless plates, m.p. 51–52°. Hilbert and Jansen[11] recorded the compound as prisms, m.p. 63–64°.

(5) After this work was completed D. D. Bly and M. G. Mellon reported [*J. Org. Chem.*, **27**, 2945 (1962)] conversion of 2-aminopyrimidine to 2-bromopyrimidine in a 26.6% yield by "reverse addition" diazotization. The scope of this method has not been established. It may be complementary in its application to the method described in the present paper.

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(8) J. P. English, J. H. Clark, R. G. Shepherd, H. W. Marson, J. Krapcho, and R. O. Roblin, *J. Am. Chem. Soc.*, **68**, 1039 (1946).

(9) J. P. English, J. H. Clark, J. W. Clapp, D. Seegar, and R. H. Ebel, *ibid.*, **68**, 453 (1946).

(10) C. Ziegler, U. S. Patent 2,609,372 (September 2, 1952).

(11) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 134 (1934).

Anal. Calcd. for $C_6H_7BrN_2O_2$: C, 32.89; H, 3.22; Br, 36.48. Found: C, 32.91; H, 3.15; Br, 36.49.

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Studies on Sphingolipids. VIII. Separation of the Diastereoisomeric Dihydrosphingosines. A Simplified Synthesis[1]

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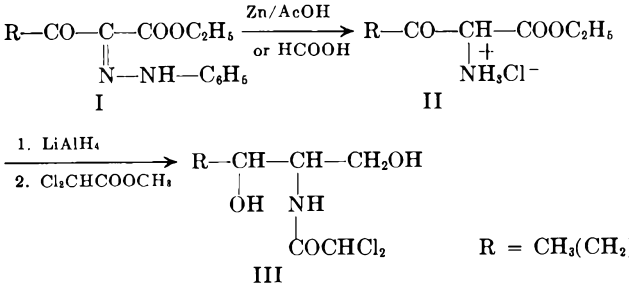
Most syntheses of dihydrosphingosine lead to a mixture of the two possible diastereoisomers,[2-6] whose separation is difficult to achieve. In the course of a recent investigation we observed that pure *erythro*-N-dichloroacetyldihydrosphingosine crystallized from the crude mixture and could thus be separated from its steric counterpart.

In a previous report[7] we described a synthesis of dihydrosphingosine which involved reductive acetylation of the phenylhydrazone I and a selective reduction of the resulting ethyl 2-acetamido-3-oxooctadecanoate with lithium aluminum hydride to give N-acetyldihydrosphingosine. While deacetylation proceeded satisfactorily when run on a relatively small scale, we experienced difficulties with the preparation of larger quantities of dihydrosphingosine, since considerable amounts of the amide resisted hydrolysis even after prolonged reaction.

Reduction of phenylhydrazones of type I with zinc and acetic acid usually is effected in the presence of acetic anhydride with formation of an acetamido group.[7-9] We have found that acetylation can be avoided by employing moist acetic acid, and we were able to isolate the keto ester II as the hydrochloride in 89% yield. The same result was achieved with formic acid at a slightly elevated temperature.



The crude mixture of isomers resulting from the reduction of the hydrochloride II with lithium aluminum hydride was treated directly with methyl dichloroacetate[10] and pure *erythro*-N-dichloroacetyldihydrosphingosine (III) was obtained after one crystallization. Mild alkaline hydrolysis afforded dihydrosphingosine.

The present synthesis offers a convenient method for the preparation of dihydrosphingosine in batches of ten to twenty grams.

Experimental

Ethyl 2-Amino-3-oxooctadecanoate Hydrochloride (II). (A) With Zinc Formic Acid.—To a vigorously stirred suspension of zinc powder (10 g.) in 98% formic acid (100 cc.) the phenylhydrazone I (8.56 g.) was added in portions, the temperature being maintained at 45–50°. After the addition was complete, the mixture was stirred for 20 min., cooled, and the zinc filtered off. The filtrate was poured into cold 2 *N* hydrochloric acid (100 cc.) and the product was filtered, washed with water, and dried. Crystallization from ten volumes of tetrahydrofuran yielded 6.7 g. (89%) of II, m.p. 126–128° (lit.[11] m.p. 114–116°).

Anal. Calcd. for $C_{20}H_{40}NO_3Cl$: C, 63.53; H, 10.64; Cl, 9.39; N, 3.70. Found: C, 63.30; H, 10.47; Cl, 9.27; N, 4.04.

(B) With Zinc–Acetic Acid.—A solution of the phenylhydrazone (8.56 g.) in 97% acetic acid (70 cc.) was added during 30 min. to a stirred suspension of zinc powder (10 g.) in 97% acetic acid (30 cc.), the temperature being maintained at 18–22° by external cooling. After stirring the colorless mixture for 15 min., the zinc was filtered off and the filtrate poured into cold 2 *N* hydrochloric acid (100 cc.). Crystallization from tetrahydrofuran yielded 6.5–6.7 g. of II, m.p. 126–128°.

***erythro*-N-Dichloroacetyldihydrosphingosine (III).**—A solution of the ester hydrochloride II (25 g.) in dry tetrahydrofuran (500 cc.) was added to a cold suspension of lithium aluminum hydride (10 g.) in dry tetrahydrofuran (250 cc.). After stirring at 40° for 1 hr., the mixture was cooled and the excess of lithium aluminum hydride decomposed by ethyl acetate (5 cc.). Sodium potassium tartrate solution (10%, 500 cc.) was then added, followed by 2 *N* sodium hydroxide solution (50 cc.), and saturated sodium chloride solution (100 cc.). The ethereal extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The solid residue (18 g.), melting at 60–70°, was dissolved in methyl dichloroacetate (200 cc.) and the solution heated in a boiling water bath for 2 hr. To the slightly cooled mixture petroleum ether (500 cc.) was added and the precipitated product was crystallized from methanol; yield 12 g. (45%); m.p. 142–144°.

Anal. Calcd. for $C_{20}H_{39}NO_3Cl_2$: C, 58.25; H, 9.53; N, 3.40; Cl, 17.20. Found: C, 58.50; H, 9.44; N, 3.63; Cl, 17.09.

Dihydrosphingosine.—N-Dichloroacetyldihydrosphingosine (4.12 g.) was dissolved with slight warming in methanol (360 cc.), *N* sodium hydroxide solution (40 cc.) was added, and the solution was left overnight at room temperature. *N* Acetic acid (40 cc.) was added and the solution was concentrated *in vacuo* until precipitation set in. Crystallization from chloroform gave 2.45 g. (82%), m.p. 85–86°.

(1) Supported in part by a grant from Samuel Rothberg of Peoria, Ill.
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The Aqueous Chemistry of Peroxychloroacetic Acid

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There are several reports in the literature concerning the *in situ* preparations of substituted peroxyacetic

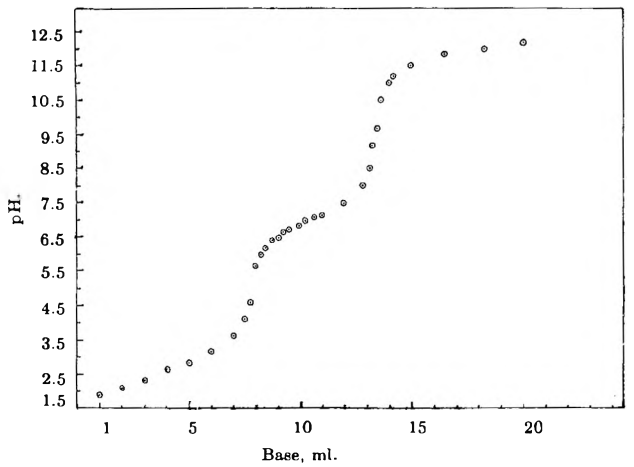

Fig. 1.—A typical basic titration curve for a sample of peroxychloroacetic acid, temp., 25°.

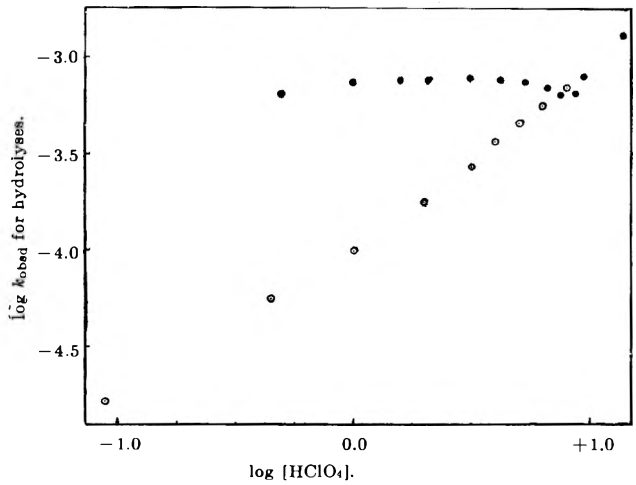

Fig. 2.—A plot of the log of the observed first-order rate constant in sec.$^{-1}$ for the hydrolysis of peroxyacetic acid and peroxychloroacetic acid *vs.* the log of the perchloric acid concentration: temp., 19.9°; ⊙, peroxyacetic acid; ●, peroxychloroacetic acid.

acids,[1] but there is available little reliable data concerning their isolation or their aqueous chemistry. In the case of peroxychloroacetic acid, most of these reports are found in the patent literature,[2] except for some early work by Panizzon.[3] He reported the preparation of peroxychloroacetic acid by its distillation (33–34° with decomposition at 3.5–4.0 mm.) from a mixture of chloroacetic anhydride and hydrogen peroxide in sulfuric acid. We have found it impossible to isolate any peroxy acid by this method. Our analysis[4] of the distillate with ceric and iodide ions showed all peroxide present to be hydrogen peroxide. This is consistent with the fact that the vapor pressure reported by Panizzon corresponds to that of hydrogen peroxide (lit.[5] 3.5–4.0 mm. at 33–34°).

Experimental

For the preparation of **peroxychloroacetic acid**, a modified version of the method of Panizzon[3] was used. Hydrogen peroxide (11.5 g. of 30% B&A reagent) was added dropwise over a period of 1 hr. to 70 g. of concentrated sulfuric acid which was immersed in an ice bath. Then 9.2 g. of chloroacetic anhydride (or 9.5 g. of chloroacetic acid) was added slowly and the resulting mixture stirred until all solid material was dissolved. The resulting clear solution was then allowed to stand for 24 hr. at room temperature after which it was extracted with three 30-ml. portions of anhydrous redistilled dichloromethane. The extracts were combined and the dichloromethane removed by evaporation under reduced pressure at 0°; precautions were taken to exclude moisture. A clear viscous liquid (3 to 4 ml.) remained after the removal of dichloromethane. Analysis[4] of the liquid showed it to contain 50–60% peroxychloroacetic acid, 1–5% hydrogen peroxide, and 40–50% chloroacetic acid. The per cent amount of the last compound was established from basic titration curves obtained using a Beckman Model G pH meter.

For the hydrolysis experiments 0.5 to 1 ml. of a freshly prepared sample of the last material was added to 50 ml. of perchloric acid solutions, varying in concentration from 0.1 to 11.6 *M*. These perchloric acid solutions were prepared by direct dilution of 72% perchloric acid (B&A reagent grade) with deionized water. The rates of hydrolysis were studied at 0, 25, and 35°, constant temperatures being maintained by means of ice and/or water baths. Care was exercised to eliminate possible errors due to trace metal-catalyzed decomposition.

Peroxyacetic acid was prepared by a method analogous to that used for the preparation of peroxychloroacetic acid, except that in this case the peroxy acid could be distilled from the reaction mixture under reduced pressure (30.5 ± 0.5° at 26 mm.). The distillate contained about 70% peroxyacetic acid, 25% acetic acid, and 5% hydrogen peroxide. In this case, as also in the case of peroxychloroacetic acid, the parent acid and the small amount of hydrogen peroxide were found to have little effect on the hydrolysis reaction, the kinetics of which are being reported now.

Measurements of the rate of oxidation of nitrosobenzene were carried out in 47% ethanol–water mixtures in a temperature-controlled Beckman DK-1 recording spectrophotometer with 1-cm. cells. These experiments were conducted under pseudo first-order conditions, 0.101 *M* nitrosobenzene being oxidized by 0.10–0.15 *M* peroxy acid.

Results and Discussion

Fig. 1 shows a typical curve of pH *vs.* milliliters of base added obtained for samples of peroxychloroacetic acid. Although active decomposition of the peroxy acid takes place at pH values near the pK_a, with rapid measurement a reproducible pK_a value of 7.2 was obtained. Thus peroxychloroacetic acid is the strongest peroxy acid known to exist in aqueous solution (with the possible exception of peroxyformic acid,[6] for which a pK_a value has been measured).

It may be pointed out that peroxy acids are known to undergo decomposition in aqueous solution by two pathways other than hydrolysis. These are (1) spontaneous decomposition in aqueous alkaline media[7,8] and (2) trace metal ion-catalyzed decomposition.[9,10] During the spontaneous decomposition of peroxyacetic acid, oxygen is evolved, while the trace metal ion-catalyzed decomposition is accompanied by the evolution of oxygen, carbon dioxide, and traces of carbon monoxide.[10] However, during the hydrolysis of peroxyacetic and peroxychloroacetic acid no gaseous products were ob-

(1) (a) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955); (b) F. Fichter, A. Fritscher, and P. Muller, *Helv. Chim. Acta*, **6**, 502 (1923).

(2) (a) J. D'Ans, German Patent 251,802 (1911); (b) I. G. Farbenindustrie, British Patent 369,716 (1931); (c) A. Grosse, U. S. Patent 2,806,045 (1957); (d) H. Krim, U. S. Patent 2,813,896 (1957).

(3) L. Panizzon, *Helv. Chim. Acta*, **16**, 1187 (1932).

(4) F. P. Greenspan and D. G. MacKeller, *Anal. Chem.*, **20**, 1061 (1948).

(5) W. C. Schumb, C. N. Satterfield, and R. L. Wentworth, "Hydrogen Peroxide," Reinhold Publishing Corp., New York, N. Y., 1955, p. 226.

(6) P. A. Giguere and A. W. Olmos, *Can. J. Chem.*, **30**, 821 (1952).

(7) (a) D. L. Ball and J. O. Edwards, *J. Am. Chem. Soc.*, **78**, 1125 (1956); (b) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **58**, 1846 (1962).

(8) E. Koubek, M. L. Haggett, C. J. Battaglia, K. M. Ibne-Rasa, H. Y. Pyun, and J. O. Edwards, accepted for publication by *J. Am. Chem. Soc.* (1963).

(9) D. L. Ball and J. O. Edwards, *J. Phys. Chem.*, **62**, 343 (1958).

(10) E. Koubek and J. O. Edwards, accepted for publication by *J. Inorg. Nucl. Chem.* (1963).

served, the only products produced being hydrogen peroxide and the parent acid. Conditions under which each of these three pathways could be studied for the decompositions of peroxyacetic and peroxychloroacetic acid were established. The results of the studies on the spontaneous decompositions and decompositions catalyzed by metal ions are the subjects of separate communications.[8,10]

In view of these facts, during the acid hydrolysis experiments both the kinetics of the disappearance of peroxy acid and the appearance of hydrogen peroxide were studied. No change in total peroxide content was noticed up to 90% reaction; *i.e.*, the rate of disappearance of peroxy acid corresponded exactly to the rate of formation of hydrogen peroxide. Therefore, acid hydrolysis was not accompanied either by decomposition to oxygen or by decomposition to oxygen and carbon dioxide. Both rates (peroxyacetic and peroxychloroacetic acids) appear to follow a first-order relationship (log concentration of peroxy acid *vs.* time gave a linear plot) to 90% reaction. The results now obtained for first-order rates of hydrolysis of the two peroxy acids as a function of the perchloric acid concentration are given in Fig. 2. The value 0.96×10^{-4} l./mole sec. for the second-order acid-catalyzed rate constant of peroxyacetic acid agrees with the value of 1.0×10^{-4} previously obtained by Bunton and co-workers.[11]

The rates of hydrolysis were measured at three temperatures (0, 24.8, and 35.3°); the rate constants are listed in Table I. The energies of activation (E_a) calculated from the rate constants given in Table I are 16.8 kcal./mole for the acid-catalyzed hydrolysis of peroxyacetic acid and 13.7 kcal./mole for the uncatalyzed hydrolysis of peroxychloroacetic acid. The entropies of activation (ΔS^*) are −22.6 cal./deg. mole and −29.3 cal./deg. mole in the same order.

Experiments to determine the effect of ionic strength upon the hydrolysis rate proved rather unsatisfactory, for the addition of sodium perchlorate led to a rapid decrease in total peroxide content. Most likely this resulted from addition of trace amounts of catalytic ions contained in the perchlorate salt.

The rates of hydrolysis of the two peroxy acids can be discussed in terms of the over-all rate law, rate = $k_O[\text{ROOH}] + k_H[\text{ROOH}][H_3O^+]$. From the apparent first-order dependence of the rate of hydrolysis of peroxyacetic acid on perchloric acid concentration, it is likely, as Bunton has pointed out, that the hydrolysis proceeds *via* nucleophilic attack by water on the unprotonated form. Nevertheless, the constant k_O must be less than 5×10^{-6} sec.$^{-1}$ and thus in 1 *M* acid the uncatalyzed rate amounts to less than 5% of the total rate of hydrolysis.

It is seen from Fig. 2 that, in the hydrolyses of the chloro substituted peroxy acid, the uncatalyzed rate is predominant over most of the acidity range, the value of k_O being 7×10^{-4} sec.$^{-1}$. Thus the uncatalyzed hydrolysis rate is much more significant than the acid-catalyzed hydrolysis over most of the acid range. However, at 8 *M* perchloric acid, the acid-catalyzed rate begins to contribute significantly to the over-all observed rate as demonstrated by the sharp increase in k_{obsd}. This behavior is not completely unexpected since the chlorine atom, while increasing the positive character of the carbonyl carbon, decreases the basicity of the carbonyl oxygen. Therefore, even though the protonated peroxychloroacetic acid is more susceptible to nucleophilic attack, its equilibrium concentration is much lower (relative to peroxyacetic acid under the same conditions), these two effects acting in opposition to each other. Tommila and Hinshelwood,[12] in their studies on the acid-catalyzed hydrolysis of benzoic acid esters, found that substituents on the benzene ring had virtually no influence on the rate of reaction; *i.e.*, k_H was found to be essentially the same for the variously substituted benzoic acid esters. Presumably the substituents exert electronic effects similar to those suggested for the chlorine atom in the peroxychloroacetic acid.

TABLE I

THE OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF PEROXYACETIC AND PEROXYCHLOROACETIC ACIDS AT VARIOUS TEMPERATURES AND AT VARIOUS CONCENTRATIONS OF PERCHLORIC ACID

Peroxyacetic acid [$HClO_4$]	k_{obs} (sec.$^{-1}$) 24.8°	35.3°	0°
0.10	1.56×10^{-5}	...	...
0.50	5.56×10^{-5}	...	...
1.00	9.65×10^{-5}	2.54×10^{-4}	...
2.00	1.78×10^{-4}	4.75×10^{-4}	...
3.00	2.65×10^{-4}	7.05×10^{-4}	...
4.00	3.42×10^{-4}	...	...
5.00	4.43×10^{-4}	...	2.96×10^{-5}
6.00	5.38×10^{-4}	...	3.43×10^{-5}
7.00	6.16×10^{-4}	...	4.82×10^{-5}
8.00	7.56×10^{-4}	...	...
Peroxychloroacetic acid			
0.50	5.85×10^{-4}	...	...
1.00	6.23×10^{-4}	1.33×10^{-3}	8.35×10^{-5}
1.50	6.84×10^{-4}	...	...
2.00	6.66×10^{-4}	1.58×10^{-3}	8.70×10^{-5}
3.00	7.24×10^{-4}	1.64×10^{-3}	8.70×10^{-5}
4.00	7.05×10^{-4}	1.70×10^{-3}	9.01×10^{-5}
5.00	6.90×10^{-4}	...	...
6.00	6.48×10^{-4}	...	...
7.00	6.65×10^{-4}	...	...
9.00	6.70×10^{-4}	...	...
10.0	8.35×10^{-4}	...	...
11.6	13×10^{-4} (initial rate)	...	...

In order to test the kinetic reactivity of peroxychloroacetic acid as an electrophile, the rate of oxidation of nitrosobenzene to nitrobenzene has been measured along with comparative data for two known peroxy acids. The second-order rate constants for the oxidation of nitrosobenzene at 30° were found to be 5.15 $\times 10^{-4}$, 35 $\times 10^{-4}$, and 167 $\times 10^{-4}$ l./mole sec. for peroxyacetic,[13] peroxymonosulfuric, and peroxychloroacetic acid, respectively.

The main disadvantages associated with this new peroxy acid appear to be the ease with which it is hydrolyzed into chloroacetic acid and hydrogen peroxide and its spontaneous decomposition[8] into chloroacetic acid and oxygen. The former is prevalent at all ranges of pH while the latter is significant near the pK_a

(11) C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *J. Chem. Soc.*, 1226 (1956).

(12) E. Tommila and C. N. Hinshelwood, *ibid.*, 1807 (1938).

(13) K. M. Ibne-Rasa, C. G. Lauro, and J. O. Edwards, *J. Am. Chem. Soc.*, **85**, 1165 (1963).

of the peroxy acid. In the case of peroxychloroacetic acid both processes take place at a much greater rate than with peroxyacetic acid.

Acknowledgment.—The authors wish to thank the U. S. Atomic Energy Commission for financing part of this work (contract AEC-1983). They also thank Dr. Khairat M. Ibne-Rasa for many helpful discussions and Miss Nan L. Sorensen for technical assistance.

2,3-Dihydro-4*H*-1,3-benzothiazinones-4

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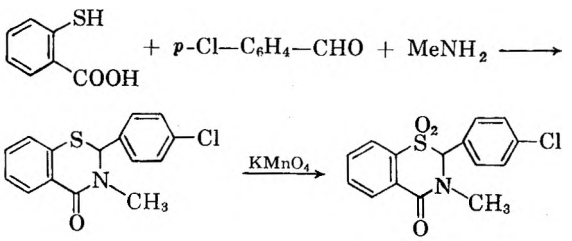
Received February 4, 1963

The only references to the synthesis of 4*H*-1,3-benzo thiazinones utilize the reaction of thiosalicylamide with aldehydes[1] or benzal chloride.[2]



(1) H. Böhme and W. Schmidt, *Arch. Pharm.*, **286**, 330 (1953).
(2) R. Boudet, *Bull. soc. chim. France*, 1518 (1955).

We have found that 2-phenyl-3-alkyl-dihydrobenzothiazinones are readily prepared from thiosalicyclic acid, an aldehyde, and a primary amine in refluxing benzene. Oxidation by permanganate in acetic acid gives the sulfone.

When methylamine was replaced by 1,1-dimethylhydrazine or by aniline, the reaction failed.

Experimental[3]

2,3-Dihydro-3-methyl-2-(*p*-chlorophenyl)-4*H*-1,3-benzothiazinone-4.—*p*-Chlorobenzaldehyde (10.0 g., 0.071 mole) was mixed with 30 ml. of anhydrous benzene previously saturated with methylamine. After 5 min. the solution turned milky. The solution was refluxed and water was removed azeotropically; the theoretical amount of water was obtained in 1 hr. The solution was cooled, powdered thiosalicyclic acid (0.071 mole) was added, and reflux was continued until another equivalent of water was removed (several hours). After cooling, the solution was rinsed with dilute base, dried, and the solvent was then removed. The residual viscous oil soon crystallized. The solid was triturated with hexane then recrystallized from benzene–isopropyl ether (11.0 g., m.p. 123.5–124°).

Anal. Calcd. for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17. Found: C, 62.17; H, 4.08.

2,3-Dihydro-3-methyl-2-(*p*-chlorophenyl)-4*H*-1,3-benzothiazin-4-one 1,1-dioxide.—An aqueous solution containing 8.3 g. (0.053 mole) potassium permanganate was added portionwise, with stirring, to a solution of 9.0 g. (0.031 mole) of the thiazinone in 90 ml. of acetic acid. Slight cooling was required to keep the temperature below 35°. The brown mixture containing a tan suspended solid was stirred an additional half hour and a small amount of sodium hydrosulfite was then added to decolorize the solution. The tan solid product was filtered and recrystallized from alcohol–acetone giving 5.5 g. of white crystals (m.p. 169–170°).

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76. Found: C, 55.69; H, 3.87.

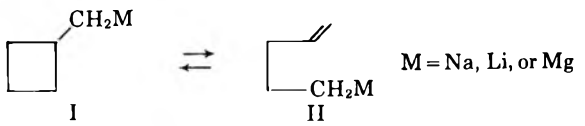
(3) All melting points are corrected. Analyses were performed by D Rolston and her staff of these laboratories.

Communications TO THE EDITOR

Intramolecular Cleavages and Double Bond Additions of Polar Organometallic Compounds[1]

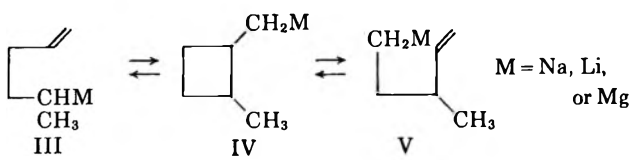
Sir:

Rearrangement of the cyclobutylmethyl organometallic compounds of sodium, lithium, and magnesium to isomeric acyclic compounds (I → II) is reported in this communication. In addition, 1-methyl-1-pent-4-enyl organometallic compounds of the same metals



I II

have been found to rearrange to 3-methyl-1-pent-4-enyl isomers (III → V); we propose that this rearrangement occurs by ring closure of the initially



III IV V

formed organometallic compounds III to cyclic isomers IV followed by ring opening to acyclic isomers V. These rearrangements are similar to that observed by Roberts and co-workers for the cyclopropylmethyl and 1-but-3-enyl Grignard reagents.[2]

The rates of some of these reactions can be measured and it should be possible to study the effects of different reaction conditions on these intramolecular cleavages and double bond additions. The Grignard reagents (studied in tetrahydrofuran) appear to rearrange much more slowly than the sodium and lithium reagents despite the use of less polar hydrocarbon media for the latter. The equilibration of isomeric organometallic compounds also permits estimation of their relative stabilities. For example, it appears that the equilibrium mixture of lithium compounds III and V in cyclohexane contains more than 99% of V, indicating a much greater stability for the primary than for the isomeric secondary organolithium compound.

1. Evidence for Ring Opening.—Treatment of cyclobutylmethyl chloride with sodium in tetradecane produced 1-pentene and methylcyclobutane in a ratio of 7:1.[3] These hydrocarbons probably arose from the action of 1-pent-4-enylsodium (II) and cyclobutylmethylsodium (I), respectively, as bases in elimination reactions.[4] Presumably cyclobutylmethylsodium (I) formed first and then underwent ring opening to form the acyclic organosodium compound II.

The lithium compound prepared at room temperature in benzene from cyclobutylmethyl bromide and lithium rearranged similarly. Samples hydrolyzed after standing for 1 or 18 hr. gave a 93:7 mixture of 1-pentene and methylcyclobutane.[6] It is likely that the rearrangement was nearly complete when the first sample was taken, since removal of the solvent under vacuum, followed by hydrolysis of the residue, reduced the methylcyclobutane to less than 0.5%. Some hydrolysis by traces of moisture presumably occurred during or shortly after formation of the reagent.

The cyclobutylmethyl Grignard reagent also was observed to rearrange at temperatures near the boiling point of tetrahydrofuran (65°).[6] This rearrangement occurs in the presence or absence of excess magnesium, with the chloride or the bromide, and with either regular Grignard reagent magnesium or sublimed magnesium. The degree of rearrangement increases with time of heating, eliminating the possibility that all of the rearrangement occurs during formation of the Grignard reagent.[7] Rearrangement to the acyclic reagent proceeds at least 99.8% to completion.

2. Evidence for Ring Closure.—Organolithium compound III was prepared by reaction of lithium with a mercury compound, b.p. 92° (0.6–0.7 mm.), synthesized from mercuric chloride, and the Grignard reagent prepared from 5-chloro-1-hexene.[8] Hydrolysis after 90 min. of a portion of a solution obtained from refluxing this mercury compound with lithium in cyclohexane gave a C_6 product which was at least 99% 3-methyl-1-pentene. The composition and the yield were unchanged after the solution had stood at room temperature for an additional 24 hr.[9] This rearranged olefin probably arose from hydrolysis of organolithium compound V; presumably organolithium compound III formed initially but then rearranged rapidly to V.

(1) Preliminary work was supported by research grant 7766 (to H. G. R.) from the National Institutes of Health and by a National Science Foundation Postdoctoral Fellowship (to E. A. H.). Recent work has been supported by grants from the Petroleum Research Fund administered by the American Chemical Society (to E. A. H. and to H. G. R.) and by equipment grants (to E. A. H.) from the Graduate School and the Institute of Technology of the University of Minnesota. Grateful acknowledgement is hereby made of this support.

(2) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 2646 (1960).

(3) Product analyses were by vapor phase chromatography. Identification of the separated components was by gas phase infrared spectra.

(4) Products of formula C_5H_8 also were formed. The nature of these products will be discussed elsewhere. Compare with W. Kirmse and W. von E. Doering, *Tetrahedron*, **11**, 266 (1960); L. Friedman and J. G. Berger, *J. Am. Chem. Soc.*, **83**, 492, 500 (1961); and P. S. Skell and A. P. Krapcho, *ibid.*, **83**, 754 (1961).

(5) It is assumed that hydrolyses of the organometallic compounds are considerably more rapid than their rearrangements. The assumption is valid at least with the Grignard reagents.

(6) R. C. Krug, I. W. Smith, and C. E. Fry [*J. Am. Chem. Soc.*, **76**, 3222 (1954)] previously have reported the reaction of a Grignard reagent from cyclobutylmethyl bromide with phenyl isocyanate. It appears that the anilide they obtained was that of cyclobutylacetic acid.[7]

(7) The structures of the original and rearranged Grignard reagents have been confirmed by carbonation to the corresponding carboylic acids (R. A. Doughty).

(8) Reaction of the mercury compound with hydrochloric acid gave a mixture of 98% of 1-hexene and 2% of 3-methyl-1-pentene. The rearranged group (1°) should be cleaved even more readily by acid than the unrearranged group (2°) [F. C. Whitmore and H. Bernstein, *J. Am. Chem. Soc.*, **60**, 2626 (1938)] so this per cent of 3-methyl-1-pentene represents maximum of rearranged groups.

(9) That the olefins observed had not formed prior to the hydrolyses was shown by pumping off the volatile material and then hydrolyzing the residue; little of the olefinic product was in the volatile portion.

Aliquots of a refluxing tetrahydrofuran solution of a Grignard reagent prepared from 5-chloro-1-hexene were hydrolyzed at intervals. The proportion of 3-methyl-1-pentene in the mixture of 1-hexene and 3-methyl-1-pentene increased, but at decreasing rate, to about 20% after 14 days. At that time volatile materials were removed from the solution under vacuum and the remaining solid hydrolyzed to give in poor yield a mixture containing 85% of 3-methyl-1-pentene and only 15% of 1-hexene. Apparently in this case, attack of the Grignard reagent on solvent to produce olefin is competitive with the slower rearrangement, so that with increasing time, a smaller fraction of the olefin in the samples analyzed was actually formed in the hydrolysis operation.

Reaction of 5-chloro-1-hexene with sodium in hydrocarbon solvents also gave 1-hexene and 3-methyl-1-pentene, with the rearranged olefin predominating. The reaction mixtures contained 1,5-hexadiene and smaller amounts of other compounds that must have formed by reaction of the chloride with the sodium compounds.

Reasonable possibilities for the mechanism of these rearrangements include a four-center process and either heterolytic or homolytic cleavage to the corresponding carbanion or free radical which then undergoes rearrangement. The increase in the facility of rearrangement with polarity of the carbon–metal bond supports the ionic mechanism or a highly polar four-center process. However, the free radical mechanism remains a possible alternative.[10] We currently are investigating this question kinetically and stereochemically and are exploring several extensions and variations of these elimination and intramolecular addition reactions.

(10) R. C. Lamb of the University of Georgia kindly has informed us of a similar cyclization noted in oxygenation of the Grignard reagent from 6-bromo-1-hexene, in which a free radical pathway appears likely. He also found some cyclization in the carbonation of the same Grignard reagent. This agrees with our findings that the Grignard rearrangement occurs in that system.

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HERMAN G. RICHEY, JR.
THOMAS C. REES

RECEIVED APRIL 29, 1963

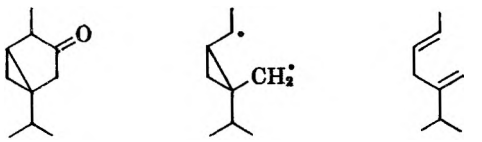
The Photolysis of Thujone

Sir:

We wish to report that the photolysis of the terpene ketone thujone (I) appears to offer an example of the participation of a cyclopropane ring in facilitating the photochemical elimination of carbon monoxide from a ketone. Thujone (I) is converted smoothly and with unusual rapidity into carbon monoxide and 2-isopropyl-1,4-hexadiene (III) on exposure to ultraviolet radiation in the wave-length region[1] 2500–3000 Å.

Infrared spectral analysis of the gaseous product showed it to be carbon monoxide (λ_{max}^{gas} 4.62, 4.73 μ), and gas–liquid chromatography of the liquid product

(1) The photolysis proceeded at an uninhibited rate and to the same products using a 30% solution of thujone in benzene.



I II III

revealed only traces of products[2] other than 2-isopropyl-1,4-hexadiene (III) [λ_{max}^{film} 6.09 μ (C=C), 7.26 and 7.35 μ (CH_3CCH_3), 3.31 and 10.29 μ (*trans*—RCH=CHR), 3.25 and 11.20 μ (CR_1R_2=CH_2); n.m.r. spectrum,[3] 65 and 79 (CH_3CHCH_3), 99 (CH_3C=C), multiplet about 132 (CH_3CHCH_3), 163 (CH_2), 285 (C=CH_2), multiplet about 327 (—CH=CH—); integral, 16 protons, in accord with the foregoing assignments. *Anal.* Calcd. for C_9H_{16}: C, 87.23; H, 12.77. Found: C, 87.51; H, 12.80]. The photolyses were carried out in quartz cells using either 150-watt high pressure Hanovia (510B1) xenon–mercury arcs or General Electric (H400A33-1) 400-watt "Dark Light" arcs with the external envelope removed. Manometric measurements were made in a nitrogen-filled system using mercury-filled burets.

Under given photochemical conditions the rates of carbon monoxide evolution (first 10% of reaction) from thujone,[4] cyclopentanone, and cyclohexanone as neat liquids were respectively 0.79, 0.047, and 0.025 ml. per minute. Since the integrated absorption intensities [$\int \epsilon \, d\nu$] of thujone, cyclopentanone, and cyclohexanone for the wave-length interval 2600–3300 Å. were, respectively, 44.5, 29.2, and 27.5 in arbitrary units, the fifteen- to thirtyfold greater photolysis rate for thujone reasonably cannot be attributed to its somewhat greater absorption in the photolytic region and may, instead, be ascribed to the presence of the cyclopropane ring in the homoallylic position.

Photolysis of solutions of thujone dissolved in ten times its volume of either cyclohexene or 1-propanol proceeded at rates comparable to those found for the neat liquid; and gas–liquid chromatographic and infrared spectral analysis of the photolyzate showed only traces of products other than the diene III. These results are taken to indicate that any intermediate radical such as II is capable of at best only very brief existence, and that the transition of thujone from its photoexcited state to the diene III and carbon monoxide is made unusually efficient by participation of the neighboring cyclopropane ring system. A similar facilitation of the photolysis of the 3-cyclopentenone system by the electrons of the double bond would be predicted. The clean-cut nature of such photochemical reactions may prove useful in synthesis and in gasometric actinometry in the photochemically important 2500–3000-Å. region.[5]

Acknowledgment.—We wish to express our appreciation to the National Science Foundation (G-9476) and

(2) The ultraviolet absorption spectrum of the gas chromatographically homogeneous diene III showed weak absorption at λ_{max}^{EtOH} 231 mμ indicative of less than 5% of conjugated diene in the material.

(3) At 60 Mc., in deuteriochloroform. Chemical shifts are in cycles per second referred to tetramethylsilane as internal standard at 0 c.p.s.

(4) Whether (−)-thujone or (+)-isothujone was used made no difference in the rate.

(5) Thujone is readily available through efficient fractional distillation of thuja oil (P.R. Dreyer, Inc., New York, N.Y.). The fraction having b.p. 83.2–83.9° at 15.9 mm., $n^{25}D$ 1.4502, is suitable.

the Air Force Office of Scientific Research and Development (AFOSR-62-116) for their generous support of this investigation.

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J. EDWARD STARR
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MATTHEW K. SAKATA

RECEIVED APRIL 16, 1963

Substitutions by Ligands of Low Valent Transition Metals. A Preparation of Tolanes and Heterocyclics from Aryl Iodides and Cuprous Acetylides

Sir:

In the course of our studies of the reduction of multiple bonds by low valent transition metal ions,[1] we have had occasion to prepare a variety of unsymmetrical tolanes. We have found that these substances are conveniently obtained by the interaction of aryl iodides with cuprous acetylides. The reaction is best carried out in refluxing pyridine in a nitrogen atmosphere.[2]

$$ArI + CuC{\equiv}C{-}Ph \xrightarrow[N_2]{\text{Pyridine}} Ar{-}C{\equiv}C{-}Ph + CuI$$

Some illustrative yields for the process are depicted (Table I).

TABLE I
YIELDS OF TOLANES FROM ARYL IODIDES AND CUPROUS PHENYLACETYLIDE

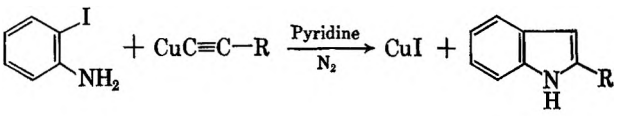
Aryl iodide	Product	Yield, %[a]
Iodobenzene	Diphenylacetylene	90
p-Methoxyiodobenzene	*p*-Methoxytolane	83
o-Methoxyiodobenzene	*o*-Methoxytolane	80
p-Nitroiodobenzene	*p*-Nitrotolane	74
o-Nitroiodobenzene	*o*-Nitrotolane	84

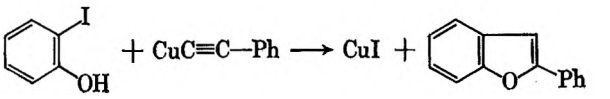
[a] All yields reported in this communication refer to the purified product. Microanalyses, physical constants, and spectra are correct for all substances reported herein.

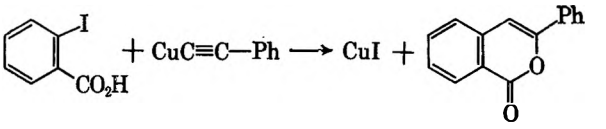
When the starting halide bears an *ortho* nucleophilic substituent, cyclization to the corresponding heterocycle occurs exclusively. In a reaction typical of both the tolane and heterocyclic synthesis, 3 g. of cuprous phenylacetylide and 4.03 g. of *o*-iodophenol were placed in a flask containing 200 ml. of pyridine which had been purged thoroughly with nitrogen. The reaction solution was refluxed for six hours in a nitrogen atmosphere. During this time the color changed from yellow to a dark reddish brown. The cooled solution was diluted with water and extracted with ether. The washed and dried ether extracts were concentrated and crystallized. The crude α-phenylbenzofuran was recrystallized from hot ethanol to yield 3.2 g. of pure material.[3]

(1) C. E. Castro and R. D. Stephens, Abstracts of Papers, Organic Division, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 23 Q.

(2) In the presence of oxygen, coupling of the acetylene occurs.

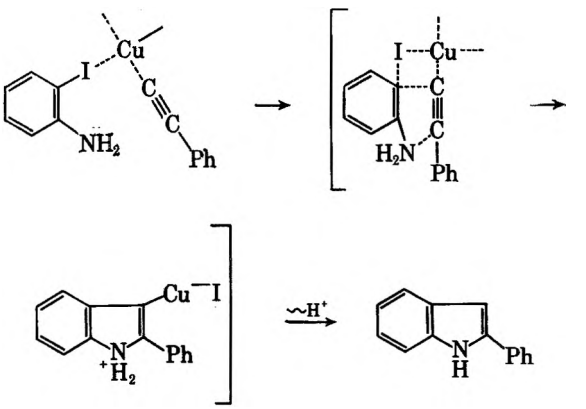






The foregoing set of transformations are indicative of the scope of the facile heterocyclic synthesis.

Moreover, *o*-aninotolane when exposed to cuprous iodide and cuprous phenylacetylide in pyridine *was not* cyclized but recovered quantitatively. This finding suggests that the substitution of halide and the cyclization take place within the same copper complex.



Under proper conditions both the tolane and heterocyclic syntheses should be catalytic in copper. This point, as well as the scope and mechanism of these reactions, is under scrutiny.[4]

(3) This conversion has been effected in pyridine, dimethylsulfoxide, dimethylformamide, and acetic acid; in all solvents yields of better than 80% were obtained.

(4) The authors are indebted to the National Science Foundation for a grant (G19145) in support of this work.

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The Synthesis of Isothiazoles from Disalts of Dimercaptomethylenemalononitrile

Sir:

Mononuclear isothiazoles have been unknown until recently and few syntheses of this ring system have been described.[1-5]

(1) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

(2) (a) J. Goerdeler, *Angew. Chem.*, **74**, 498 (1962); (b) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **94**, 2950 (1961); (c) J. Goerdeler, *Angew. Chem.*, **72**, 77 (1960).

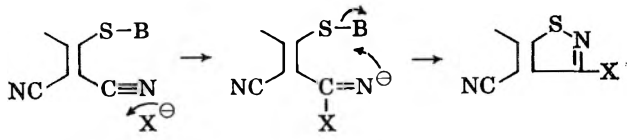
(3) F. Willie, *ibid.*, **74**, 467 (1962).

(4) F. Hubenett, F. H. Flock, and H. Hoffman, *ibid.*, **74**, 653 (1962).

(5) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, 252 (1960).

Only one general synthetic method is available for the synthesis of mononuclear isothiazoles having other than hydrocarbon substituents (the ring closure of β-iminothioamides described independently by A. Adams and R. Slack and by J. Goerdeler).

We wish to report the novel synthesis of substituted isothiazoles by the ring closure of di(sodiomercapto)-methylenemalononitrile (**1**) under oxidizing conditions. This reaction appears to occur by an addition of a nucleophilic agent to the nitrile group and ring closure on sulfur with elimination of an anion.



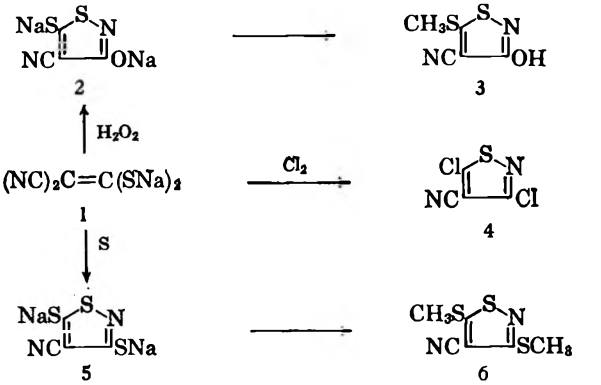
Cyclizations to form two condensed ring isothiazoles have earlier been reported from this laboratory.[6-7]

With one equivalent of hydrogen peroxide, the disodium salt[7,8] (**1**) in aqueous solution was converted to the disodium salt of 3-hydroxy-5-mercapto-4-isothiazole (**2**) in 97% yield. *Anal.* Calcd. for $C_4S_2N_2ONa_2$: C, 23.7; S, 31.7; Na, 22.8. Found: C, 22.4; H, 1.02; S, 31.3; Na, 21.1 ± 2%. $\lambda_{max}^{methanol}$ 320 mμ (ε 13,300), 290 (9800), 213 (11,000). The infrared spectrum (Nujol) showed strong bands at 4.55, 6.65, and 7.6 μ. Alkylation of **2** with one equivalent of methyl iodide followed by acidification yielded the methylthio derivative **3** (71%), m.p. 237–242°. *Anal.* Calcd. for $C_5H_4N_2OS_2$: C, 34.9; H, 2.34; S, 37.3; N, 16.3. Found: C, 34.9; H, 2.43; S, 37.3; N, 16.2. λ_{max}^{alc} 277 mμ (ε 11,500). The infrared spectrum (Nujol) showed strong bands at 3.4, 3.65, 3.75, 3.85, 4.50, 6.10, 6.45, 6.65, and 7.7 μ. Compound **3** readily dissolved in sodium carbonate solution and was recovered unchanged by acidification.

A second method, involving the reaction of the anhydrous sodium salt **1** with chlorine in boiling carbon tetrachloride, gave a 57% yield of 3,5-dichloro-4-isothiazolecarbonitrile (**4**), m.p. 65–66°. *Anal.* Calcd. for $C_4N_2Cl_2S$: C, 26.8; Cl, 39.6; S, 17.9; mol. wt., 179. Found: C, 27.1; Cl, 39.4; S, 17.8; mol. wt., 196 (Rast, acetone). The infrared spectrum showed major bands at 4.5, 6.65, and 7.52 μ.

(6) H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.*, **84**, 4746 (1962).
(7) W. R. Hatchard, U. S. Patent 3,048,596 (1962).
(8) J. D. Kendall and H. D. Edwards, U. S. Patent 2,493,071 (1950).

Sulfur, as the oxidizing agent, dissolved in a boiling methanol solution of **1** to give a quantitative yield of the disodium salt of 3,5-dimercapto-4-isothiazolecarbonitrile (**5**). *Anal.* Calcd. for $C_4N_2S_3Na_2$: C, 22.0; N, 12.8; S, 44.1. Found: C, 22.3; N, 12.7; S, 42.8. $\lambda_{max}^{H_2O}$ 330 mμ (ε 7070), 303 (12,900), 260 (10,500), 240 (sh) (9250), and 218 (14,300). With two moles of methyl iodide, **5** was converted to 3,5-bis-(methylthio)-4-isothiazolecarbonitrile (**6**), m.p. 131–131.5°, in 80% yield. *Anal.* Calcd. for $C_6H_6N_2S_3$: C, 35.6; H, 2.9; S, 47.5. Found: C, 35.8; H, 2.9; S, 47.9. λ_{max}^{alc} 284 mμ (ε 13,300) 230 (11,700), 215 (11,100). The infrared spectrum showed strong bands at 4.50, 6.65, 6.79, and 7.6 μ.



The ultraviolet and infrared absorption spectra of these compounds are consistent with the proposed structures and with the meager published information on spectra of isothiazole derivatives.[2b] The ultraviolet spectra differ considerably from those of the starting di(sodiomercapto)methylenemalononitrile (**1**) [λ_{max}^{alc} 342 mμ (ε 18,600), 272 (5400)] and the corresponding di(methylthio)methylenemalononitrile[8] [λ_{max}^{alk} 330 mμ (ε 13,200), 290 (sh) (6800)]. The infrared spectra show characteristic absorption bands between 6.6–6.85 and 7.5–7.7 μ, that have been attributed to the isothiazole ring.[2b]

Further details of these reaction products and of a variety of their derivatives will be described in future papers.

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